Phase 1/2 Clinical Study of Niraparib in Combination with Pembrolizumab in Patients with Advanced or Metastatic Triple-Negative Breast Cancer and in Patients with Recurrent Ovarian Cancer

Sponsor:
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Sponsor Protocol No.:	3000-PN162-01-001
IND No(s).:	100,996 and 117,580
EudraCT No.:	2015-003398-14
Study Drug Names:	Niraparib capsules/pembrolizumab for injection
Development Phase:	1/2
Date of Original Protocol:	19 October 2015
Date of Protocol Amendment 1:	28 July 2016
Date of Protocol Amendment 2:	01 March 2017
Version of Protocol:	3.0

The study will be conducted according to the protocol and in compliance with Good Clinical Practice (GCP), with the Declaration of Helsinki, and with other applicable regulatory requirements.

Confidentiality Statement

All information contained in this document is privileged and confidential to TESARO. Any distribution, copying, or disclosure is strictly prohibited without prior written approval by TESARO.

SPONSOR SIGNATURE PAGE

Declaration of Sponsor or Responsible Medical Officer

Title: Phase 1/2 Clinical Study of Niraparib in Combination with Pembrolizumab in Patients with Advanced or Metastatic Triple-Negative Breast Cancer and in Patients with Recurrent Ovarian Cancer

This study protocol was subjected to critical review and has been approved by the Sponsor. The information it contains is consistent with the current risk/benefit evaluation of the investigational products as well as with the moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki and the guidelines on Good Clinical Practice.

_____ _____

[redacted] **Date**

Senior Medical Director
TESARO, Inc.

INVESTIGATOR SIGNATURE PAGE

Declaration of the Principal Investigator

Title: Phase 1/2 Clinical Study of Niraparib in Combination with Pembrolizumab in Patients with Advanced or Metastatic Triple-Negative Breast Cancer and in Patients with Recurrent Ovarian Cancer

I have read this study protocol, including all appendices. By signing this protocol, I agree to conduct the clinical study, following approval by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB), in accordance with the study protocol, the current International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP), and applicable regulatory requirements. I will ensure that all personnel involved in the study under my direction will be informed about the contents of this study protocol and will receive all necessary instructions for performing the study according to the study protocol.

Principal Investigator

_____ _____

Name: **Date**
Title:
Institution:

SYNOPSIS

<table>
<tr><td colspan="2">Name of Sponsor/Company: TESARO, Inc.</td></tr>
<tr><td colspan="2">Name of Investigational Product: niraparib and pembrolizumab</td></tr>
<tr><td colspan="2">Name of Active Ingredient: niraparib and pembrolizumab</td></tr>
<tr><td colspan="2">Title of Study: Phase 1/2 Clinical Study of Niraparib in Combination with Pembrolizumab in Patients with Advanced or Metastatic Triple-Negative Breast Cancer and in Patients with Recurrent Ovarian Cancer</td></tr>
<tr><td colspan="2">Study Center(s): Phase 1: approximately 6 centers in the United States; Phase 2: approximately 40 centers in the United States</td></tr>
<tr><td>Study Period (years):
Estimated date first patient enrolled: April 2016
Estimated date last patient completed: November 2019</td><td>Phase of Development: 1/2</td></tr>
<tr><td colspan="2">Objectives:
Primary objectives:
• Phase 1: To evaluate dose-limiting toxicities (DLTs) of combination treatment with niraparib and pembrolizumab during the first cycle of treatment, and to establish a recommended Phase 2 dose (RP2D) and schedule
• Phase 2: To estimate the clinical activity of combination treatment with niraparib and pembrolizumab in terms of objective response rate (ORR) as assessed by the Investigators using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 separately for the triple-negative breast cancer (TNBC) and ovarian cancer (OC) cohorts.
Secondary objectives:
• Phase 1 and Phase 2: To evaluate the safety and tolerability of combination treatment with niraparib and pembrolizumab using Common Terminology Criteria for Adverse Events (CTCAE, v.4.03)
• Phase 2: To evaluate additional measures of clinical benefit as assessed by the Investigators, including:
– ORR by immune-related RECIST (irRECIST)
– Duration of response (DOR) by RECIST v1.1 and irRECIST;
– Disease control rate (DCR) by RECIST v1.1 and irRECIST;</td></tr>
</table>

- Progression-free survival (PFS) by RECIST v1.1 and by irRECIST;
- Overall survival (OS).

- Phase 1 and 2: To evaluate the pharmacokinetics (PK) of niraparib and associated major metabolite M1 during combination treatment.

Exploratory objectives (both phases):

- To identify the biomarker-based patient population that would derive benefit from the combination treatment based on the tumor tissue molecular profile, molecular profile of tumor-infiltrating lymphocytes (TILs), and circulating biomarkers.
- To correlate homologous recombination deficiency (HRD) status with other immune-related biomarkers and with efficacy outcomes.

Methodology:

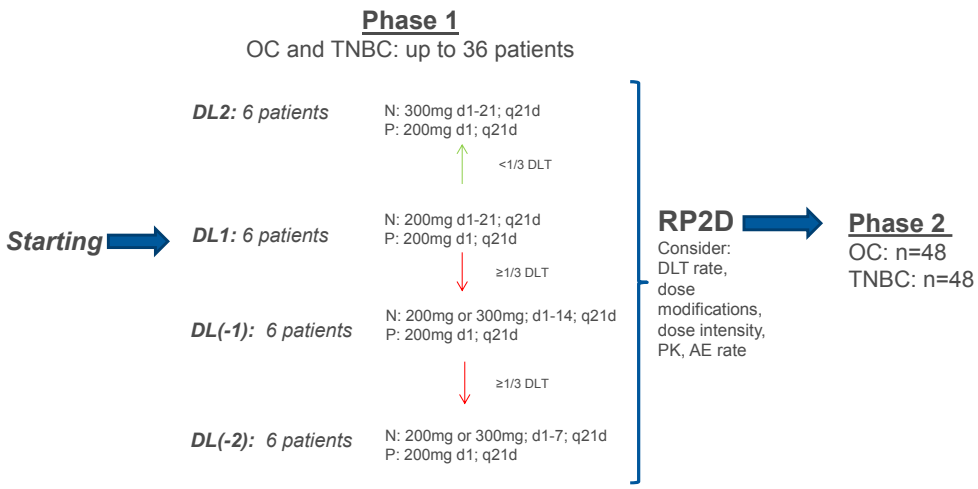
Overall

This is a multicenter, open-label, single-arm Phase 1/2 study evaluating the safety and efficacy of combination treatment with niraparib and pembrolizumab in patients with previously treated TNBC or OC. Specifically, patients eligible for this study are those with:

- Advanced or metastatic TNBC (in Phase 1 patients may have received up to 4 lines of cytotoxic therapy for advanced/metastatic disease or in Phase 2, up to 2 lines of cytotoxic therapy for advanced/metastatic disease); or
- Advanced, recurrent epithelial (for Phase 1: any serous, endometroid, mucinous, clear cell; for Phase 2: high-grade serous or endometroid) ovarian, fallopian tube, or primary peritoneal cancer who are currently platinum-resistant but previously experienced a response lasting for at least 6 months to first-line platinum-based therapy (in Phase 1 patients may have received up to 5 lines of cytotoxic therapy or in Phase 2, up to 4 lines of cytotoxic therapy).-Study treatment should be considered an appropriate option by the Investigator.

The study will be conducted in 2 parts. The Phase 1 portion of the study will be a dose-escalation evaluation to determine the RP2D and schedule of niraparib to be administered in combination with the recommended dose of pembrolizumab, and the Phase 2 portion will further evaluate the RP2D and schedule in 2 cohorts of approximately 48 patients each with TNBC or OC as described above.

The study will be conducted in conformance with Good Clinical Practice (GCP). The study schema is provided below.



Abbreviations: AE = adverse event; d = day(s); DL = dose level; DLT = dose-limiting toxicity; OC = ovarian cancer; PK = pharmacokinetics; N = niraparib; P = pembrolizumab; RP2D = recommended Phase 2 dose; q21d = every 21 days; TNBC = triple-negative breast cancer.

Phase 1 Dose Escalation

At Dose Level 1, a cohort of 6 patients with either TNBC or OC will be enrolled. After all patients in Dose Level 1 who are evaluable for safety have completed Cycle 1 of combination treatment, the next higher dose level (Dose Level 2) will be open for enrollment if less than one-third of patients (ie, < 2 of 6 patients or < 4 of 12 patients) in Dose Level 1 experience a DLT during Cycle 1 (see DLT definition below).

Based on current single-agent niraparib experience (see niraparib Investigator's Brochure), hematological laboratory abnormalities are expected in a significant proportion of patients. If 2 of 6 initially enrolled patients in a cohort experience hematologic DLTs, a lower dose level will be evaluated. If, however, the 2 observed DLTs include 1 hematologic DLT and 1 non-hematologic DLT or 2 non-hematologic DLTs, a cohort may be expanded up to approximately 12 patients to better characterize the safety of the combination treatment.

Once Dose Level 1 is determined to be safe, a cohort of 6 patients with either TNBC or OC will be enrolled in Dose Level 2. No further dose escalation will be considered if Dose Level 2 is reached.

The maximum tolerated dose (MTD) will be defined as the highest dose with DLTs observed in less than one-third of patients (ie, < 2 of 6 patients or < 4 of 12 patients) during Cycle 1 of combination treatment. If one-third or more of the evaluable patients experiences a DLT, then this dose will be considered to exceed the MTD and a lower dose level may be opened for enrollment if not yet evaluated. Alternative dosing schedules may be explored.

Additional cohorts of 6 patients may be opened to evaluate Dose Level (-1) or Dose Level (-2), which will explore lower niraparib dose intensity, for example, by introducing an alternative dosing schedule following agreement by the Investigators and Sponsor.

The RP2D will be determined following discussion and agreement between Investigators and the Sponsor (see Section 9.12) based on an evaluation of multiple endpoints, which may include the DLT rate in first and subsequent cycles of combination treatment, the rate of dose modifications for non-DLT adverse events (AEs), the ability to manage toxicities, PK, niraparib

dose intensity, and signs of clinical efficacy. The goal will be to identify the dose/regimen of niraparib with the greatest dose intensity that can be safely combined with the recommended dose/regimen of pembrolizumab.

In the Phase 1 portion of this study, 14 patients with advanced TNBC or OC were enrolled in Dose Level 1 or Dose Level 2. Twelve patients were eligible for DLT evaluation. In Dose Level 1, 1 of 6 DLT-eligible patients experienced multiple DLTs including Grade 3 anemia, Grade 4 neutropenia, and Grade 4 thrombocytopenia. In Dose Level 2, 1 of 6 DLT-eligible patients experienced 1 DLT, Grade 4 thrombocytopenia; an additional patient experienced an adverse event that was deemed to be a DLT-equivalent; the patient had epistaxis on C1D17 and Grade 4 thrombocytopenia on C2D1.

DLT criteria (as assessed during Cycle 1, ie, during the first 21 days of treatment - Day 1 through Day 21):

- Any treatment-related Grade ≥ 3 non-hematologic clinical (non-laboratory) AE
- Any treatment-related Grade 3 or Grade 4 non-hematologic laboratory abnormality if:
  - Medical intervention is required to treat the patient, or
  - The abnormality leads to hospitalization, or
  - The abnormality persists for ≥ 7 days.
- Any treatment-related hematologic toxicity specifically defined as:
  - Thrombocytopenia Grade 4 for ≥ 7 days, or Grade 3 or 4 associated with bleeding or requiring platelet transfusion;
  - Neutropenia Grade 4 for ≥ 7 days, or Grade 3 or 4 associated with infection or febrile neutropenia;
  - Anemia Grade 4, or Grade 3 or 4 requiring blood transfusion
- Any treatment-related AE leading to niraparib dose interruption per the following criteria:
  - A dose interruption per dose modification rules (see Section 5.4.1, Table 3) for a non-DLT laboratory abnormality (eg, for Grade 2 or 3 thrombocytopenia or for Grade 3 anemia or neutropenia) lasting ≥ 14 days
  - A dose interruption per dose modification rules (see Section 5.4.1, Table 2) for non-hematologic AE leading to < 80% of an intended dose being administered (eg, niraparib dose interruption for > 4 days within Cycle 1).

Note that niraparib dosing has been safely managed with dose interruptions and/or adjustments for AEs, including laboratory abnormalities, while maintaining activity in the single-agent setting (see Section 5.4.1, Table 3 and niraparib Investigator's Brochure). Therefore, niraparib dose interruption and/or reduction for an AE that does not meet a DLT definition as described above will be considered a non-DLT modification. The non-DLT dose modifications will not be considered in determining the MTD but will be considered in determining the niraparib dose

intensity and RP2D.

Phase 2: Efficacy Phase

The Phase 2 portion of the study will commence after the RP2D is determined during the Phase 1 portion. Two cohorts of approximately 48 patients each with advanced or metastatic TNBC or recurrent OC as outlined above will be enrolled.

Patients in this phase of the study will receive the RP2D dose: niraparib 200 mg/day PO on days 1-21 and pembrolizumab 200 mg IV on day 1 of each 21-day cycle; niraparib dose may be escalated on or after C3D1 from 200 mg daily to 300 mg daily if hemoglobin ≥ 9 g/dL, platelets ≥ 100,000/μL and neutrophils ≥ 1500/μL for all labs performed during the first two cycles after discussion with Medical Monitor or Designee.

Pembrolizumab/niraparib combination treatment may continue for up to 2 years or until disease progression, unacceptable toxicity, patient withdrawal, Investigator's decision, or death. Continued treatment with niraparib beyond 2 years may be considered following discussion between the Sponsor and Investigator.

General Study Conduct: Phase 1 and 2

All patients will begin treatment with niraparib and pembrolizumab on Cycle 1/Day 1; additional on-treatment assessments will be conducted on Days 8 and 15 of Cycle 1 and on Day 1 of all subsequent cycles. Safety assessments conducted throughout the treatment period include symptom-directed physical examination, vital signs, ECGs, ECOG performance status, and clinical laboratory assessments (complete blood count [CBC], coagulation [Phase 1 only], chemistry, thyroid stimulating hormone [TSH], triiodothyronine [T3] or free T3 [FT3], free thyroxine [FT4], urinalysis, cancer antigen-125 [CA-125] [OC patients only], and pregnancy testing). Radiographic evaluations (computed tomography/magnetic resonance imaging [CT/MRI] of chest [all TNBC patients and OC patients with abnormal screening scan or with clinical indication], abdomen, and pelvis) to assess extent of disease will be conducted every 9 weeks (63 days ±7 days) while on study treatment independent of cycle delays and/or dose interruptions, and/or at any time when progression of disease is suspected. Brain scan will be conducted if clinically indicated; bone scans will be conducted per standard of care. After 1 year of radiographic assessments, patients will have imaging performed every 12 weeks (84 ±7 days). If a patient discontinues treatment for a reason other than progression or death, withdrawal of consent, or loss to follow-up, scans and CA-125 testing (OC patients only) should continue at the specified intervals (ie, every 9 weeks for the first year and every 12 weeks thereafter). All radiographic images/scans will be sent to a central imaging vendor upon acquisition and archived for potential future evaluation. Per RECIST v1.1, complete response (CR) or partial response (PR) should be confirmed; tumor imaging for confirmation of response may be performed at the earliest 4 weeks after the first indication of response, or at the next scheduled scan (ie, 9 weeks later), whichever is clinically indicated. Blood sampling for PK and biomarker evaluations will be conducted for patients in both Phase 1 and Phase 2.

In patients who consent to fresh biopsies, serial fresh biopsies will be obtained for exploratory biomarker analysis at 3 time points: during the screening period, 1 to 3 days before or on C3D1 prior to pembrolizumab infusion and, whenever possible, at the time of disease progression (note: although the biopsy is voluntary, it is highly encouraged). The serial biopsies at different

time points should preferably be on the same lesion. A core biopsy is recommended (details are provided in the Study Manual); if an excisional or incisional biopsy is to be performed, it must be conducted on a non-target lesion. If a patient has had a biopsy within 12 weeks prior to entering screening, that biopsy may be accepted in lieu of the screening biopsy. Blood samples will also be obtained for biomarker analysis predose on Day 1 of Cycle 1 and Cycle 2, as well as at the end of treatment (EOT).

All patients will undergo an EOT visit within 7 days of the last dose of study treatment and a safety follow-up visit conducted 30 days (+7 days) post-treatment. Thereafter, all patients will enter the post-treatment period for telephone assessment of survival status and the occurrence of any new malignancies every 90 days (±14 days).

All AEs will be collected and recorded for each patient from the day of signing the informed consent form until 30 days after last study drug administration; serious adverse events (SAEs) and Events of Clinical Interest (ECI) (see Section 6.1.6) are required to be captured through 90 days after cessation of study treatment (or to a minimum of 30 days post treatment if the patient starts alternate anticancer therapy), and any pregnancies that occur within 120 days post-treatment are to be captured. All AEs and SAEs experienced by a patient, irrespective of the suspected causality, will be monitored until the AE or SAE has resolved, until abnormal laboratory values have returned to baseline or normalized, until there is a satisfactory explanation for the changes observed, until the patient is lost to follow-up, or until the patient has died.

Number of Patients (Planned):

Phase 1: A total of approximately 18 patients (up to 36 patients may be included)

Phase 2: A total of approximately 96 patients (ie, approximately 48 patients enrolled into each cohort of TNBC and OC patients)

Criteria for Inclusion:

To be considered eligible to participate in this study, all of the following requirements must be met:

1. Patient is male or female, at least 18 years of age. Male patients are only for TNBC and not OC.
2. Patient has histologically proven advanced (unresectable) or metastatic cancer as outlined below according to study phase and disease type:
   a. Phase 1 patients (breast or ovarian cancer)
      – Patients with advanced or metastatic breast cancer must have disease that is HER2-negative, estrogen receptor-negative, and progesterone receptor-negative (ie, TNBC). Patients with disease recurrence or progression following neoadjuvant or adjuvant therapy are eligible. Patients with advanced or metastatic disease may have up to 4 lines of cytotoxic therapy. Neoadjuvant and adjuvant therapies are not counted towards lines of therapy. Targeted small molecules (eg, tyrosine kinase inhibitors), hormonal agents and monoclonal

antibodies that inhibit angiogenesis (eg, bevacizumab, afilbercept) are not counted in the number of lines of therapy.

- Patients must have any epithelial (ie, serous, endometroid, mucinous, clear cell) ovarian, fallopian tube, or primary peritoneal cancer. Patients must have experienced a response lasting at least 6 months to first-line platinum-based therapy but currently considered to have platinum-resistant disease per investigator's assessment (e.g, patient is not eligible for further platinum containing treatment). Patients may have received up to 5 lines of cytotoxic therapy for advanced or metastatic cancer. Neoadjuvant and adjuvant therapies are not counted towards lines of therapy. Treatment with small molecules (eg, tyrosine kinase inhibitors), hormonal agents and monoclonal antibodies that inhibit angiogenesis (eg, bevacizumab, aflibercept) are not counted in the number of lines of therapy.

b. Phase 2 patients (breast or ovarian cancer)

- Patients with advanced or metastatic breast cancer must have TNBC. Patients with disease recurrence or progression following neoadjuvant or adjuvant therapy are eligible. Patients with advanced or metastatic disease may have received up to 2 lines of cytotoxic therapy. Adjuvant and/or neoadjuvant therapies are not counted in the number of lines of therapy. Targeted small molecules (eg, tyrosine kinase inhibitors), hormonal agents and monoclonal antibodies that inhibit angiogenesis (eg, bevacizumab, afilbercept) are not counted. TNBC patients who have previously received platinum chemotherapy in the metastatic setting are allowed to enroll in the study as long as they did not progress while on or within 8 weeks from the day of the last platinum administration.

- Patients must have with high-grade serous or endometroid ovarian, fallopian tube, or primary peritoneal cancer. Patients must have experienced a response lasting at least 6 months to first-line platinum-based therapy but currently considered to have platinum-resistant disease per investigator's assessment (e.g, patient is not eligible for further platinum containing treatment). Patients may have had up to 4 lines of cytotoxic therapy for advanced or metastatic cancer. Neoadjuvant, adjuvant, and the combination of both will be considered as one line of therapy. Treatment with small molecules (eg, tyrosine kinase inhibitors), hormonal agents and monoclonal antibodies that inhibit angiogenesis (eg, bevacizumab, aflibercept) are not counted in the number of lines of therapy.

3. Patient has archival tumor tissue available that is formalin-fixed and paraffin-embedded.
   a. For patients who do not have archival tissue, tissue from a fresh biopsy must be obtained prior to study treatment initiation.
   b. Serial fresh tumor tissue samples will be collected in patients with lesions amenable for a biopsy who consent to such a procedure.
4. Patient has measurable lesions by RECIST v1.1.

5. Patient has an ECOG performance status of 0 to 1.
6. Patient has adequate organ function, defined as (Note: complete blood count [CBC] test should be obtained without transfusion or receipt of colony stimulating factors before 2 weeks of obtaining sample):
    a. Absolute neutrophil count (ANC) ≥ 1500/μL
    b. Platelets ≥ 100,000/μL
    c. Hemoglobin ≥ 9 g/dL or ≥ 5.6 mmol/L
    d. Serum creatinine ≤ 1.5× upper limit of normal (ULN) or calculated creatinine clearance ≥ 60 mL/min using Cockcroft-Gault equation for patients with creatinine levels > 1.5× institutional ULN
    e. Total bilirubin ≤ 1.5× ULN OR direct bilirubin ≤ 1× ULN
    f. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5× ULN unless liver metastases are present, in which case they must be ≤ 5× ULN
    g. International normalized ratio (INR) or prothrombin time (PT) ≤ 1.5× ULN unless patient is receiving anticoagulant therapy as long as PT or partial thromboplastin time (PTT) is within therapeutic range of intended use of anticoagulants
    h. Activated partial thromboplastin time (aPTT) ≤ 1.5× ULN unless patient is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
7. Patient is able to take oral medications.
8. Female patient has a negative serum pregnancy test within 72 hours prior to taking study medication if of childbearing potential, or agrees to abstain from activities that could result in pregnancy from enrollment through 120 days after the last dose of study treatment, or be of non-childbearing potential. Non-childbearing potential is defined as (by other than medical reasons):
    a. ≥ 45 years of age and has not had menses for >1 year
    b. Amenorrheic for < 2 years without a hysterectomy and oophorectomy and a follicle-stimulating hormone (FSH) value in the postmenopausal range upon pre-study (screening) evaluation
    c. Post hysterectomy, bilateral oophorectomy or tubal ligation. Documented hysterectomy or oophorectomy must be confirmed with medical records of the actual procedure or confirmed by an ultrasound. Tubal ligation must be confirmed with medical records of the actual procedure, otherwise the patient must be willing to use 2 adequate barrier methods throughout the study, starting with the screening visit through 120 days after the last dose of study therapy. See Section 5.7.2 for a list of acceptable birth control methods. Information must be captured appropriately within the site's source documents.

    Note: Abstinence is acceptable if this is the established and preferred contraception for the patient.
9. Male patient agrees to use an adequate method of contraception (please see Section 5.7.2 for a list of acceptable birth control methods) starting with the first dose of study therapy through 120 days after the last dose of study therapy.

Note: Abstinence is acceptable if this is the established and preferred contraception for the patient.

10. Patient agrees to blood samples during screening and at the end of treatment for cytogenetic analysis.

Criteria for Exclusion:

Patients will not be eligible for study entry if any of the following criteria are met:

1. Patients with primary platinum refractory ovarian cancer (ie, progressive disease on or within 6 months of first-line platinum therapy) are not eligible in Phase 1 or Phase 2 of this study.
2. Patient has known active central nervous system (CNS) metastases and/or carcinomatous meningitis.

   Note: Patients with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging [using the identical imaging modality for each assessment, either MRI or CT scan] for at least 4 weeks prior to the first dose of study treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and have not been using steroids for at least 7 days prior to study treatment. Carcinomatous meningitis precludes a patient from study participation regardless of clinical stability.
3. Patient has a known additional malignancy that progressed or required active treatment within the last 2 years. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin that has undergone potentially curative therapy, or in situ cervical cancer.
4. Patient is considered a poor medical risk due to a serious, uncontrolled medical disorder, nonmalignant systemic disease or active infection that requires systemic therapy. Specific examples include, but are not limited to, history of (non-infectious) pneumonitis that required steroids or current pneumonitis; uncontrolled ventricular arrhythmia; recent (within 90 days) myocardial infarction; uncontrolled major seizure disorder; unstable spinal cord compression; superior vena cava syndrome; or any psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the study (including obtaining informed consent).
5. Patient has a condition (such as transfusion dependent anemia or thrombocytopenia), therapy, or laboratory abnormality that might confound the study results, or interfere with the patient's participation for the full duration of the study treatment. Patients who 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 are not eligible.
6. Patient is pregnant or breastfeeding, or expecting to conceive children within the projected duration of the study, starting with the screening visit through 120 days after the last dose of study treatment.
7. Patient has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or

any other form of immunosuppressive therapy within 7 days prior to the first dose of study treatment.

8. Patient has a known history of human immunodeficiency virus (HIV) (HIV 1/2 antibodies).
9. Patient has known active hepatitis B (eg, hepatitis B surface antigen [HBsAg] reactive) or hepatitis C (eg, hepatitis C virus ribonucleic acid [HCV RNA] [qualitative] is detected).
10. Patient has an active autoimmune disease that has required systemic treatment in the past 2 years (ie, 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, etc.) is not considered a form of systemic treatment.
11. Patient has not recovered (ie, to ≤Grade 1 or to baseline) from cytotoxic therapy-induced AEs. Note: Patient with ≤ Grade 2 neuropathy or ≤ Grade 2 alopecia is an exception to this criterion and may qualify for the study.
12. Patient is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks of the first dose of treatment.
13. Patient has had a prior cytotoxic therapy, anticancer targeted small molecules (eg, tyrosine kinase inhibitors), hormonal agents within 5 half-lives, or monoclonal antibodies (mAb) within 5 half-lives or 4 weeks (whichever is shorter) of that treatment prior to study Day 1 or radiation therapy encompassing > 20% of the bone marrow within 2 weeks or any radiation therapy within 1 week prior to study Day 1.
14. Patient has not recovered adequately from AEs and/or complications from any major surgery prior to starting therapy.
15. Patient has received prior therapy with an anti-programmed death-1 (anti-PD-1), anti-PD-1-ligand-1 (anti-PD-L1), or anti-PD-1 ligand-2 (anti-PD-L2) agent or the patient has previously participated in Merck MK-3475 (pembrolizumab) clinical studies.
16. Patient has received a live vaccine within 30 days of planned start of study therapy.
17. Patient has undergone prior treatment with a known poly(ADP-ribose) polymerase (PARP) inhibitor.
18. Patient has a heart-rate corrected QT interval (QTc) prolongation > 470 msec at screening.

    Note: If a patient has a prolonged QT interval and the prolongation is deemed to be due to a pacemaker upon Investigator evaluation (ie, the patient otherwise has no cardiac abnormalities), the patient may be eligible to participate in the study following discussion with the Medical Monitor.
19. Patient has a known hypersensitivity to niraparib or pembrolizumab components or excipients.

20. Known history or current diagnosis of myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML).

Investigational Product, Dosage, and Mode of Administration:

Niraparib

Niraparib will be administered orally (PO) throughout the 21-day cycle at the assigned dose and schedule. On Day 1 of each cycle, a niraparib dose will be administered upon completion of pembrolizumab infusion. Depending on dose schedule, 1, 2, or 3 capsules of 100 mg strength niraparib will be taken at each dose administration (total dose 100 mg, 200 mg, or 300 mg per dose schedule, respectively). Patients will be instructed to take their niraparib dose at the same time each day, preferably in the morning. Patients must swallow and not chew all capsules. The consumption of water and food is permissible.

Niraparib will be dispensed to patients on Day 1 of every cycle (every 21 days) thereafter until the patient discontinues study treatment. The Pharmacy Manual contains descriptions of the packaging of niraparib and instructions for the preparation and administration of niraparib.

Pembrolizumab

Pembrolizumab will be administered at a dose of 200 mg intravenously (IV) using a 30-minute IV infusion on Day 1 of each 21-day treatment cycle after all procedures and assessments have been completed as detailed in Table 6. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. Given the variability of infusion pumps from site to site, however, a window between -5 minutes and +10 minutes is permitted.

The Pharmacy Manual contains specific instructions for the preparation of the pembrolizumab infusion and administration of the infusion solution.

Duration of Treatment and Study Conduct:

Treatment duration for individual patient: Patients may continue the pembrolizumab/niraparib combination treatment for up to 2 years or until disease progression, unacceptable toxicity, patient withdrawal, Investigator's decision, or death. Continued treatment with niraparib beyond 2 years may be considered following discussion between the Sponsor and Investigator.

Long-term follow-up: Every 3 months (90 days), via telephone.

Planned study conduct duration: the first data cutoff will occur at approximately 18 months (ie, time from first patient enrolled/when responder or discontinuation status for all patients is known/approximately 6 months after last patient is enrolled). The final analysis of primary and secondary endpoints will be conducted at approximately 12 months after the last patient is enrolled).

Criteria for Evaluation:

Safety

- Dose-limiting toxicities during the first cycle (ie, during the first 21 days of treatment/ Cycle 1/Day 1 through Cycle 1/Day 21) (Phase 1 only)

- Incidence of treatment-emergent AEs (TEAEs) during the first cycle compared to the second and subsequent cycles
- Incidence of TEAEs occurring while patients are on treatment or up to 30 days after the last dose of study drug
- Incidence of serious adverse events (SAEs) and events of clinical interest (ECI) occurring while patients are on treatment or up to 90 days after the last dose of study drug
- Changes in clinical laboratory parameters (hematology, chemistry, coagulation, thyroid function, urinalysis), vital signs, ECOG performance status, ECG parameters, physical examinations, and usage of concomitant medications
- Whole blood samples will be collected prior to the start of the study drug and at treatment discontinuation for cytogenetic analysis

Efficacy

- Primary endpoint: ORR, defined as the proportion of patients who have achieved CR or PR, evaluated using RECIST v1.1 based on Investigator assessment
- The following secondary endpoints will also be evaluated based on Investigator assessment:
  - ORR by irRECIST
  - Duration of response, defined as the time from first documentation of response (CR or PR) until the time of first documentation of disease progression by RECIST v1.1 and by irRECIST
  - Disease control rate defined as the percentage of patients who have achieved CR, PR, or stable disease (SD) per RECIST v1.1 and irRECIST
  - Progression-free survival, defined as the time from first dose to the earlier date of assessment of progression, or death by any cause in the absence of progression, by RECIST v1.1 and by irRECIST
  - Overall survival as measured from the date of first dose to the date of death by any cause

Pharmacokinetics

Samples for PK determination will be collected from patients in both Phase 1 (plasma and serum) and Phase 2 (plasma only) and the plasma will be analyzed using liquid chromatography with mass spectroscopic detection (LC-MS-MS) for niraparib and major metabolite M1. The serum may be analyzed for pembrolizumab using enzyme-linked immunosorbent assay (ELISA). Model predicted area under the concentration × time curves (AUCs) will be derived. Parameters of interest are AUC, minimum concentration (C_{min}), maximum concentration (C_{max}), clearance after oral administration (CL/F) and volume of distribution after oral administration (V_z/F), AUC at steady state (AUC_{ss}), C_{min} at steady state ($C_{min,ss}$), C_{max} at steady state ($C_{max,ss}$).

Biomarkers

Biomarker classifiers will be evaluated in archival and fresh tumor samples obtained during screening; in addition, in the subset of patients who undergo serial biopsies, biomarkers will be evaluated in fresh tumor samples obtained 1 to 3 days before or on C3D1 prior to pembrolizumab infusion and, whenever possible, at the time of disease progression. Blood samples for biomarker analysis will be obtained predose on Day 1 of Cycle 1 and Cycle 2, as well as at the EOT visit. Tumor and blood markers, including mutations in homologous recombination genes, such as breast cancer gene 1 and 2 (BRCA1 and 2) mutations, may be explored. The magnitude of homologous recombination deficiency (HRD) positivity and tumor immune microenvironment may be evaluated. Programmed death ligand-1 (PD-L1) expression and other related markers in tumor and tumor-infiltrating immune cells may be explored.

HRD status and other biomarkers may be correlated with efficacy outcomes.

Statistical Methods:

Sample Size Considerations

Phase 1: A total sample size of approximately 18 patients is estimated for the Phase 1 portion of the study to provide initial comparison of incidence of DLTs and safety profiles of the combination treatment between dose schedules in each patient population. More patients could be enrolled (eg, if the Dose Level -2 is explored or if expansion at any dose level is required to better understand safety and tolerability); up to a total of 36 patients may be enrolled.

Phase 2: A total of approximately 96 evaluable patients (approximately 48 patients in each tumor type) will be enrolled to ensure understanding of the activity of the combination treatment and to obtain adequate representation of different molecular cancer subtypes and biomarkers.

Analysis Populations

Three analysis populations will be defined as follows:

- Safety Population: All patients who receive any amount of study drug. The assessment of DLTs in Phase 1 will include only those patients completing the first cycle of therapy, unless the patient discontinued study drug due to a DLT.
- Full Analysis Set (FAS): All patients who receive any amount of study drug. The primary analysis of efficacy endpoints will be performed on the FAS population.
- Per-Protocol Population: All patients who receive at least two cycles of study drug andhave at least one protocol-required post-baseline disease assessments and have no major protocol violations that would impact efficacy evaluations. Supportive analyses of efficacy endpoints will be performed on the per-protocol population.

General Methods

All analyses will include summary statistics, including number and percentage for categorical variables and number of patients, mean, standard deviation, median, minimum, and maximum for continuous variables. Time-to-event analyses will be performed using Kaplan-Meier methods. As the Phase 2 portion of the study is single-arm, any statistical analysis to be performed among subgroups is for descriptive and future study purposes. Further detail will be

provided in the study statistical analysis plan.

Safety

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) for purposes of summarization. All AEs occurring during the study will be included in by-patient data listings and tabulated by MedDRA system organ class and preferred term. Safety endpoints for AEs include the following: incidence of DLTs, TEAEs, ECI, TEAEs leading to death, SAEs and AEs leading to discontinuation; tabulations will be produced by MedDRA system organ class and preferred term. Tabulations of TEAEs will also be produced by severity and by relationship to study drug.

Additional safety summaries will be provided for clinical laboratory tests, vital signs, ECOG performance status, and ECGs.

Results of cytogenetic analysis, including incidence of cytogenetic abnormalities at end of study treatment, will be summarized.

Efficacy

ORR and DCR will be summarized using descriptive statistics including number, percentage and 1-sided 90% CI.

Duration of response, PFS, and OS will be summarized using Kaplan-Meier analysis, including number and percentage of events, number and percentage of censored patients, and 25^{th}, 50^{th}, and 75^{th} percentiles of times to event with 95% CIs.

Pharmacokinetics

Pharmacokinetic parameters will be summarized by study phase and dose schedule using descriptive statistics.

Biomarkers

The incidence of biomarkers will be summarized using descriptive statistics. Comparisons of efficacy endpoints between biomarker subpopulations may be performed.

Interim Analysis

To minimize the risk of exposing patients to an ineffective treatment, a series of response assessments will be performed when 6, 12, and 18 of 48 Phase 2 patients from each cancer type have at least 2 post-baseline tumor assessments. A formal decision regarding futility, which could result in stopping the study early, will be conducted separately for the TNBC and OC cohorts and will only be made from the analysis of 24 patients within each cohort. The earlier response assessments, however, will inform the conduct of the formal interim analysis as follows: If no responder is observed in all three response assessments from 6, 12, and 18 patients, then enrollment will be suspended after 24 patients have been enrolled, and no further patients will be enrolled until the result of the formal interim analysis of 24 patients is known. If ≥1 responder is observed in any single response assessment from 6, 12, or 18 patients, then enrollment will not be curtailed. The decision rule regarding the formal interim analysis at N=24 is as follows: If there are fewer than 3 responders out of 24, enrollment may be closed and the corresponding cohort may be stopped for futility. Otherwise, the study will continue to

the planned enrollment of approximately 48 patients.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADL	activities of daily living
ADP	adenosine diphosphate
AE	adverse event
ALT	alanine aminotransferase
alt-NHEJ	alternative nonhomologous end-joining
AML	acute myeloid leukemia
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
ATM	ataxia telangiectasia mutated
ATR	ATM and Rad3-related
AUC	area under the concentration × time curve
AUC_{ss}	area under the concentration × time curve at steady state
BCG	bacille Calmette-Guerin
BER	base excision repair
BP	blood pressure
BRCA	breast cancer (gene)
CA-125	cancer antigen 125
CBC	complete blood count
CHK	check point kinases
CI	confidence interval
CL/F	clearance after oral administration
C_{max}	maximum concentration
$C_{max,ss}$	maximum concentration at steady state
C_{min}	minimum concentration
$C_{min,ss}$	minimum concentration at steady state
CNS	central nervous system
CR	complete response
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450

Abbreviation	Definition
DCR	disease control rate
DKA	diabetic ketoacidosis
DL	dose level
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
ECG	electrocardiogram
ECI	events of clinical interest
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
ELISA	enzyme-linked immunosorbent assay
EOT	end of treatment
ER	estrogen receptor
FT3	free triiodothyronine
FT4	free thyroxine
FAS	full analysis set
FSH	follicle-stimulating hormone
$gBRCA^{mut}$	germline breast cancer gene mutation
GCIG	Gynecologic Cancer Intergroup
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
GM-CSF	granulocyte macrophage colony-stimulating factor
HBsAg	hepatitis B surface antigen
HCV RNA	hepatitis C virus ribonucleic acid
HER2	human epidermal growth factor receptor
HIV	human immunodeficiency virus
HR	hazard ratio
HRD	homologous recombination deficiency
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
Ig	immunoglobulin
IgG	immunoglobulin G
INR	international normalized ratio

Abbreviation	Definition
IRB	Institutional Review Board
irRECIST	immune-related Response Evaluation Criteria in Solid Tumors
ITIM	immunoreceptor tyrosine-based inhibition motif
ITSM	immunoreceptor tyrosine-based switch motif
IV	intravenous(ly)
KM	Kaplan-Meier
LC-MS-MS	liquid chromatography with mass spectroscopic detection
mAb	monoclonal antibody
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MMR	mismatch repair deficiency
NBS1	Nijmegen breakage syndrome 1
NER	nucleotide excision repair
NHEJ	nonhomologous end-joining
OC	primary peritoneal ovarian cancer
ORR	objective response rate
OS	overall survival
PARP	poly(ADP-ribose) polymerase
PD	progressive disease
PD-1	programmed death-1
PD-L1	programmed death ligand-1
PD-L2	programmed death ligand-2
PET	positron emission tomography
PFS	progression-free survival
P-gp	P-glycoprotein
PK	pharmacokinetics
PO	oral(ly)
PR	partial response
PR	progesterone receptor
PT	prothrombin time
PTT	partial thromboplastin time
QD	once daily

Abbreviation	Definition
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
T3	triiodothyronine
TEAE	treatment-emergent adverse event
TIL	tumor-infiltrating lymphocytes
TNBC	triple-negative breast cancer
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
V-type	variable-type
V_z/F	volume of distribution after oral administration
WHO	World Health Organization

1. INTRODUCTION

1.1. Background

1.1.1. PARP and Homologous Recombination Deficiency

Poly(ADP-ribose) polymerases (PARP)1 and PARP2 are zinc-finger deoxyribonucleic acid (DNA)-binding enzymes that play a crucial role in DNA repair.[1] Upon formation of DNA breaks, PARP binds at the end of broken DNA strands, a process that activates its enzymatic activity. Activated PARP catalyzes the addition of long polymers of adenosine diphosphate (ADP)-ribose onto PARP and several other proteins associated with chromatin, including histones and various DNA repair proteins. This results in chromatin relaxation, fast recruitment of DNA repair proteins, and efficient repair of DNA breaks. In this manner, PARP plays a key role in sensing DNA damage and converting it into intracellular signals that activate the base excision repair (BER) and single-strand break repair pathways.[1, 2]

Normal cells repair up to 10,000 DNA defects daily, and single-strand breaks are the most common form of DNA damage. Cells that are unable to repair this burden of DNA damage, such as those with defects in the homologous recombination or BER pathways, are at risk for accumulating multiple lesions that will ultimately trigger apoptosis. They enter the S phase (DNA replication) of the cell cycle with unrepaired single- and double-strand breaks. Pre-existing single-strand breaks are converted to double-strand breaks as the replication machinery passes.[1] Accumulated double-strand breaks present during S phase are repaired by homologous recombination . Homologous recombination is the preferred repair pathway because it is associated with a much lower error rate than other forms of repair. Cells unable to perform DNA repair via homologous recombination (eg, due to inactivation of genes required for homologous recombination, such as breast cancer gene [BRCA]1- or BRCA2-mutated cells) are at risk for accumulating multiple lesions that will ultimately trigger apoptosis. These cells accumulate stalled replication forks during S phase and are more likely to use the error-prone nonhomologous end-joining (NHEJ) or alternative (alt)-NHEJ pathways to repair double-strand breaks in DNA. Accumulation of errors in DNA by NHEJ contributes to mutation burden that promotes the development of cancer. Over time, the buildup of excessive DNA errors in combination with the inability to complete S phase (because of stalled replication forks) contributes to cell death.

Treatment with PARP inhibitors could represent a novel opportunity to selectively kill a subset of cancer cells with deficiencies in DNA repair pathways. For example, a tumor arising in a patient with a germline BRCA mutation (gBRCA^{mut}) has a defective homologous recombination DNA repair pathway and would be increasingly dependent on NHEJ, alt-NHEJ, and BER for maintenance of genomic integrity. PARP inhibitors block alt-NHEJ and BER, forcing tumors with BRCA deficiencies to use the error-prone NHEJ to fix double-strand breaks.[1] Non-BRCA deficiencies in homologous recombination DNA repair genes could also enhance tumor cell sensitivity to PARP inhibitors.[3] The rationale for anticancer activity in a subset of non-gBRCA^{mut} tumors is that they share distinctive DNA repair defects with gBRCA^{mut} carriers, a phenomenon broadly described as “BRCAness.”[4] DNA repair defects can be caused by germline or somatic alterations to the homologous recombination DNA repair pathway. In a recent analysis of

approximately 500 high-grade serous ovarian adenocarcinoma tumors, approximately 50% contained homologous recombination defects.[5] A subset of these tumors had biologically plausible molecular alterations that may make them sensitive to PARP inhibition by niraparib. A similar analysis of triple-negative breast cancer (TNBC) indicates up to 40% of these patients have tumors with homologous recombination defects.[6]

Homologous recombination is a complex pathway, and several genes other than BRCA1 and BRCA2 are required either to sense or repair DNA double-strand breaks via the homologous recombination pathway. Therefore, PARP inhibitors are also selectively cytotoxic for cancer cells with deficiencies in DNA repair proteins other than BRCA1 and BRCA2, including RecA homologs (RAD51 and RAD54), X-ray repair complementing defective repair in Chinese hamster cells (XRCC2 and XRCC3), DSS1, replication protein A1 (RPA1), ataxia telangiectasia mutated (ATM), ATM and Rad3-related (ATR), check point kinases (CHK1, CHK2), Nijmegen breakage syndrome 1 (NBS1), and the components of the Fanconi anemia repair pathway.[1, 4, 7]

Clinical studies have shown that PARP inhibitors are active for recurrent ovarian cancer (OC).[1-3, 8-11] Clinical anticancer activity has been observed in patients with and without gBRCA^{mut} and in patients who are platinum-sensitive and platinum-resistant. PARP inhibition appears to be most active in patients with gBRCA^{mut} platinum-sensitive disease.[3, 9] Additionally, maintenance therapy in patients with relapsed, platinum-sensitive OC appears promising.[10] Of patients with a BRCA mutation, median progression-free survival (PFS) was significantly longer in the PARP inhibitor group than in the placebo group (11.2 months vs. 4.3 months; hazard ratio: 0.18; $p< 0.0001$). Similar findings were noted for patients with wild-type BRCA, although the difference between groups was smaller (7.4 months vs. 5.5 months; hazard ratio: 0.54; $p = 0.007$).

Recent clinical studies also have shown PARP inhibitors to be active in breast and ovarian cancer. Clinical anticancer activity with PARP inhibitors has been seen in both patients with gBRCA^{mut} and without gBRCA^{mut}; however, activity is more robust in patients with the germline mutation.[1, 3, 8, 10-12]

In summary, treatment with PARP1/2 inhibitors represents a novel opportunity to selectively kill a subset of cancer cell types by exploiting their deficiencies in DNA repair. Human cancers exhibit genomic instability and an increased mutation rate due to underlying defects in DNA repair. These deficiencies render cancer cells more dependent on the remaining DNA repair pathways, and targeting these pathways is expected to have a much greater impact on the survival of the tumor cells than on normal cells.

1.1.2. Immune Surveillance and PD-1 Inhibitors

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades.[13] Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and prognosis in various malignancies.[14-26] In particular, the presence of CD8+ T cells and the ratio of CD8+ effector T cells/FoxP3+ regulatory T cells seem to correlate with improved prognosis and long-term survival in many solid tumors.[22, 27-33]

The programmed death-1 (PD-1) receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control.[34] 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 CD28 and CTLA-4, which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2). The structures of murine PD-1 alone [35] and in complex with its ligands were first resolved [36, 37], and more recently the nuclear magnetic resonance-based structure of the human PD-1 extracellular region and analyses of its interactions with its ligands were also reported.[38] PD-1 and family members are type I transmembrane glycoproteins containing an Ig variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail, which is 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 (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules, such as CD3ζ, PKCθ and ZAP70, which are involved in the CD3 T cell signaling cascade.[39] The mechanism by which PD-1 down-modulates T cell responses is similar to, but distinct from, that of CTLA-4.[40] PD-1 was shown to be expressed on activated lymphocytes, including peripheral CD4+ and CD8+ T cells, B cells, T regs, and natural killer cells.[41] Expression has also been shown during thymic development on CD4-/CD8- (double-negative) T cells, [42] as well as subsets of macrophages [43] and dendritic cells.[44] The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types.[45] PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is predominantly expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments.[45] Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T cell activation triggered through the T cell receptor. PD-L2 is thought to control immune T cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T cell function in peripheral tissues. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T cell inhibitor, [46, 47] which, via its interaction with the PD-1 receptor on tumor-specific T cells, plays a critical role in immune evasion by tumors.[48] As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in cancer.[49]

1.2. Study Treatments

1.2.1. Niraparib

Niraparib is a potent, orally active PARP1 and PARP2 inhibitor being developed as a treatment for patients with tumors that harbor defects in the homologous recombination DNA repair pathway or that are driven by PARP-mediated transcription factors.

Nonclinical data on niraparib are discussed in detail in the Investigator's Brochure. Briefly, in nonclinical models, niraparib has been observed to inhibit normal DNA repair mechanisms and induce synthetic lethality when administered to cells with homologous recombination defects. In a BRCA1-mutant xenograft study, niraparib dosed orally caused tumor regression, which was mirrored by > 90% reduction in tumor weight compared with control. In a BRCA2-mutant xenograft study, niraparib-dosed mice showed 55% to 60% growth inhibition, both by tumor volume and weight.

Niraparib displayed strong antitumor activity in in vivo studies with BRCA1-mutant breast cancer (MDA-MB-436), BRCA2-mutant pancreatic cancer (CAPAN-1), ATM-mutant mantle cell lymphoma (GRANTA-519), serous OC (OVCAR3), and colorectal cancer (HT29 and DLD-1) xenograft models and with patient-derived Ewing sarcoma mice models. Utilizing patient-derived ovarian and breast cancer xenograft models, niraparib demonstrated response in both BRCA mutation and BRCA wild-type tumors.

Niraparib clinical data are discussed in detail in the niraparib Investigator's Brochure. In the Phase 1 clinical program, niraparib, as a monotherapy or in combination with chemotherapy, has been administered to 144 patients.

In the Phase 1 program (n=144), the most common (> 20.0% of patients) adverse events (AEs), were fatigue (58.3%), nausea (54.9%), anemia (50.7%), constipation (39.6%), thrombocytopenia (37.5%), vomiting (36.8%), decreased appetite (31.9%), neutropenia (28.5%), headache (26.4%), diarrhea (21.5%), dyspnea (21.5%), cough (20.8%), and leukopenia (20.8%).

In the randomized, double-blind, Phase 3 NOVA trial (Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer), a total of 553 patients were randomized at 107 centers worldwide. Patients were categorized according to the presence or absence of a germline *BRCA* mutation (g*BRCA* cohort and non-g*BRCA* cohort) and the type of non-g*BRCA* mutation and were randomly assigned in a 2:1 ratio to receive niraparib (300 mg) or placebo once daily. The primary end point was progression-free survival. The study enrolled 203 patients in the gBRCAmut cohort and 350 patients in the non-gBRCAmut cohort. Among the 350 patients in the non-gBRCAmut cohort, 162 had tumors that were defined as HRDpos and 134 had tumors that were HRD negative (HRDneg). HRD status was not determined (HRDnd) for 54 patients.

Demographic and baseline characteristics were well balanced. Table 1 shows the results for the PFS primary endpoint for each of the 3 primary efficacy populations (ie, gBRCAmut cohort, HRDpos cohort, and overall non-gBRCAmut cohort). In addition, median PFS in patients with HRD negative (HRDneg) tumors was 6.9 months (95% CI: 5.6, 9.6) in the niraparib arm, versus 3.8 months (95% CI: 3.7, 5.6) in the placebo arm, with a hazard ratio (HR) of 0.58 (95% CI: 0.361, 0.922) (p=0.0226).

Table 1 Progression-Free Survival in Ovarian Cancer Patients in NOVA

	gBRCAmut Cohort		**non-gBRCAmut Cohort (regardless of HRD status)**		**HRDpos (within non-gBRCAmut cohort)**	
	Niraparib (N=138)	**Placebo (N=65)**	**Niraparib (N=234)**	**Placebo (N=116)**	**Niraparib (N=106)**	**Placebo (N=56)**
PFS Median (95% CI)[a]	21.0 (12.9, NR)	5.5 (3.8, 7.2)	9.3 (7.2, 11.2)	3.9 (3.7, 5.5)	12.9 (8.1, 15.9)	3.8 (3.5, 5.7)
p-value	<0.0001		<0.0001		<0.0001	

	gBRCAmut Cohort		non-gBRCAmut Cohort (regardless of HRD status)		HRDpos (within non-gBRCAmut cohort)	
	Niraparib (N=138)	Placebo (N=65)	Niraparib (N=234)	Placebo (N=116)	Niraparib (N=106)	Placebo (N=56)
Hazard Ratio (Nir:Plac) (95% CI)	0.27 (0.173, 0.410)		0.45 (0.338, 0.607)		0.38 (0.243, 0.586)	

Progression-free survival is defined as the time in months from the date of randomization to progression or death.

The primary data to support the safety of treatment with niraparib are derived from the NOVA main study in which a total of 546 patients received study treatment.

All 367 patients who received niraparib and 171 (96%) of 179 patients who received placebo experienced at least 1 treatment-emergent adverse event (TEAE). The high rate of TEAEs in the placebo group indicates the burden of prior chemotherapy and the patient's underlying ovarian cancer. Review of the data across study cohorts for TEAE incidence showed that, in general, the results were similar in the g*BRCA*mut and non-g*BRCA*mut cohorts. In the overall safety population, for the niraparib versus placebo treatment arms, the incidences of Grade 3/4 TEAEs (74% vs. 23%), serious adverse events (SAEs) (30% vs. 15%), TEAEs leading to treatment interruption (69% vs. 5%), TEAEs leading to dose reduction (67% vs. 15%), and TEAEs leading to treatment discontinuation (15% vs 2%) were higher for niraparib. There were no on-treatment deaths reported.

The most commonly observed non-hematologic TEAEs (all grades) observed in niraparib-compared to placebo-treated patients were nausea (74% vs. 35%), fatigue (46% vs. 32%), constipation (40% vs. 20%), and vomiting (34% vs. 16%). The majority of the non-hematological TEAEs were mild to moderate in severity. The most commonly observed hematologic TEAEs (all grades) of niraparib were anemia (49%), thrombocytopenia (46%), and neutropenia (18%). Although Grade 3/4 hematologic laboratory events were common at the initiation of treatment, no severe clinical sequelae were observed, and relatively few patients discontinued due to these AEs. Dose adjustment based on individual tolerability during the first 3 cycles substantially reduced the incidence of these events beyond Cycle 3, indicating the overall effectiveness of the approach to dose modification. These TEAEs can be monitored routinely using standard assessments of hematological laboratory parameters, as is routine for patients with ovarian cancer receiving anti-cancer therapies. In the NOVA study, niraparib dose adjustment tended to occur early with most patients reaching their individual adjusted dose level at the end of Month 3 (ie Cycle 3) of treatment. ~36% pts were kept on 300mg and ~64% pts had dose adjustment after 3 cycles in NOVA. However, in the Phase 1 portion of this study (3000-PN162-01-001) no patients were able to tolerate the 300 mg dose of niraparib.

Myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) have been observed in patients receiving treatment with olaparib, a PARP inhibitor; given the common mechanism of action, MDS and AML therefore represent a potential risk to patients receiving niraparib. In the Phase 3 NOVA study, the incidence of MDS/AML in patients who received niraparib (5 of 367;

1.4%) was similar to its incidence in patients who received placebo (2 of 179; 1.1%). Guidance on monitoring patients for new events of MDS/AML and the follow-up of patients with suspected MDS/AML is provided in Section 6.1.8 and Section 7.

Study PR-30-5011-C1 (NOVA QTc substudy n=26) is an open-label evaluation of the effects of niraparib on QTc measurements in patients with histologically diagnosed ovarian cancer, fallopian tube cancer, or primary peritoneal cancer. There were no reports of clinically significant abnormal electrocardiogram (ECG) changes, including QTc interval prolongation, attributed to niraparib. Administration of niraparib at the therapeutic dose did not prolong the QT interval. There was no correlation between the exposure level (ie, plasma concentration) of niraparib and QTc changes (ie,ΔQTcF).

Clinical activity data for niraparib administered as monotherapy in patients with OC are available from 1 early-phase clinical study. In the Phase 1/2 study PN001, 104 patients with advanced solid tumors who had received a median of 5 prior therapies were enrolled; 49 had OC (13 platinum-sensitive, 35 platinum-resistant, and 1 platinum-refractory).[11] Of the 49 patients, 22 had confirmed BRCA1 or BRCA2 mutation, of whom 20 were radiologically assessable. Eight (40%) of these 20 patients achieved a confirmed partial response (PR) by Response Evaluation Criteria in Solid Tumors (RECIST) and cancer antigen (CA)-125 Gynecologic Cancer Intergroup (GCIG) criteria at doses ranging from 80 to 400 mg per day. Median response duration was 387 days (range: 159 to 518 days). Three (33%) of 9 patients with platinum-resistant BRCA-mutant OC had PR by RECIST and CA-125 criteria. Additionally, a 50% response rate (5 of 10 evaluable patients) was observed at daily doses ranging from 290 to 300 mg among patients with BRCA-mutant OC who had received more than 3 lines of prior chemotherapy (data on file).

1.2.2. Pembrolizumab

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the programmed cell death 1 (PD 1) receptor, thus inhibiting its interaction with programmed cell death ligand 1 (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 intravenous (IV) immunotherapy for advanced malignancies. Keytruda™ (pembrolizumab) is indicated for the treatment of patients across a number of indications. For more details on specific indications refer to the Investigator brochure.

1.3. Rationale for Current Study

Current treatment options for patients with advanced or metastatic TNBC and patients with recurrent OC are limited, with no approved standard of care.

Triple-negative breast cancer is an aggressive histologic subtype of breast cancer, clinically defined by lack of expression of the estrogen receptor (ER-) and progesterone receptor (PR-) and lack of overexpression or amplification of HER2-receptor. The malignancy constitutes an aggressive form of the disease regardless of stage at diagnosis, and in patients with metastatic TNBC, there are currently no approved therapies or standard of care.

Similarly for recurrent OC, there are no approved treatments or standard of care. Although the National Comprehensive Cancer Network guidelines recommend treatment with single-agent

topotecan, doxorubicin, or gemcitabine, the optimal combination and sequence of these agents is unclear, and the exact population who would derive the most benefit is not well defined.

Over recent years, research has revealed the importance of TILs in controlling the clinical progression of various cancers and their presence in a tumor is associated with response to immune checkpoint inhibitors.[50] Accumulating evidence suggests that basal-type TNBC may be the ER(-) breast cancer most regulated by intratumoral T cells and thus the most potentially responsive to immunotherapies.[51] In addition, the frequency of BRCA1/2 deficiency, both BRCA mutations and silencing of BRCA expression, in TNBC is between 45% and 70%.[6] Similarly in OC, intraepithelial CD8+ T-cells correlated with the presence of mutation or loss of expression of BRCA1 through promoter methylation.[52] Collectively, metastatic TNBC and OC patient populations that were sensitive to agents targeting defects in DNA repair are likely to overlap with those tumors with an active yet checkpoint-blocked immune response.

Despite promising activity of PD-1 inhibitors observed in some types of cancer, including melanoma and NSCLC,[53] activity in TNBC (objective response rate [ORR] of 18.5% with pembrolizumab) and ovarian cancer (ORR of 11%-12% on pembrolizumab or avelumab) observed thus far have been modest.[54-56] Although promising in selected patients with BRCA mutations or potentially with homologous recombination deficiency, modest activity of PARP inhibitors in unselected ovarian cancer patients with resistant disease has been observed (ORR of 16% with niraparib and 0% with olaparib).[3, 11] Synergistic interactions have been observed, however, between immune checkpoint inhibitors and PARP inhibitors; nonclinical experiments in syngeneic mouse models have shown an increased response rate to the combination of anti-PD-1 and niraparib over either agent alone, providing additional support to investigate this combination in patients.[57-59] Exposure of a tumor in vivo to PARP inhibitor results in increased cancer cell death by 2 independent mechanisms. First, through the mechanism of synthetic lethality, the PARP inhibitor can kill HRD tumors through apoptosis. Second, the PARP inhibitor can increase the number of CD8+ T cells and natural killer (NK) cells, as well as their production of IFN-γ and TNF-α, resulting in an improved response to checkpoint blockade.[59] Accordingly, the biomarkers for this combination clinical study will include a wide range of assays, including the measurement of tumor cell death, genomic changes, apoptosis, and immune response.

Given the unmet medical need of patients with advanced or metastatic TNBC and patients with platinum-resistant recurrent OC, the non-overlapping safety and metabolic profile (see the current versions of the niraparib Investigator's Brochure and the pembrolizumab Investigator's Brochure for details), and preclinical data suggesting possible synergistic interaction between immune checkpoint inhibitors and PARP inhibitors along with a potential overlap for PD-l- and PARP-sensitive patient populations, this study is designed to evaluate the combination of niraparib and pembrolizumab in these populations.

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objectives of this study, by phase, are as follows:

- Phase 1: To evaluate dose-limiting toxicities (DLTs) of combination treatment with niraparib and pembrolizumab during the first cycle of treatment, and to establish a recommended Phase 2 dose (RP2D) and schedule.
- Phase 2: To estimate the clinical activity of combination treatment with niraparib and pembrolizumab in terms of ORR as assessed by the Investigators using RECIST v1.1 separately for the TNBC and OC cohorts.

2.2. Secondary Objectives

The secondary objectives of the study are as follows:

- Phase 1 and Phase 2: To evaluate the safety and tolerability of combination treatment with niraparib and pembrolizumab using Common Terminology Criteria for Adverse Events (CTCAE, v.4.03).
- Phase 2: To evaluate additional measures of clinical benefit as assessed by the Investigators, including:
  - ORR by immune-related RECIST (irRECIST)
  - Duration of response (DOR) by RECIST v1.1 and by irRECIST;
  - Disease control rate (DCR) by RECIST v1.1 and irRECIST;
  - Progression-free survival (PFS) by RECIST v1.1 and by irRECIST;
  - Overall survival (OS).
- Phase 1 and Phase 2: To evaluate the pharmacokinetics (PK) of niraparib and associated major metabolite M1 during combination treatment.

2.3. Exploratory Objectives

The exploratory objectives of the study for both phases are as follows:

- To identify the biomarker-based patient population that would derive benefit from the combination treatment based on the tumor tissue molecular profile, molecular profile of TILs, and circulating biomarkers.
- To correlate homologous recombination deficiency (HRD) status with other immune-related biomarkers and with efficacy outcomes.

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design and Plan

3.1.1. Overview

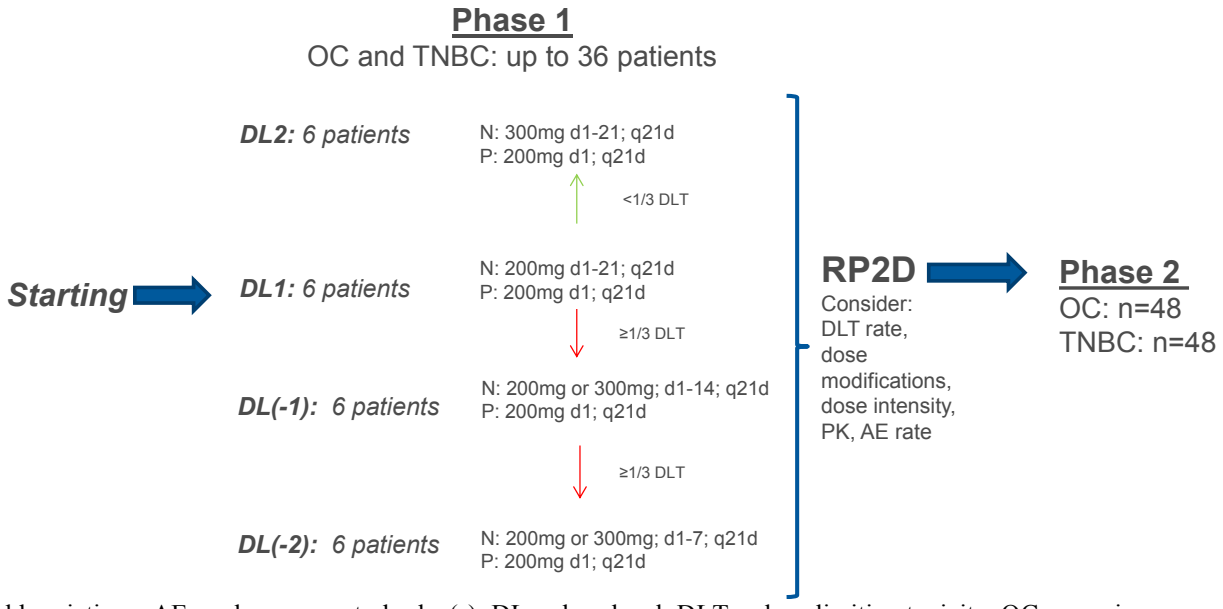
This is a multicenter, open-label, single-arm Phase 1/2 study evaluating the safety and efficacy of combination treatment with niraparib and pembrolizumab in patients with previously treated TNBC or OC. Specifically, patients eligible for this study are those with:

- Advanced or metastatic TNBC (in Phase 1 patients may have received up to 4 lines of cytotoxic therapy for advanced/metastatic disease or in Phase 2, up to 2 lines of cytotoxic therapy for advanced/metastatic disease); or
- Advanced, recurrent epithelial (for Phase 1: any serous, endometroid, mucinous, clear cell; for Phase 2: high-grade serous or endometroid) ovarian, fallopian tube, or primary peritoneal cancer who are currently platinum-resistant but previously experienced a response lasting for at least 6 months to first-line platinum-based therapy (in Phase 1 patients may have received up to 5 lines of cytotoxic therapy or in Phase 2, up to 4 lines of cytotoxic therapy).

Study treatment should be considered an appropriate option by the Investigator. The study will be conducted in 2 parts. The Phase 1 portion of the study will be a dose-escalation evaluation to determine the RP2D and schedule of niraparib to be administered in combination with the recommended dose of pembrolizumab, and the Phase 2 portion will further evaluate the RP2D and schedule in 2 cohorts of approximately 48 patients each with TNBC or OC as described above. See Section 3.1.2.1 for the RP2D.

Figure 1 presents an overview of the planned study schema. The schedule of events for the study is provided in Table 6.

Figure 1 Study Schema



Abbreviations: AE = adverse event; d= day(s); DL = dose level; DLT = dose-limiting toxicity; OC = ovarian cancer; PK = pharmacokinetics; q21d = every 21 days; N = niraparib; P = pembrolizumab; RP2D = recommended Phase 2 dose; TNBC = triple-negative breast cancer.

The study will be conducted in conformance with Good Clinical Practice (GCP).

3.1.2. Phase 1 Dose Escalation

The following are the planned dose levels and treatment schedule for the Phase 1 portion of the study. Initially, 6 patients will be enrolled within a cohort. Based on current single-agent niraparib experience (see niraparib Investigator's Brochure), hematological laboratory abnormalities are expected in a significant proportion of patients; therefore, cohorts may be expanded up to approximately 12 patients if needed to better characterize the safety of the combination treatment.

- Dose Level 1: niraparib 200 mg/day orally (PO) on Days 1-21 and pembrolizumab 200 mg intravenously (IV) on Day 1 of each 21-day cycle.
- Dose Level 2: niraparib 300 mg/day PO on Days 1-21 and pembrolizumab 200 mg IV on Day 1 of each 21-day cycle.
- Dose Level (-1): niraparib 200 or 300 mg/day PO on Days 1-14 of each 21-day cycle and pembrolizumab 200 mg IV on Day 1 of each 21-day cycle. Schedule of niraparib administration will be determined by agreement between Investigators and Sponsor (see Section 9.12).
- Dose Level (-2): niraparib 200 or 300 mg/day PO on Days 1 – 7 of each 21-day cycle and pembrolizumab 200 mg IV on Day 1 of each 21-day cycle. Schedule of niraparib administration will be determined by agreement between Investigators and Sponsor (see Section 9.12).

Dosing will initiate at Dose Level 1 with a cohort of 6 patients with either TNBC or OC enrolled and treated with a combination of niraparib 200 mg PO daily for Days 1-21 and pembrolizumab

200 mg IV on Day 1 every 21 days. After all patients in Dose Level 1 who are evaluable for safety have completed Cycle 1 of combination treatment, a review of the safety of treatment will be conducted by the Investigators and Sponsor (see Section 9.12). A patient will be considered non-evaluable if, for any reason other than safety, the patient is unable to complete the 21-day combination treatment DLT observation period or is unable to take > 80% of the intended dose of either agent. Patients in Phase 1 considered unevaluable may be replaced after consultation between the Sponsor and Principal Investigator. If 2 of 6 initially enrolled patients in a cohort experience hematologic DLTs, a lower dose level will be opened. If, however, the 2 observed DLTs include 1 hematologic DLT and 1 non-hematologic DLT or 2 non-hematologic DLTs, a cohort may be expanded up to approximately 12 patients to better characterize the safety of the combination treatment. Following the safety review, the next higher dose level (Dose Level 2) will be open for enrollment if less than one-third of patients (ie, < 2 of 6 patients or < 4 of 12 patients) in Dose Level 1 experience a DLT during Cycle 1 (see Section 5.3 for the definition of DLT).

Once Dose Level 1 is determined to be safe, a cohort of 6 patients with either TNBC or OC will be enrolled in Dose Level 2 and treated with a combination of niraparib 300 mg PO daily for Days 1-21 and pembrolizumab 200 mg IV on Day 1 every 21 days. No further dose escalation will be considered if Dose Level 2 is reached.

The maximum tolerated dose (MTD) will be defined as the highest dose with DLTs observed in less than one-third of patients (ie, < 2 of 6 patients or < 4 of 12 patients) during Cycle 1 of combination treatment. If one-third or more of the evaluable patients experiences a DLT, then this dose will be considered to exceed the MTD and a lower dose level may be opened for enrollment if not yet evaluated. Alternative dosing schedules may be explored.

Additional cohorts of 6 patients may be opened to evaluate Dose Level (-1) or Dose Level (-2), which will explore lower niraparib dose intensity by, for example, introducing an alternative dosing schedule, following agreement by the Investigators and Sponsor (see Section 9.12).

Patients in Phase 1 who complete the 21-day DLT evaluation period may continue the pembrolizumab/niraparib combination treatment for up to 2 years unless specific withdrawal criteria are met (Section 4.3). Continued treatment with niraparib beyond 2 years may be considered following discussion between the Sponsor and Investigator. Appropriate niraparib dose modification can be made according to Section 5.4.1.

3.1.2.1. Recommended Phase 2 Dose

The RP2D was determined following discussion and agreement between Investigators and the Sponsor based on evaluation of multiple endpoints, which may include the DLT rate in first and subsequent cycles of combination treatment, the rate of dose modifications for non-DLT AEs, the ability to manage toxicities, PK, niraparib dose intensity, and signs of clinical efficacy. The goal will be to identify the dose/regimen of niraparib with the greatest dose intensity that can be safely combined with the recommended dose/regimen of pembrolizumab.

In the Phase 1 portion of this study, 14 patients with advanced TNBC or OC were enrolled in Dose Level 1 or Dose Level 2. Twelve patients were eligible for DLT evaluation. In Dose Level (DL) 1, 1 of 6 DLT-eligible patients experienced multiple DLTs including Grade 3 anemia, Grade 4 neutropenia, and Grade 4 thrombocytopenia. In Dose Level 2, 1 of 6 DLT-eligible patients experienced 1 DLT, Grade 4 thrombocytopenia; an additional patient experienced an adverse event

that was deemed to be a DLT-equivalent; she had epistaxis on C1D17 and Grade 4 thrombocytopenia on C2D1. Based on the observed DLTs in DL1 and DL2, the RP2D to be implemented in the Phase 2 portion of this study is niraparib 200 mg/day PO on days 1-21 and pembrolizumab 200 mg IV on day 1 of each 21-day cycle; niraparib dose may be escalated on or after C3D1 from 200 mg daily to 300 mg daily if hemoglobin ≥ 9 g/dL, platelets ≥ 100,000/μL and neutrophils ≥ 1500/μL for all labs performed during the first two cycles after discussion with Medical Monitor or Designee.

3.1.3. Phase 2 Expansion

The Phase 2 portion of the study will commence after the RP2D is determined during the Phase 1 portion. Two cohorts of approximately 48 patients each with advanced TNBC or OC as outlined above will be evaluated.

Patients in this phase of the study will receive the RP2D as described in Section 3.1.2.1. Combination pembrolizumab/niraparib treatment may continue for up to 2 years unless specific withdrawal criteria are met (Section 4.3). Continued treatment with niraparib beyond 2 years may be considered following discussion between the Sponsor and Investigator.

3.1.4. General Study Conduct: Phase 1 and 2

Following informed consent, all patients in both Phase 1 and Phase 2 will undergo screening procedures within 21 days prior to the first dose of study treatment to determine eligibility for study entry. Screening procedures include medical, surgical, cancer, and medication history; complete physical examination, including vital signs, height, and weight; Eastern Cooperative Oncology Group (ECOG) performance status; clinical laboratory tests (complete blood count [CBC], coagulation, chemistry, thyroid-stimulating hormone [TSH], triiodothyronine [T3] or free T3 [FT3], free thyroxine [FT4], urinalysis, pregnancy test for women of childbearing potential, serum CA-125 [OC patients only]) and electrocardiogram (ECG). Tumor samples must be available from all patients (fresh samples or archived paraffin blocks; see Study Manual for details on sample collection and preparation) and will be sent to a centralized laboratory for biomarker testing. Radiographic evaluations (computed tomography [CT, preferred method] or magnetic resonance imaging [MRI, if clinically indicated]) of the chest, abdomen, and pelvis must be conducted at screening to determine extent of disease and confirm presence of measurable disease. Brain scan will be conducted if clinically indicated; bone scans will be conducted per standard of care. Scans performed prior to the signing of the informed consent form (ICF) as part of routine clinical management are acceptable for use as initial tumor imaging if they are of diagnostic quality and are performed within 21 days prior to first dose date.

All patients will begin treatment with niraparib and pembrolizumab on Cycle 1/Day 1; additional on-treatment assessments will be conducted on Days 8 and 15 of Cycle 1 and on Day 1 of all subsequent cycles. Safety assessments conducted throughout the treatment period include symptom-directed physical examination, vital signs, ECGs, ECOG performance status, and clinical laboratory assessments (CBC, coagulation [Phase 1 only], chemistry, TSH, T3 or FT3, FT4, urinalysis, CA-125 [OC patients only], and pregnancy testing). Radiographic evaluations (CT/MRI of chest [all TNBC patients and OC patients with abnormal screening scan or with clinical indication], abdomen, and pelvis) to assess extent of disease will be conducted every 9 weeks (63 days ±7 days) after Cycle 1/Day 1 while on study treatment independent of cycle delays and/or dose

interruptions and/or at any time when progression of disease is suspected. The same modality (CT or MRI) should be used throughout the study for a given patient. Brain scans will be conducted if clinically indicated; bone scans will be conducted per standard of care. After 1 year of radiographic assessments, patients will have imaging performed every 12 weeks (84 ±7 days) until disease progression. If a patient discontinues treatment for a reason other than progression or death, withdrawal of consent, or loss to follow-up, scans and CA-125 testing (OC patients only) should continue at the specified intervals (ie, every 9 weeks for the first year and every 12 weeks thereafter). All radiographic images/scans will be sent to a central imaging vendor upon acquisition and archived for future evaluation if needed. Per RECIST v1.1, patients who achieved complete response (CR) or partial response (PR) should have the response confirmed; tumor imaging for confirmation of response may be performed at the earliest 4 weeks after the first indication of response, or at the next scheduled scan (ie, 9 weeks later), whichever is clinically indicated. Blood sampling for PK and biomarker evaluations will be conducted for patients in both Phase 1 and Phase 2 (see Section 6.4).

In patients who consent to fresh biopsies, serial fresh biopsies will be obtained for exploratory biomarker analysis at 3 time points: during the screening period, 1 to 3 days before or on C3D1 prior to pembrolizumab infusion and, whenever possible, at the time of disease progression (note: although the biopsy is voluntary, it is highly encouraged). The serial biopsies at different time points should be on the same lesion preferably. A core biopsy is recommended (details are provided in the Study Manual); if an excisional or incisional biopsy is to be performed, it must be conducted on a non-target lesion. If a patient has had a biopsy within 12 weeks prior to entering screening, that biopsy may be accepted as the screening biopsy. Blood samples will also be obtained for biomarker analysis predose on Day 1 of Cycle 1 and Cycle 2, as well as at the end of treatment (EOT).

All patients will undergo an EOT visit within 7 days of the last dose of study treatment and a safety follow-up visit conducted 30 days (+7 days) post-treatment. Thereafter, all patients will enter the post-treatment period for telephone assessment of survival status and the occurrence of any new malignancies every 90 days (±14 days).

All AEs will be collected and recorded for each patient from the day of signing the ICF until 30 days after last study drug administration; serious adverse events (SAEs) and Events of Clinical Interest (ECIs) (see Section 6.1.6) are required to be captured through 90 days after cessation of study treatment (or to a minimum of 30 days post-treatment if the patient starts alternate anticancer therapy), and any pregnancies are to be captured through 120 days post-treatment. All AEs and SAEs experienced by a patient, irrespective of the suspected causality, will be monitored until the AE or SAE has resolved, until abnormal laboratory values have returned to baseline or normalized, until there is a satisfactory explanation for the changes observed, until the patient is lost to follow-up, or until the patient has died.

4. STUDY POPULATION

4.1. Inclusion Criteria

To be considered eligible to participate in this study, all of the following requirements must be met:

1. Patient is male or female, at least 18 years of age. Male patients are only for TNBC and not OC.
2. Patient has histologically proven advanced (unresectable) or metastatic cancer as outlined below according to study phase and disease type:
   a. Phase 1 patients (breast or ovarian cancer)
      – Patients with advanced or metastatic breast cancer must have disease that is HER2-negative, estrogen receptor-negative, and progesterone receptor-negative (ie, triple-negative breast cancer, TNBC). Patients with disease recurrence or progression following neoadjuvant or adjuvant therapy are eligible. Patients with advanced or metastatic disease may have up to 4 lines of cytotoxic therapy. Neoadjuvant and adjuvant therapies are not counted towards lines of therapy. Targeted small molecules (eg, tyrosine kinase inhibitors), hormonal agents and monoclonal antibodies that inhibit angiogenesis (eg, bevacizumab, afilbercept) are not counted in the number of lines of therapy.
      – Patients must have any epithelial (ie, serous, endometroid, mucinous, clear cell) ovarian, fallopian tube, or primary peritoneal cancer. Patients must have experienced a response lasting at least 6 months to first-line platinum-based therapy but currently considered to have platinum-resistant disease per investigator's assessment (e.g, patient is not eligible for further platinum containing treatment). Patients may have received up to 5 lines of cytotoxic therapy for advanced or metastatic cancer. Neoadjuvant and adjuvant therapies are not counted towards lines of therapy. Treatment with small molecules (eg, tyrosine kinase inhibitors), hormonal agents and monoclonal antibodies that inhibit angiogenesis (eg, bevacizumab, aflibercept) are not counted in the number of lines of therapy.
   b. Phase 2 patients (breast or ovarian cancer)
      – Patients with advanced or metastatic breast cancer must have TNBC. Patients with disease recurrence or progression following neoadjuvant or adjuvant therapy are eligible. Patients with advanced or metastatic disease may have received up to 2 lines of cytotoxic therapy. Adjuvant and/or neoadjuvant therapies are not counted in the number of lines of therapy. Targeted small molecules (eg, tyrosine kinase inhibitors), hormonal agents and monoclonal antibodies that inhibit angiogenesis (eg, bevacizumab, afilbercept) are not counted. TNBC patients who have previously received platinum chemotherapy in the metastatic setting are allowed to enroll in the study as long as they did not progress while on or within 8 weeks from the day of the last platinum administration.

- Patients must have with high-grade serous or endometroid ovarian, fallopian tube, or primary peritoneal cancer. Patients must have experienced a response lasting at least 6 months to first-line platinum-based therapy but currently considered to have platinum-resistant disease per investigator's assessment (eg, patient is not eligible for further platinum containing treatment). Patients may have had up to 4 lines of cytotoxic therapy for advanced or metastatic disease cancer. Neoadjuvant, adjuvant, and the combination of both will be considered as one line of therapy. Treatment with small molecules (eg, tyrosine kinase inhibitors), hormonal agents and monoclonal antibodies that inhibit angiogenesis (eg, bevacizumab, aflibercept) are not counted in the number of lines of therapy.

3. Patient has archival tumor tissue available that is formalin-fixed and paraffin-embedded.
   a. For patients who do not have archival tissue, tissue from a fresh biopsy must be obtained prior to study treatment initiation.
   b. Serial fresh tumor tissue samples will be collected in patients with lesions amenable for a biopsy who consent to such a procedure.
4. Patient has measurable lesions by RECIST v1.1.
5. Patient has an ECOG performance status of 0 to 1.
6. Patient has adequate organ function, defined as (Note: CBC test should be obtained without transfusion or receipt of colony stimulating factors within 2 weeks before obtaining sample):
   a. Absolute neutrophil count (ANC) ≥ 1,500/μL
   b. Platelets ≥ 100,000/μL
   c. Hemoglobin ≥ 9 g/dL or ≥ 5.6 mmol/L
   d. Serum creatinine ≤ 1.5× upper limit of normal (ULN) or calculated creatinine clearance ≥ 60 mL/min using Cockcroft-Gault equation for patients with creatinine levels > 1.5× institutional ULN
   e. Total bilirubin ≤ 1.5× ULN OR direct bilirubin ≤ 1× ULN
   f. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5× ULN unless liver metastases are present, in which case they must be ≤ 5× ULN
   g. International normalized ratio (INR) or prothrombin time (PT) ≤ 1.5× ULN unless patient is receiving anticoagulant therapy as long as PT or partial thromboplastin time (PTT) is within therapeutic range of intended use of anticoagulants
   h. Activated partial thromboplastin time (aPTT) ≤ 1.5× ULN unless patient is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
7. Patient is able to take oral medications.
8. Female patient has a negative serum pregnancy test within 72 hours prior to taking study medication if of childbearing potential, or agrees to abstain from activities that could result in pregnancy from enrollment through 120 days after the last dose of study treatment, or be of non-childbearing potential. Non-childbearing potential is defined as (by other than medical reasons):
   a. ≥ 45 years of age and has not had menses for > 1 year

b. Amenorrheic for < 2 years without a hysterectomy and oophorectomy and a follicle-stimulating hormone (FSH) value in the postmenopausal range upon pre-study (screening) evaluation
c. Post hysterectomy, bilateral oophorectomy, or tubal ligation. Documented hysterectomy or oophorectomy must be confirmed with medical records of the actual procedure or confirmed by an ultrasound. Tubal ligation must be confirmed with medical records of the actual procedure, otherwise the patient must be willing to use 2 adequate barrier methods throughout the study, starting with the screening visit through 120 days after the last dose of study therapy. Please see Section 5.7.2 for a list of acceptable birth control methods. Information must be captured appropriately within the site's source documents.

   Note: Abstinence is acceptable if this is the established and preferred contraception for the patient.

9. Male patient agrees to use an adequate method of contraception (please see Section 5.7.2 for a list of acceptable birth control methods) starting with the first dose of study therapy through 120 days after the last dose of study therapy.

   Note: Abstinence is acceptable if this is the established and preferred contraception for the patient.

10. Patient agrees to blood samples during screening and at the end of treatment for cytogenetic analysis.

4.2. Exclusion Criteria

Patients will not be eligible for study entry if any of the following criteria are met:

1. Patients with primary platinum refractory ovarian cancer (ie, progressive disease on or within 6 months of first-line platinum therapy) are not eligible in Phase 1 or Phase 2 of this study.
2. Patient has known active central nervous system (CNS) metastases and/or carcinomatous meningitis.

   Note: Patients with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging [using the identical imaging modality for each assessment, either MRI or CT scan] for at least 4 weeks prior to the first dose of study treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and have not been using steroids for at least 7 days prior to study treatment. Carcinomatous meningitis precludes a patient from study participation regardless of clinical stability.
3. Patient has a known additional malignancy that progressed or required active treatment within the last 2 years. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin that has undergone potentially curative therapy, or in situ cervical cancer.
4. Patient is considered a poor medical risk due to a serious, uncontrolled medical disorder, nonmalignant systemic disease or active infection that requires systemic therapy. Specific

examples include, but are not limited to, has history of (non-infectious) pneumonitis that required steroids or current pneumonitis; uncontrolled ventricular arrhythmia; recent (within 90 days) myocardial infarction; uncontrolled major seizure disorder; unstable spinal cord compression; superior vena cava syndrome; or any psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the study (including obtaining informed consent).

5. Patient has a condition (such as transfusion dependent anemia or thrombocytopenia), therapy, or laboratory abnormality that might confound the study results, or interfere with the patient's participation for the full duration of the study treatment. Patients who 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 are not eligible.
6. Patient is pregnant or breastfeeding, or expecting to conceive children within the projected duration of the study, starting with the screening visit through 120 days after the last dose of study treatment.
7. Patient has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of study treatment.
8. Patient has a known history of human immunodeficiency virus (HIV) (HIV 1/2 antibodies).
9. Patient has known active hepatitis B (eg, hepatitis B surface antigen [HBsAg] reactive) or hepatitis C (eg, hepatitis C virus ribonucleic acid [HCV RNA] [qualitative] is detected).
10. Patient has an active autoimmune disease that has required systemic treatment in the past 2 years (ie, 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, etc.) is not considered a form of systemic treatment.
11. Patient has not recovered (i.e, to ≤Grade 1 or to baseline) from cytotoxic therapy-induced AEs. Note: Patient with ≤ Grade 2 neuropathy or ≤ Grade 2 alopecia is an exception to this criterion and may qualify for the study.
12. Patient is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks of the first dose of treatment.
13. Patient has had a prior cytotoxic therapy, anticancer targeted small molecules (eg, tyrosine kinase inhibitors), hormonal agents within 5 half-lives, or monoclonal antibodies (mAb) within 5 half-lives or 4 weeks (whichever is shorter) of that treatment prior to study Day 1or radiation therapy encompassing > 20% of the bone marrow within 2 weeks or any radiation therapy within 1 week prior to study Day 1.
14. Patient has not recovered adequately from AEs and/or complications from any major surgery prior to starting therapy.
15. Patient has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or the patient has previously participated in Merck MK-3475 (pembrolizumab) clinical studies.

16. Patient has received a live vaccine within 30 days of planned start of study therapy.
17. Patient has undergone prior treatment with a known PARP inhibitor.
18. Patient has a heart-rate corrected QT interval (QTc) prolongation > 470 msec at screening.

    Note: If a patient has a prolonged QT interval and the prolongation is deemed to be due to a pacemaker upon Investigator evaluation (ie, the patient otherwise has no cardiac abnormalities), the patient may be eligible to participate in the study following discussion with the Medical Monitor.
19. Patient has a known hypersensitivity to niraparib or pembrolizumab components or excipients.
20. Known history or current diagnosis of MDS or AML.

4.3. Patient Withdrawal and Replacement

4.3.1. Discontinuation from Treatment

Patients may be discontinued from study treatment at any time. Specific examples of reasons for discontinuing all study treatments are given below.

- Adverse event
- Disease progression as outlined in Section 6.3 or based on clinical criteria by Investigator
- Risk to patient as judged by the Investigator and/or Sponsor
- Severe noncompliance with the protocol as judged by the Investigator and/or Sponsor
- Patient request
- Patient becomes pregnant
- Sponsor decision to terminate study

Details of required niraparib dose modifications, including interruptions, dose reductions, and permanent discontinuations, related to toxicity are provided in Section 5.4.1.

Details of required pembrolizumab dose interruptions and permanent discontinuation related to toxicity are provided in Section 5.4.2.

Note: If a patient is required to be discontinued from one of the study medications in the combination, treatment with the other study medication may be continued per decision of the Investigator in consultation with Sponsor.

Discontinuation of treatment may be considered for patients who have attained a confirmed CR, have been treated for at least 24 weeks with study treatments, and had at least 2 cycles of treatment beyond the date when the initial CR was declared.

Patients who discontinue from all study treatments will continue to receive follow-up assessments (see Table 6) as part of the study unless they are discontinued from the study (Section 4.3.2).

4.3.2. Discontinuation from the Study

Patients may be discontinued from the study for any of the following reasons:

- Withdrawal of consent by the patient, who is at any time free to discontinue their participation in the study, without prejudice to further treatment
- Death from any cause
- Loss to follow-up
- Sponsor decision to terminate study
- Investigator's decision

If a patient is lost to follow-up or withdraws from study treatment, attempts should be made to contact the patient to determine the reason for discontinuation. For patients who are lost to follow-up, at least 3 documented attempts, including one via certified mail, should be made to contact the patient before considering the patient lost to follow-up.

4.3.3. Replacement of Patients

After consultation between the Sponsor and the Principal Investigator, enrollment may be extended to replace patient(s) that become non-evaluable for safety during Phase 1.

In Phase 2, if a patient discontinues study treatment prior to the first assessment of disease (either scheduled radiological assessment at 9 weeks post treatment initiation or clinically indicated disease assessment prior to 9 weeks), the patient should be replaced for the purposes of efficacy analysis after consultation between the Sponsor and Principal Investigator.

4.4. Patient Identification and Randomization

4.4.1. Patient Identification

All patients who enter into the screening period of the study (defined as the point at which the patient signs the ICF) will receive a unique patient identification number. This number will be used to identify the patient throughout the study and must be used on all study documentation related to that patient. A patient will be considered enrolled when the patient has been consented, screened, and all eligibility criteria have been confirmed in the electronic case report form (eCRF). The patient identification number must remain constant throughout the entire study; it must not be changed at the time of enrollment.

4.4.2. Randomization Scheme

Not applicable, as this is a single-arm study.

5. STUDY MEDICATION

5.1. Identity

5.1.1. Niraparib

Niraparib ([3S]-3-[4-{7-(aminocarbonyl)-2H-indazol-2-yl} phenyl] piperidine [tosylate monohydrate salt]) is an orally available, potent, highly selective PARP1 and PARP2 inhibitor. The excipients for niraparib are lactose monohydrate and magnesium stearate. Niraparib will be supplied as 100-mg capsules.

5.1.2. Pembrolizumab

Pembrolizumab is a potent and highly selective humanized mAb of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Pembrolizumab Powder for Solution for Infusion is a sterile, non-pyrogenic lyophilized powder for IV infusion supplied in single-use Type I glass vial containing 50 mg of pembrolizumab. The product is preservative-free, white to off-white powder and free from visible foreign matter.

5.2. Administration

5.2.1. Niraparib

Niraparib will be supplied as 100-mg capsules and will be administered orally once daily (QD) continuously starting on Cycle 1/Day 1. The daily dose to be administered each day (ie, 300 mg as 3 × 100-mg capsules, 200 mg as 2 × 100-mg capsules, or 100 mg as 1 × 100-mg capsules) will depend on the phase of the study, and in Phase 1, the cohort assignment. See Section 3.1.2.1 for the RP2D of the combination. Patients will be instructed to take their dose at the same time each day, preferably in the morning. Patients must swallow and not chew all capsules. The consumption of water and food is permissible.

Niraparib capsules will be dispensed to patients on Cycle 1/Day 1 and on Day 1 of every cycle (21-day cycles) thereafter until the patient discontinues study treatment. On Day 1 of each cycle, a niraparib dose will be administered at the clinic upon completion of the pembrolizumab infusion.

Details on the administration of niraparib can be found in the Pharmacy Manual.

5.2.2. Pembrolizumab

Pembrolizumab will be administered at the study site on Day 1 of each 21-day treatment cycle after all procedures and assessments have been completed as detailed in Table 6. Pembrolizumab may be administered up to 3 days before or after the scheduled Day 1 of each cycle after Cycle 2 due to administrative reasons.

Pembrolizumab will be administered at a dose of 200 mg IV using a 30-minute IV infusion. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. Given the variability of infusion pumps from site to site, however, a window between -5 minutes and +10 minutes is permitted.

See Section 3.1.2.1 for the RP2D of the combination.

The Pharmacy Manual contains specific instructions for the preparation of the pembrolizumab infusion and administration of the infusion solution.

5.3. Dose-Limiting Toxicity

The following are to be considered DLTs for this study (as assessed during Cycle 1, ie, during the first 21 days of treatment, Day 1 through Day 21 during Phase 1):

- Any treatment-related Grade ≥ 3 non-hematologic clinical (non-laboratory) AE
- Any treatment-related Grade 3 or Grade 4 non-hematologic laboratory abnormality if:
  - Medical intervention is required to treat the patient, or
  - The abnormality leads to hospitalization, or
  - The abnormality persists for ≥ 7 days.
- Any treatment-related hematologic toxicity specifically defined as:
  - Thrombocytopenia Grade 4 for ≥ 7 days, or Grade 3 or 4 associated with bleeding or requiring platelet transfusion;
  - Neutropenia Grade 4 for ≥ 7 days, or Grade 3 or 4 associated with infection or febrile neutropenia;
  - Anemia Grade 4, or Grade 3 or 4 requiring blood transfusion.
- Any treatment-related AE leading to niraparib dose interruption per the following criteria:
  - A dose interruption per dose modification rules (see Section 5.4.1, Table 3) for a non-DLT laboratory abnormality (eg, for Grade 2 or 3 thrombocytopenia or for Grade 3 anemia or neutropenia) lasting ≥ 14 days.
  - A dose interruption per dose modification rules (see Section 5.4.1, Table 2) for non-hematologic AE leading to < 80% of an intended dose being administered (eg, niraparib dose interruption for > 4 days within Cycle 1).

Note that niraparib dosing has been safely managed with dose interruptions and/or adjustments for AEs, including laboratory abnormalities, while maintaining activity in the single-agent setting (see see Section 5.4.1, Table 2 and Table 3, and niraparib Investigator's Brochure). Therefore, niraparib dose interruption and/or reduction for an AE that does not meet a DLT definition as described above will be considered a non-DLT modification. The non-DLT dose modifications will not be considered in determining the MTD but will be considered in determining the niraparib dose intensity and RP2D.

5.4. Dose Modification

Study treatment dosing interruptions are permitted in the case of medical / surgical events or logistical reasons not related to study therapy (eg, surgery, unrelated medical events, patient

vacation, and/or holidays). Patients should be placed back on study therapy within 28 days of the scheduled interruption, unless otherwise discussed with the Sponsor.

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

5.4.1. Niraparib

Dose interruption of niraparib may be implemented per the Investigator's judgement after Cycle 1 in patients enrolled in Phase 1 and at any time in patients enrolled in Phase 2. See the following sections for permitted duration of interruption prior to required discontinuation from treatment.

Intra-patient Dose Escalation

For patients in Phase 1, the dose of niraparib may be increased after Cycle 1 to a higher dose level that has been found to be safe during the dose escalation phase following discussion with the Sponsor.

See Section 3.1.2.1 for the RP2D.

Niraparib Dose Modifications for Non-Hematologic Toxicity

Treatment with niraparib must be interrupted for any treatment-related non-hematologic CTCAE Grade 3 or 4 event. Once resolved to Grade ≤ 1, the patient may restart treatment with niraparib with a dose level reduction (see Table 2) unless prophylaxis is considered feasible. If the event recurs at a similar or worse grade, treatment should be interrupted again and, upon resolution, a further dose reduction must be made to a lower dose level, if available, or niraparib dosing should be discontinued. If the toxicity requiring dose interruption has not resolved to CTCAE Grade ≤ 1 during a maximum 4-week (28-day) dose interruption period, and/or the patient has already undergone a maximum of 2 dose reductions (to a minimum dose of 100 mg QD), the patient must permanently discontinue treatment with niraparib. Once the dose of niraparib has been reduced, any re-escalation must be discussed with the Sponsor. Note that treatment with pembrolizumab may continue if discontinuation criteria as outlined in Section 5.4.2 have not been met.

Table 2 Niraparib Dose Reductions for Non-Hematologic Toxicity

Event	Dose [a,b]
Initial dose	300 mg QD
1st dose reduction for treatment-related CTCAE Grade 3 or 4 AE or SAE where prophylaxis is not considered feasible	200 mg QD
2nd dose reduction for treatment-related CTCAE Grade 3 or 4 AE or SAE where prophylaxis is not considered feasible	100 mg QD
Continued treatment-related CTCAE Grade 3 or 4 AE or SAE ≥ 28 days	Discontinue niraparib

Abbreviations: AE = adverse event; CTCAE = Common Terminology for Adverse Events; QD = once daily; SAE = serious adverse event.

[a] Dose not to be decreased below 100 mg daily.

[b] **If initial dose is below 300 mg, the same dose reduction principles will apply with fewer dose modification steps available.**

Niraparib Dose Modifications for Hematologic Toxicity

The dose interruption/modification criteria for niraparib for hematologic toxicities will be based on blood counts and are outlined in Table 3.

For thrombocytopenia, patients with a platelet count ≥ 25,000 to < 75,000/μL must have niraparib interrupted and have blood counts monitored twice weekly until recovery to ≥ 100,000/μL; upon recovery, niraparib can be resumed at the same dose for the first occurrence with once weekly monitoring for 3 weeks to confirm no recurrence of thrombocytopenia. For a further recurrence of platelet count at this level or any occurrence of platelet count < 25,000/μL, dose interruption followed by dose reduction upon recovery to ≥ 100,000/μL with subsequent monitoring once weekly for 3 weeks to ensure the safety of the new dose level is required (see Table 2).

For Grade 3 or 4 neutropenia or anemia, treatment with niraparib must be interrupted with blood counts monitored twice weekly for neutropenia and once or twice weekly for anemia until recovery to ≤ Grade 1. Niraparib dosing should be resumed with a dose level reduction (see Table 2) at that time and the patient monitored once weekly for 3 weeks to ensure the safety of the new dose level. If clinically indicated, use of G-CSF is allowed according to current American Society of Clinical Oncology (ASCO) guidelines.[60]

If the hematologic toxicity does not recover to the specified level within 4 weeks (28 days) of dose interruption and/or the patient has already undergone a maximum of 2 dose reductions (to a minimum dose of 100 mg QD), then niraparib should be discontinued.

Any patient requiring transfusion of platelets or red blood cells (1 or more units) or hematopoietic growth factor support must undergo a niraparib dose reduction upon recovery if study treatment is resumed.

It is strongly recommended that the patient be referred to a hematologist for further evaluation (1) if transfusions are required on more than 1 occasion or (2) if the treatment-related hematologic toxicities have not recovered to CTCAE ≤ Grade 1 within 4 weeks. If a diagnosis of MDS/AML is confirmed by a hematologist, the patient must permanently discontinue niraparib. Note that treatment with pembrolizumab may continue following discussion with the Sponsor if discontinuation criteria as outlined in Section 5.4.2 have not been met.

The reason for interruption, reduction, or discontinuation of niraparib should be recorded in the eCRF.

Table 3 Management of Hematologic Toxicities*

Laboratory Abnormality	Intervention
Platelet count 25,000 to < 75,000/μL	Niraparib must be interrupted until platelet count is ≥ 100,000/μL with twice-weekly CBC monitored until recovery. Niraparib may then be resumed at same dose. After recovery, blood counts once weekly for 3 weeks.
Further occurrence of platelet count 25,000 to < 75,000/μL	Niraparib must be interrupted until platelet count is ≥ 100,000/μL with twice-weekly CBCs monitored until recovery. Niraparib may then be resumed at a reduced dose (see Table 2); after recovery, blood counts once weekly for 3 weeks to ensure the safety of the new dose level. A further dose reduction[a] should be made if an additional treatment interruption is needed in less than 3 weeks after resuming treatment.
Platelet count < 25,000/μL[b]	Niraparib must be interrupted until platelet count is ≥ 100,000/μL with twice-weekly CBCs monitored until recovery. Niraparib may then be resumed at a reduced dose[a] (see Table 2); after recovery, blood counts once weekly for 3 weeks to ensure the safety of the new dose level.
Neutrophil < 1,000/μL	Niraparib must be interrupted until neutrophil counts are ≥ 1,500/μL with twice-weekly CBCs monitored until recovery. Niraparib may then be resumed at a reduced dose[a] (see Table 2); after recovery, blood counts once weekly for 3 weeks to ensure the safety of the new dose level.
Hemoglobin ≤ 8 g/dL	Niraparib must be interrupted until hemoglobin is ≥ 9 g/dL with once- or twice-weekly CBCs monitored until recovery. Niraparib may then be resumed at a reduced dose[a] (see Table 2); after recovery, blood counts once weekly for 3 weeks to ensure the safety of the new dose level.

Abbreviations: CBC = complete blood count.
* If blood counts do not recover within 28 days to normal values (ie, platelets ≥ 100,000/μL, hemoglobin ≥ 9 g/dL, neutrophils ≥ 1,500/μL) niraparib should be discontinued.
[a] Dose not to be decreased below 100 mg daily.
[b] For patients with platelet count ≤ 10,000/μL, prophylactic platelet transfusion per guidelines should be considered.[61, 62] For patients taking anticoagulation or antiplatelet drugs, consider the risk/benefit of interrupting these drugs and/or prophylactic transfusion at an alternate threshold, such as ≤ 20,000/μL.

5.4.2. Pembrolizumab

Adverse events (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These AEs may occur shortly after the first dose or several months after the last dose of treatment. Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs per Table 4. See also Section 6.1.6, Events of Clinical Interest (ECIs).

Table 4 provides detailed information for dose interruptions and discontinuations related to toxicity for pembrolizumab. No dose reductions of pembrolizumab are permitted. Note that treatment with

niraparib may continue following discussion with the Sponsor if discontinuation criteria as outlined in Section 5.4.1 have not been met.

The reason for interruption or discontinuation of pembrolizumab should be recorded in the eCRF.

Table 4 Pembrolizumab Dose Modifications for Non-hematologic Toxicities

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Treatment Discontinuation
Diarrhea/colitis	2-3	Toxicity resolves to Grade 0-1.	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue.	Permanently discontinue.
AST, ALT, or increased bilirubin	2	Toxicity resolves to Grade 0-1.	Toxicity does not resolve within 12 weeks of last dose.
	3-4	Permanently discontinue (see exception below).[a]	Permanently discontinue.
Type 1 diabetes mellitus (if new onset) or hyperglycemia	T1DM or 3-4	Hold pembrolizumab for new onset Type 1 diabetes mellitus or Grade 3-4 hyperglycemia associated with evidence of beta cell failure.	Resume pembrolizumab when patients are clinically and metabolically stable.
Hypophysitis	2-4	Toxicity resolves to Grade 0-1. Therapy with pembrolizumab can be continued while endocrine replacement therapy is instituted.	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
Hyperthyroidism	3	Toxicity resolves to Grade 0-1.	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue.	Permanently discontinue.
Hypothyroidism		Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted.	Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted.
Infusion reaction	2[b]	Toxicity resolves to Grade 0-1.	Permanently discontinue if toxicity develops despite adequate premedication.
	3-4	Permanently discontinue.	Permanently discontinue.

Table 4 Pembrolizumab Dose Modifications for Non-hematologic Toxicities (Continued)

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Treatment Discontinuation
Pneumonitis	2	Toxicity resolves to Grade 0-1.	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	3-4 or Recurrent 2	Permanently discontinue.	Permanently discontinue.
Renal failure or nephritis	2	Toxicity resolves to Grade 0-1.	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	3-4	Permanently discontinue.	Permanently discontinue.
All other drug-related toxicity[c]	3 or severe	Toxicity resolves to Grade 0-1.	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue.	Permanently discontinue.

Abbreviations: AE = adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; T1DM=type 1 diabetes mellitus.
Note: Permanently discontinue for any severe or Grade 3 (Grade 2 for pneumonitis) drug-related AE that recurs or any life-threatening event.
[a] For patients with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by greater than or equal to 50% relative to baseline and lasts for at least 1 week then patients should be discontinued.
[b] If symptoms resolve within one 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 subject should be premedicated for the next scheduled dose; Refer to Section 5.7.3 Infusion Treatment Guidelines for further management details.
[c] Patients with intolerable or persistent Grade 2 drug-related AE may hold study medication at physician discretion. Permanently discontinue study drug for persistent Grade 2 adverse reactions for which treatment with study drug has been held, that do not recover to Grade 0-1 within 12 weeks of the last dose.

5.5. Packaging, Labeling, and Storage

Niraparib 100-mg capsules will be packed in high-density polyethylene bottles with child-resistant closures.

Pembrolizumab for injection is supplied as 50-mg lyophilized powder single-use vials.

The label text of the study treatments will comply with Good Manufacturing Practice and national legislation to meet the requirements of the participating countries. The study treatment will be open-label and non-patient-specific.

All study treatment supplies must be stored in accordance with the Pharmacy Manual instructions and package labeling. Until dispensed or administered to the patients, the study treatment will be stored in a securely locked area, accessible to authorized personnel only.

5.6. Drug Accountability

The Investigator or designee is responsible for maintaining accurate dispensing records of the study treatments throughout the clinical study.

Details of maintaining drug accountability, including information on the accountability log, will be provided in the Pharmacy Manual.

All dispensation and accountability records will be available for Sponsor review. The study monitor will assume the responsibility to reconcile the study treatment accountability log. The pharmacist will dispense study treatment for each patient according to the protocol and Pharmacy Manual, if applicable.

5.7. Previous and Concomitant Medications

Any medication the patient takes during the study other than the study treatments, including herbal and other nontraditional remedies, is considered a concomitant medication. All concomitant medications must be recorded in the eCRF. The following information must be recorded in the eCRF for each concomitant medication: generic name, route of administration, start date, stop date, dosage, and indication. Any changes in the dosage or regimen of a concomitant medication must be recorded in the eCRF.

At screening, patients will be asked what medications they have taken during the last 30 days. At each subsequent study visit, patients will be asked what concomitant medications they are currently taking or have taken since the previous visit.

Niraparib has potential to induce cytochrome P450 (CYP)1A2 and is a substrate for P-glycoprotein (P-gp); therefore , investigators should be advised to use caution with drugs that are sensitive substrates for CYP1A2 (see Appendix A).

The niraparib safety profile includes risk for thrombocytopenia; therefore, investigators should be advised to use caution with anticoagulation and antiplatelet drugs.

5.7.1. Prohibited Medications

Patients are prohibited from receiving the following therapies during the screening and treatment phase of this study:

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than niraparib and pembrolizumab
- Radiation therapy is prohibited if encompassing > 20% of the bone marrow within 2 weeks or any radiation therapy within 1 week prior to study Day 1.

  Note: The following may be considered exceptions on a case-by-case basis after consultation with the Sponsor: Radiation therapy to pre-existing small areas of painful metastases that cannot be managed with local or systemic analgesics (excluding palliative radiotherapy encompassing > 20% of the bone marrow) as long as no evidence of disease progression is present. The patient must have clear measurable disease outside the radiated field. Administration of palliative radiation therapy may be considered clinical progression for the purposes of determining PFS.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an ECI of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

  Note: Inhaled steroids are allowed for the management of asthma.
- Live vaccines within 30 days prior to the first dose of study treatment and while participating in the study. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, bacille Calmette-Guerin (BCG), and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed. Intranasal influenza vaccines (eg, Flu-Mist®) are live attenuated vaccines, however, and are not allowed.
- Prophylactic cytokines (G-CSF) should not be administered in the first cycle of the study but may be administered in subsequent cycles according to current ASCO guidelines.[60]

If there is a clinical indication for any medication or vaccination specifically prohibited during the study, discontinuation from study therapy may be required. The Investigator should discuss any questions regarding this with the Sponsor. The final decision on any supportive therapy or vaccination rests with the Investigator and/or the patient's primary physician. The decision to continue the patient on study therapy, however, requires the mutual agreement of the Investigator, the Sponsor, and the patient.

5.7.2. Contraception

Pembrolizumab and niraparib are known to have properties that require the patient to use contraception. For details on niraparib, please refer to the Investigator's Brochure.

Pembrolizumab may have adverse effects on a fetus in utero. Furthermore, it is not known if pembrolizumab has transient adverse effects on the composition of sperm. Therefore, non-pregnant, non-breastfeeding women may only be enrolled if they are willing to use 2 methods of birth control or are considered highly unlikely to conceive. Highly unlikely to conceive is defined as 1) surgically sterilized, or 2) postmenopausal (a woman who is ≥ 45 years of age and has not had menses for > 1 year will be considered postmenopausal), or 3) not heterosexually active for the duration of the study. The 2 birth control methods can be either 2 barrier methods or a barrier method plus a hormonal method to prevent pregnancy. Patients should start using birth control from screening throughout the study period up to 120 days after the last dose of pembrolizumab.

The following are considered adequate barrier methods of contraception: diaphragm, condom (by the partner), copper intrauterine device, sponge, or spermicide per local regulations or guidelines. Appropriate hormonal contraceptives will include any registered and marketed contraceptive agent that contains an estrogen and/or a progestational agent (including oral, subcutaneous, intrauterine, or intramuscular agents). Abstinence is acceptable if this is the established and preferred contraception for the patient.

Patients should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study they must adhere to the contraception requirement (described above) for the duration of the study and through 120 days after the last study treatment. If there is any question that a patient will not reliably comply with the requirements for contraception, that patient should not be entered into the study.

5.7.3. Rescue Medications and Supportive Care Guidelines During Treatment with Pembrolizumab

Patients 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 below. 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.

Note: it may be necessary to perform additional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

The following text details specific guidance by type of AE.

- **Pneumonitis:**
  - For Grade 2 events, treat with systemic corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
  - For Grade 3-4 events, immediately treat with IV steroids. Administer additional anti-inflammatory measures, as needed.

- Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.

- **Diarrhea/Colitis:**

  Patients should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus).

  - All patients who experience 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. For Grade 2 or higher diarrhea, consider gastrointestinal consultation and endoscopy to confirm or rule out colitis.
  - For Grade 2 diarrhea/colitis that persists greater than 3 days, administer oral corticosteroids.
  - For Grade 3 or 4 diarrhea/colitis that persists > 1 week, treat with IV steroids followed by high-dose oral steroids.
  - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

- **Type 1 diabetes mellitus (if new onset, including diabetic ketoacidosis [DKA]) or ≥ Grade 3 hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis:**

  - For Type 1 diabetes mellitus or Grade 3-4 hyperglycemia
    - Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.
    - Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.

- **Hypophysitis:**

  - For Grade 2 events, treat with corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
  - For Grade 3-4 events, treat with an initial dose of IV corticosteroids followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

- **Hyperthyroidism or Hypothyroidism:**

  Thyroid disorders can occur at any time during treatment. Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.

  – Grade 2 hyperthyroidism events (and Grade 2-4 hypothyroidism):

    - In hyperthyroidism, non-selective beta-blockers (eg, propranolol) are suggested as initial therapy.
    - In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyronine, is indicated per standard of care.

  – Grade 3-4 hyperthyroidism

    - Treat with an initial dose of IV corticosteroids followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

- **Hepatic:**

  – For Grade 2 events, monitor liver function tests more frequently until returned to baseline values (consider weekly).

    – Treat with IV or oral corticosteroids.

  – For Grade 3-4 events, treat with intravenous corticosteroids for 24 to 48 hours.

  – When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.

- **Renal Failure or Nephritis:**

  – For Grade 2 events, treat with corticosteroids.

  – For Grade 3-4 events, treat with systemic corticosteroids.

  – When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

- **Management of Infusion Reactions**:

  Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.

  Table 5 shows treatment guidelines for patients who experience an infusion reaction associated with administration of pembrolizumab.

Table 5 Pembrolizumab Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the Investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hrs	**Stop infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the Investigator. 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 patient should be premedicated for the next scheduled dose. **Patients who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study treatment administration.**	Patient may be premedicated 1.5 hour (± 30 minutes) prior to infusion of pembrolizumab with: Diphenhydramine 50 mg PO (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg PO (or equivalent dose of antipyretic).
Grades 3 or 4 Grade 3: 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) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the Investigator. Hospitalization may be indicated. **Patient is permanently discontinued from further study treatment administration.**	No subsequent dosing

Abbreviations: IV=intravenous; NSAID=nonsteroidal anti-inflammatory; PO=oral.
Note: Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.

5.7.4. Other Study Restrictions

Patients who are blood donors should not donate blood during the study and for 90 days after the last dose of study treatment.

Patients should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea, or vomiting.

6. ENDPOINTS AND METHODS OF ASSESSMENT

6.1. Safety Endpoints

Safety parameters evaluated during the conduct of the study include treatment-emergent AEs (TEAEs), clinical laboratory values (hematology, chemistry, coagulation, thyroid function, urinalysis), vital signs, ECGs, physical examination findings, and use of concomitant medications. Additionally, the relationship between cytogenetic abnormalities and safety parameters may be explored.

6.1.1. Definitions

Adverse event: An *adverse event* is any untoward medical occurrence that occurs in a patient or clinical investigation subject administered a pharmaceutical product, and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including clinically significant abnormal laboratory findings), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the product.

Adverse events may include the onset of new illness and the exacerbation of pre-existing medical conditions. An AE can include an undesirable medical condition occurring at any time, including baseline or washout periods, even if no study treatment has been administered.

A *treatment-emergent adverse event* will be defined as any new AE that begins, or any preexisting condition that worsens in severity, after at least 1 dose of study treatment has been administered.

Serious adverse event: A *serious adverse event* is defined as any untoward medical occurrence that, at any dose:

- Results in death
- Is life-threatening
  - Note: This means that the patient is at immediate risk of death at the time of the event; it does not mean that the event hypothetically might have caused death if it were more severe
- Requires inpatient hospitalization or prolongation of existing hospitalization
  - Any AE that prolongs hospitalization will be considered an SAE.
  - Exception: Planned hospitalization (eg, for observation, protocol compliance, elective procedures, social reasons, etc.) will not be considered an SAE; however, the reason for the planned hospitalization should be captured in medical history.
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect

- Is an important medical event(s)
  - An important medical event may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or require intervention to prevent one of the above outcomes. Examples of such events are 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.

6.1.2. Assessment of Adverse Events

Each AE will be assessed by the Investigator with regard to intensity and causality with regard to study treatment as outlined in the following sections.

6.1.2.1. Intensity

Investigators should assess the severity of AEs according to CTCAE. In general, CTCAE (v4.03) severity grades are:

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). (Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.)

Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL. (Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.)

Grade 4: Life-threatening consequences; urgent intervention indicated

Grade 5: Death related to AE

A distinction should be made between **serious** and **severe** AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria above in Section 6.1.1. For example, a mild degree of gastrointestinal bleeding requiring an overnight hospitalization for monitoring purposes may be considered an SAE but is not necessarily severe. Similarly, an AE that is severe in intensity is not necessarily an SAE. For example, alopecia may be assessed as severe in intensity but may not be considered an SAE.

6.1.2.2. Causality

The Investigator will assess the causality/relationship between the study drug and the AE. One of the following categories should be selected based on medical judgment, considering the definitions and all contributing factors:

- Related: A clinical event, including laboratory test abnormality, occurs in a plausible time relationship to treatment administration, and which concurrent disease or other

drugs or chemicals cannot explain. The response to withdrawal of the treatment should be clinically plausible.

- Possibly related: A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the treatment, unlikely to be attributed to concurrent disease or other drugs or chemicals.
- Unlikely related: A clinical event, including laboratory test abnormality, with a temporal relationship to treatment administration which makes a causal relationship improbable, or in which other drugs, chemicals or underlying disease provide likely explanations.
- Unrelated: A clinical event, including laboratory test abnormality, with little or no temporal relationship with treatment administration. Typically explained by extraneous factors (eg, concomitant disease, environmental factors, or other drugs or chemicals).

6.1.3. Collecting and Recording Adverse Events

All AEs, regardless of the source of identification (eg, physical examination, laboratory assessment, ECG, reported by patient), must be documented in the eCRF.

All AEs will be collected and recorded in the eCRF for each patient from the day of signed informed consent until 30 days after the last dose of study treatment; SAEs will be monitored through 90 days after the last dose of study treatment (or to a minimum of 30 days post-treatment if the patient starts alternate anticancer therapy). All AEs and SAEs experienced by a patient, irrespective of the suspected causality, will be monitored until the AE or SAE has resolved, any abnormal laboratory values have returned to baseline or normal levels, until there is a satisfactory explanation for the changes observed, until the patient is lost to follow-up, or until the patient has died.

If an Investigator becomes aware of an SAE after the specified follow-up period post treatment discontinuation and considers the SAE related to investigational product, the Investigator should report the SAE to the Sponsor according to timelines for reporting SAEs described in this section.

Adverse events may be volunteered spontaneously by the study patient, or discovered by the study staff during physical examinations or by asking an open, non-leading question such as: “How have you been feeling since you were last asked?” The Investigator will document the nature of AE, date of onset of the AE (and time, if known), date of outcome of the AE (and time, if known), severity of the AE, action taken with study drug as a result of the AE, assessment of the seriousness of the AE, and assessment of the causal relationship of the AE to study drug and/or study procedure.

All AEs should be recorded individually in the patient’s own words (verbatim) unless, in the opinion of the Investigator, the AEs constitute components of a recognized condition, disease, or syndrome. In the latter case, the condition, disease, or syndrome should be named rather than each individual symptom.

Concomitant illnesses that existed before entry into the study will not be considered an AE unless the illness worsens during the treatment period. Pre-existing conditions will be recorded in the eCRF as well as on the SAE Report Form medical history section.

6.1.4. Reporting Disease Progression

The event of disease progression is an efficacy criterion and is therefore not considered an AE. Disease progression should be reported within the eCRF. If AEs/SAEs occur in relation to disease progression, the AEs/SAEs must be reported per AE/SAE reporting requirements described in Section 6.1.3 and Section 6.1.5.

6.1.5. Serious Adverse Events

6.1.5.1. Reporting of Serious Adverse Events

The Investigator must report all SAEs within 24 hours of becoming aware of the initial SAE or any follow-up information regarding the SAE using the SAE reporting contact information as printed on the SAE forms and in the SAE Completion guidelines.

For all SAEs, an SAE report form must be completed by the Investigator for all initial and follow-up SAEs. A follow-up SAE report must be completed each time an Investigator becomes aware of any additional information regarding the SAE. For the follow-up SAE Report Form, the following fields must be completed on each form: follow-up number, site number, patient/subject number, protocol number, and the SAE term(s) and date of awareness. Additionally, only the appropriate field(s) on the SAE Report Form where the Investigator received additional or updated information should be completed. Previously provided information does not have to be entered on the follow-up SAE Report Form.

Initial and follow-up SAE reports and any additional supporting documentation (eg, hospital reports, consultant reports, death certificates, autopsy reports, etc.) included with the SAE report should be sent to the Sponsor (or designee) within 24 hours of the Investigator/site awareness or receipt. If supporting documentation is provided, the Investigator should highlight all relevant and pertinent information. Also, any additional SAE documentation must be a clear photocopy with the patient's personal identifiers removed. The Investigator must sign and date all SAE forms.

The minimum information required for an initial SAE report is:

- Name of person sending the report (ie, name, address of Investigator)
- Patient identification (screening/randomization number, initials [if permitted by local data privacy regulations], NOT patient name)
  - Protocol number
  - Description of SAE
  - Causality assessment
  - Seriousness assessment

In case the Investigator has no ability to either fax or email an SAE (eg, due to technical issues), pharmacovigilance can be contacted by phone. If an SAE is reported via phone and during usual

business hours, the Sponsor pharmacovigilance (or designee) will capture the information on a telephone contact form or similar method. Outside usual business hours, the message will be recorded and the required follow-up actions initiated during the next business day. Once technical issues are resolved, the Investigator should fax or email the completed SAE form to the Sponsor (or designee).

After receipt of the initial report, the Sponsor (or designee) will review the information and, if necessary, contact the Investigator to obtain further information.

6.1.5.2. Submission and Distribution of Adverse Events/Serious Adverse Events

Per regulatory requirements, if an SAE is required to be submitted to a Regulatory Authority a copy of this report (CIOMS or MedWatch 3500A) will be distributed to the Investigators/site. The Investigator/site will submit a copy the report to their respective Institutional Review Board (IRB) or Independent Ethics Committee (IEC).

6.1.6. Events of Clinical Interest

Selected non-serious AEs and SAEs are also known as Events of Clinical Interest (ECIs) and must be recorded as such on the eCRF and reported within 24 hours to the Sponsor as noted for SAEs in Section 6.1.5.1.

6.1.6.1. Pembrolizumab

Patients are to be monitored through 90 days after the last dose of study treatment for the following ECI:

1. An overdose of pembrolizumab that is not associated with clinical symptoms or abnormal laboratory results. For this study, an overdose is defined as a dose ≥ 1000 mg (5 times the dose) of pembrolizumab. No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, the patient should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated
2. An elevated AST or ALT value that is ≥ 3× ULN concurrent with an elevated total bilirubin value that is ≥ 2× ULN and, at the same time, an alkaline phosphatase value that is < 2× ULN, as determined by protocol-specified laboratory testing or unscheduled laboratory testing.

   Note: These criteria are based upon available regulatory guidance documents.[63] 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 Trial File Binder (or equivalent).

6.1.6.2. Niraparib

Patients are to be monitored through 90 days after the last dose of study treatment for the following ECI:

1. Myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML). ECIs must be reported to the Sponsor as soon as the Investigator becomes aware of them.

2. An overdose is defined as the accidental or intentional ingestion or infusing of any dose of study treatment that exceeds the dose described in the protocol. Overdoses are not considered AEs; however, all overdoses should be recorded on a Serious Adverse Event Form (Section 6.1.5.1) within 24 hours of becoming aware. An overdose should be reported even if it does not result in an AE. Overdoses do not need to be recorded on the eCRF; dosing information is recorded on the eCRF.
3. In conjunction with the survival assessment, new malignancy information will be collected for all patients via telephone every 90 (±14) days (Section 7.2.10). Additionally, the relationship between cytogenetic abnormalities and safety parameters may be explored.

6.1.7. Pregnancy Reporting and Follow-up

Pregnancies occurring in patients enrolled in a study or in a female partner of a male patient must be reported and followed to outcome. If a female patient inadvertently becomes pregnant while on study treatment, the patient will immediately be removed from the study. Any pregnancies that occur within 120 days following the last dose of study treatment must be captured in the eCRF.

The Investigator should complete the Initial Pregnancy Notification report form and forward it to the Sponsor (or designee) within 24 hours of knowledge of the pregnancy. If there is an associated serious outcome, then both the Initial Pregnancy Notification report form and SAE report form should be completed.

The site will follow-up with the patient at least monthly and document the patient's status until the pregnancy has been completed or terminated. The 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. The Pregnancy Outcome report form should be completed and submitted to the Sponsor within 24 hours after the Investigator becomes aware of the pregnancy outcome.

In the event the pregnancy outcome occurs following the end of the study and database lock, the Investigator will report the pregnancy outcome to the Sponsor (or designee) within 24 hours after the outcome of the pregnancy is known to the Investigator in accordance with the procedure for reporting SAEs (see Section 6.1.5).

Pregnancy alone is not regarded as an AE unless there is a possibility that the study drug may have interfered with the effectiveness of a contraceptive medication. Elective abortions without complications should not be considered AEs unless they were therapeutic abortions. Hospitalization for normal delivery of a healthy newborn should not be considered an SAE. Pregnancy is not considered an SAE unless there is an associated serious outcome. Spontaneous abortions should always be reported as SAEs.

Any SAE that occurs during pregnancy must be recorded on the SAE Report Form (eg, maternal serious complications, therapeutic abortion, ectopic pregnancy, stillbirth, neonatal death, congenital anomaly, birth defect) and reported within 24 hours in accordance with the procedure for reporting SAEs.

6.1.8. Clinical Laboratory Assessments

The following laboratory variables will be determined in accordance with the schedule of events (Table 6). These tests will be performed by the local laboratory at the clinical site.

- **Complete blood count:**
  - Hemoglobin
  - Mean corpuscular volume
  - White blood cell count
  - Platelets
  - Mean platelet volume (optional)*
  - Differential white cell count

  * Note: Although mean platelet volume collection is optional, it is highly encouraged, especially for patients with high-grade thrombocytopenia.
- **Coagulation factors:**
  - International normalized ratio
  - Activated partial thromboplastin time
- **Serum chemistry:**
  - Sodium
  - Potassium
  - Calcium
  - Magnesium
  - Chloride
  - Glucose (fasting at baseline)
  - Creatinine
  - Urea or blood urea nitrogen
  - Amylase
  - Total bilirubin
  - Alkaline phosphatase
  - Aspartate aminotransferase
  - Alanine aminotransferase
  - Total protein
  - Albumin
  - Lactate dehydrogenase
- **Urinalysis:**
  - Specific gravity
  - Leukocyte esterase
  - Nitrite
  - Blood
  - Bilirubin
  - Protein
  - Glucose
  - Ketones
  - Urobilinogen
- **TSH, T3, or FT3, and FT4**
- **Serum CA-125 (OC patients only)**
- **Serum pregnancy testing / urine pregnancy testing**

Any laboratory values assessed as clinically significant should be recorded as an AE. If SAE criteria are met or the laboratory abnormality is an ECI (see Section 6.1.6), the event should be recorded and reported according to the SAE reporting process (see Section 6.1.5).

Hematological testing may occur more frequently than is specified in Table 6 when additional testing is medically indicated per Investigator judgment or if the event meets the criteria for niraparib dose modification (see Section 5.4.1). Additional tests may be performed at a laboratory facility other than the study site, but test results must be reported to the study site, the study site must keep a copy of test results with the patient's study file, and the results must be entered into the eCRF.

It is strongly recommended that any suspected MDS/AML case reported while a patient is receiving treatment or followed for post-treatment assessments be referred to a local hematologist, who must perform bone marrow aspirate and biopsy testing. A whole blood sample will also be collected for cytogenetic analysis (mutations of select myeloid-associated genes). Testing completed as part of standard of care is sufficient as long as the methods are acceptable to the Sponsor's Medical Monitor. The study site must receive a copy of the hematologist's report of aspirate/biopsy findings, which must include a classification according to World Health Organization (WHO),[64] and other sample testing reports related to MDS/AML. Report data will be entered in the appropriate eCRF pages and the site must keep a copy of all reports with the patient's study file.

Whole blood samples will be collected prior to the start of the study drug and at treatment discontinuation for cytogenetic analysis. Further details on sample collection and analysis can be found in the Study Manual.

6.1.9. Physical Examination and Vital Signs

Physical examinations, including height (screening only), weight, and vital signs (blood pressure [BP], pulse, and temperature), will be performed in accordance with the schedule of events (Table 6).

Any physical examination or vital signs assessed as clinically significant should be recorded as an AE or SAE. If SAE criteria are met or the abnormality is an ECI (see Section 6.1.6), the event should be recorded and reported according to the SAE reporting process (see Section 6.1.5).

6.1.10. Eastern Cooperative Oncology Group Performance Status

Performance status will be assessed using the ECOG scale (see Appendix G) in accordance with the schedule of events (Table 6). The same observer should assess performance status each time.

6.1.11. Additional Safety Assessments

All patients will undergo ECGs in accordance with the schedule of events (Table 6). Electrocardiograms should be performed prior to blood draws for PK. Patients will be supine and rested for approximately 2 minutes before ECGs are recorded.

Any ECG findings assessed as clinically significant should be recorded as an AE. If SAE criteria are met or the abnormality is an ECI (see Section 6.1.6), the event should be recorded and reported according to the SAE reporting process (see Section 6.1.5).

6.2. Demographics and Baseline Characteristics

Demographics and baseline characteristics consist of those variables that are assessed at screening/baseline.

6.2.1. Patient Eligibility

Compliance with inclusion and exclusion criteria will be assessed as outlined in Section 4.1 and Section 4.2.

6.2.2. Patient Demography

Patient demography consists of age at screening, race, ethnicity, and sex.

6.2.3. Disease History

For disease history the following will be documented:

- Date of first diagnosis
- Tumor type
- Stage at time of initial diagnosis
- Histology and grade of disease at diagnosis and most recent biopsy if additional biopsy performed
- Information on first anticancer treatment:
  - Intent (adjuvant, neoadjuvant, curative, palliative) (TNBC patients)
  - Date of start of first treatment
  - Agents used in first treatment
  - Date of last dose of first treatment
- Information on second and subsequent anticancer treatments:
  - Intent (adjuvant, neoadjuvant, curative, palliative) (TNBC patients)
  - Dates of start of all subsequent treatments
  - Agents in all subsequent treatments
  - Dates of last dose of all subsequent treatments
- Best response and toxicities (including hematologic events) for each prior anticancer treatment
- Date of recurrence for each prior anticancer treatment

6.2.4. Medical and Surgical History

Major medical and surgical history (including medication history), including history of thrombocytopenia, neutropenia, leukopenia, or anemia, will be collected. Details of any prior invasive malignancy will be collected. Medical and surgical history will be obtained by interviewing the patient or by reviewing the patient's medical records.

6.2.5. Previous and Concomitant Medications

Previous and concomitant medication will be documented as described in Section 5.7 Medications will be coded using World Health Organization Anatomical Therapeutic Chemical classification.

6.3. Efficacy Endpoint(s)

6.3.1. Evaluation of Tumor Response

6.3.1.1. Overview

The efficacy of combination treatment with niraparib and pembrolizumab will be evaluated by assessment of tumor response to treatment according to RECIST v1.1 [65] and irRECIST (see Section 6.3.1.3 and Section 6.3.1.4, respectively) per investigator assessment. Tumor marker data (CA-125) will not be used for defining objective responses or disease progression; however CA-125 can be used for clinical decisions. Clinical criteria such as the GCIG criteria [66] (see Appendix F) will also be considered for management of OC patients with clinical events (eg, bowel obstruction) without radiographic evidence of disease progression. The Study Committee will adjudicate such cases (see Section 9.12).

Response to treatment will primarily be based on Investigator evaluation of radiographic images. All radiographic images/scans at the time points specified in Table 6, as well as any unscheduled images/scans, will be sent by the study sites to the central imaging vendor upon acquisition and archived for potential future evaluation.

The process for image collection and transmission to the central imaging vendor can be found in the Site Imaging Manual.

Tumor imaging (chest, abdomen, and pelvis [plus brain if clinically indicated]) should be performed by CT (preferred). Magnetic resonance imaging should only be used when CT is contraindicated or for imaging of the brain, but the same imaging technique should be used in a patient throughout the study. CT scan is the more commonly used modality and is preferred for the majority of patients. An MRI can be utilized if clinically appropriate. Positron emission tomography/CT may be used according to RECIST guidelines.

If the chest (OC patients only) and/or brain (OC and TNBC patients) CT/MRI is clear at screening, repeat imaging of these areas is not required in the absence of clinical indication requiring follow-up.

Bone scans should be conducted per standard of care.

6.3.1.2. Timing of Radiographic Evaluations

All patients will undergo serial radiographic assessments to assess tumor response. Initial tumor imaging at screening must be performed within 21 days prior to the date of the first dose of study treatment. Scans performed prior to the signing of the ICF as part of routine clinical management are acceptable for use as initial tumor imaging if they are of diagnostic quality and performed within 21 days prior to first dose date.

The first on-study imaging assessment should be performed at 9 weeks (63 ± 7 days) from the date of first dose of study treatment; in the case of progressive disease (PD), a confirmatory image will be required 4 weeks later (eg, 13 weeks [91 ±7 days]) (see Section 6.3.1.4). Subsequent tumor imaging should be performed every 9 weeks (63 ± 7 days) or more frequently if clinically indicated and at the time of suspected disease progression. After 1 year of radiographic assessments, patients will have imaging performed every 12 weeks (84 ±7 days). Imaging should not be delayed for delays in cycle starts or extension of combination treatment cycle intervals.

Per RECIST v1.1 (see Appendix D), CR or PR should be confirmed by a repeat tumor imaging assessment. The tumor imaging for confirmation of response may be performed at the earliest 4 weeks after the first indication of response, or at the next scheduled scan (ie, 9 weeks later), whichever is clinically indicated.

Continue to perform imaging until whichever of the following occurs:

- The start of new anticancer treatment
- Withdrawal of consent
- Death
- End of the study (when responder or discontinuation status for all patients is known)

Patients who discontinue study treatment for reasons other than PD will continue post-treatment imaging studies for disease status follow-up at the same frequency as already followed, eg, every 9 or 12 weeks (± 7 days) depending on the length of treatment with the study combination drugs, until disease progression, start of a non–study anticancer treatment, withdrawal of consent to study participation, becoming lost to follow-up, death, or end of the study.

6.3.1.3. Assessment of Response by RECIST

RECIST v1.1 will be used by the Investigator as the primary measure for assessment of tumor response, date of disease progression, and as a basis for all protocol guidelines related to disease status. Note that irRECIST will be followed in cases of disease progression to assess continuation of treatment in clinically stable patients until progression is confirmed (see Section 6.3.1.4).

Details on RECIST v1.1, including evaluation of target and non-target lesions and definitions of response are provided in Appendix D.

6.3.1.4. Assessment of Response by Immune-Related RECIST

RECIST v1.1 will be adapted to account for the unique tumor response characteristics seen during treatment with pembrolizumab. Immunotherapeutic agents such as pembrolizumab may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents and can manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions. Standard RECIST v1.1 may, thus, not provide an accurate response assessment of immunotherapeutic agents such as pembrolizumab. irRECIST will be used by local site Investigators to assess tumor response and progression and make treatment decisions.

Therefore, RECIST v1.1 will be used with the following adaptations (ie, irRECIST) (see also Appendix E).

- If repeat imaging shows < 20% increase in tumor burden compared with nadir, stable or improved previous new lesion (if identified as cause for initial PD), and stable/improved non-target disease (if identified as cause for initial PD), treatment may be continued / resumed, and the next tumor imaging should be conducted according to the protocol schedule of every 9 weeks (63 ± 7 days) (or every 12 weeks [84 ± 7 days] if after 1 year).
- If repeat imaging confirms PD due to any of the scenarios listed below, patients will be discontinued from study therapy.

  In determining whether or not the tumor burden has increased or decreased per irRECIST, the local site Investigator should consider all target and non-target lesions, as well as any incremental new lesion(s).

  If ANY of the following occur by irRECIST on repeat imaging, PD is confirmed:

  – Tumor burden remains ≥ 20% and at least 5-mm absolute increase compared with nadir
  – Non-target disease resulting in initial PD is worse (qualitative)
  – New lesion resulting in initial PD is worse (qualitative)
  – Additional new lesion(s) since last evaluation
  – Additional new non-target progression since last evaluation

In patients who have initial evidence of radiological PD, it is at the discretion of the treating physician whether to continue a patient on study treatment until repeat imaging is obtained. This clinical judgment decision should be based on the patient's overall clinical condition, including performance status, clinical symptoms, and laboratory data. Patients may receive pembrolizumab treatment while waiting for confirmation of PD if they are clinically stable as defined by the following criteria:

- Absence of signs and symptoms indicating clinically significant progression of disease, including worsening of laboratory values
- No decline in ECOG performance status
- Absence of rapid progression of disease
- Absence of progressive tumor at critical anatomical sites (eg, cord compression) requiring urgent alternative medical intervention

When feasible, patients should not be discontinued until progression is confirmed. This allowance to continue treatment despite initial radiologic progression takes into account the observation that some patients can have a transient tumor flare in the first few months after the start of immunotherapy but with subsequent disease response. Patients who are deemed clinically unstable are not required to have repeat imaging for confirmation of progressive disease.

6.3.2. Efficacy Endpoints

6.3.2.1. Objective Response Rate

The primary efficacy endpoint is ORR, defined as the proportion of patients achieving CR or PR as assessed by the Investigator per RECIST (v1.1) (Appendix D). Tumor assessments after the initiation of further anticancer therapy are excluded for the assessment of best overall response.

ORR by irRECIST (Section 6.3.1.4) will also be evaluated as a secondary endpoint.

6.3.2.2. Duration of Response

Duration of response will be evaluated as a secondary endpoint and is defined as the time from first documentation of CR or PR by RECIST v1.1 until: (1) the time of first documentation of disease progression per RECIST v1.1 (Appendix D); and (2) the time of first documentation of disease progression per irRECIST (Section 6.3.1.4). Note that date of progression based on either RECIST v1.1 or irRECIST may be overwritten in patients with OC if clinical criteria (Appendix F) indicate earlier progression as adjudicated by the Study Committee (Section 9.12).

DOR by irRECIST (Section 6.3.1.4) will also be evaluated as a secondary endpoint.

6.3.2.3. Disease Control Rate

Disease control rate will be assessed as a secondary endpoint and is defined as the proportion of patients achieving CR, PR, or stable disease (SD) as assessed by the Investigator per RECIST v1.1 (Appendix D) and irRECIST (Section 6.3.1.4).

6.3.2.4. Progression-Free Survival

Progression-free survival will be assessed as a secondary endpoint and is defined as the time from enrollment to the earlier date of assessment of progression or death by any cause in the absence of progression based on: (1) the time of first documentation of disease progression per RECIST v1.1 (Appendix D); and (2) the time of first documentation of disease progression per irRECIST (Section 6.3.1.4). Note that date of progression based on either RECIST v1.1 or irRECIST may be overwritten in patients with OC if clinical criteria (Appendix F) indicate earlier progression as adjudicated by the Study Committee (Section 9.12).

6.3.2.5. Overall Survival

Overall survival will be assessed as a secondary endpoint and is defined as the time from date of first dose of study treatment to the date of death by any cause. New malignancy information will also be collected as part of this assessment (Section 7.2.10).

6.4. Pharmacokinetics

Pharmacokinetic samples will be collected from patients in both Phase 1 and Phase 2. An overview of sampling times for blood for PK analysis and concurrent ECG assessments, see Table 8 (Phase 1) and Table 9 (Phase 2).

For niraparib and major metabolite M1, the plasma samples from both Phase 1 and Phase 2 patients will be analyzed using liquid chromatography with mass spectroscopic detection (LC-MS-MS). For pembrolizumab in Phase 1, serum PK samples will be collected according to

the schedule defined in Section 6.4.1, and the samples in an individual patient may be analyzed using enzyme-linked immunosorbent assay (ELISA) if required for understanding of AEs.

The timing of each required sample collection listed in Table 7 and Table 8 for niraparib and major metabolite M1, and pembrolizumab for PK blood draws will be recorded.

Complete instructions for collection, processing, shipping, and handling of samples are detailed in the Study Manual.

6.4.1. Phase 1

For all patients in Phase 1, blood samples for measurements of plasma levels of niraparib and M1 will be obtained on Day 1 of Cycles 1 and 2 at the following time points: 0 (predose within 30 minutes) and 1 hour (±5 minutes), 2 hours (±5 minutes), 4 hours (±5 minutes), 6 hours (±5 minutes), 8 hours (±10 minutes), and 24 hours (±30 minutes) postdose.

In addition, blood samples for measurements of drug levels of niraparib and M1 will be obtained on Day 1 of Cycles 4 and 8 at the following time points: 0 (predose within 30 minutes) and 2 hours (±15 minutes) postdose.

For all patients in Phase 1, blood samples for pembrolizumab will only be analyzed to understand an AE in an individual patient. The samples will be collected according to the following schedule, stored, and analyzed as needed. Predose blood samples for trough measurement of serum levels of pembrolizumab will be obtained at Cycles 1, 2, 4, and 8. All predose trough samples should be drawn within 30 minutes (±5 minutes) before infusion of pembrolizumab. Additional postdose peak PK serum samples will be drawn within 30 minutes after the end of the pembrolizumab infusion at Cycles 1 and 8. An additional single PK serum sample should be drawn at 24 hours (±30 minutes) (Day 2), 168 hours (±2 hours) (Day 8), and 336 hours (±4 hours) (Day 15) after Cycle 1 dosing.

6.4.2. Phase 2

For patients in Phase 2, blood samples for measurements of plasma levels of niraparib and M1 will be obtained on Day 1 of Cycles 1, 2, 4, and 8 at the following time points: 0 (predose within 30 minutes) and 2 hours (±15 minutes) postdose.

6.4.3. Determination of Pharmacokinetic Parameters

Model predicted area under the concentration × time curves (AUCs) will be derived. Parameters of interest are AUC, minimum concentration (C_{min}), maximum concentration (C_{max}), clearance after oral administration (CL/F), volume of distribution after oral administration (V_z/F), AUC at steady state (AUC_{ss}), C_{min} at steady state ($C_{min,ss}$), and C_{max} at steady state ($C_{max,ss}$).

6.5. Biomarkers

Biomarker classifiers will be evaluated in archival OC and TNBC tumor samples obtained during screening. In addition, in the subset of patients who undergo serial biopsies, biomarkers will be evaluated in fresh tumor samples obtained at screening, 1 to 3 days before or on C3D1 prior to pembrolizumab infusion and, whenever possible, at the time of disease progression. Core biopsies (3 to 6) are preferred; fine needle aspirate, frozen sample, plastic embedded sample, cell block, clot, or cytologic specimen will not be acceptable for analysis.

Blood samples for biomarker analysis will be obtained predose on Day 1 of Cycles 1 and Cycle 2, as well as at the EOT visit for analysis of tumor-related circulating biomarkers, such as circulating tumor cells and circulating tumor DNA. Biopsy samples will be collected and managed centrally, and tumor sections will be distributed to the designated translational research laboratories. DNA/RNA will be extracted from samples at a central location and analyzed for exploratory biomarkers including HRD mutational status of genes relevant for OC and TNBC, and RNA expression. Immunohistochemistry for PD-L1, as well as additional immune checkpoint proteins and markers for infiltrating immune cellswill also be performed. Other exploratory analyses may be performed with the remaining samples.

HRD status, PD-L1 positivity and other biomarkers will be correlated with efficacy outcomes. Special attention will be devoted to subsets of OC and TNBC which may have distinct underlying DNA repair pathway deficiency (homologous recombination, nucleotide excision repair (NER), and mismatch repair (MMR) deficiency) and distinct drug responses.

Details on blood and tissue sample collection and analysis can be found in the Study Manual.

Samples from blood and tumor will be stored and may be used at a later time for biomarker testing, including potential to bridging to candidate companion diagnostic assays.

7. STUDY CONDUCT

7.1. Schedule of Procedures

A schedule of study procedures is provided in Table 6 and Table 7.

Table 6 Schedule of Events

Cycle/Visit:	Screening	Cycle 1				Subsequent Cycles[1]		EOT[2]	Safety Follow-up	Follow-up Assessments (every 90 ± 14 days) via telephone
Day: / Procedure:	-21 to -1	1	2[3]	8[4]	15	Cycle n, Day 1	Cycle 2, Day 2[3]		30 + 7 days	
Informed consent	X									
Inclusion/exclusion criteria review	X	X								
Demographics	X									
Medical, surgical, cancer, and medication history	X									
Archival tissue[5]	X									
Optional serial tumor biopsy[6]	X [6,7]					X[6]		X[6]		
Blood sample for exploratory biomarkers		X				X[8]		X		
Blood sample for PK[9]		X	**X[3]**	**X[3]**	**X[3]**	X	**X[3]**			
Tumor assessment (RECIST and irRECIST)	X[7,10]					X[10]		X[10]	X[10]	X[10]
Laboratory assessments:						X[11]			X[12]	
CBC[13]	X[7]	X[14]		X[4]	X	X		X	X	
Serum chemistry	X[7]	X[14]			X	X		X	X	X[15]
Coagulation	X[7]				**X[3]**	**X[3]**,16				
Pregnancy test	X[7,17]					X[17]			X[17]	X[17]
Serum CA-125 (OC patients only)	X[7]	X[14]				X		X[18]	X[18]	
Urinalysis	X[7]	X[14]				X		X	X	
TSH, T3 or FT3, and FT4	X[7,19]					X[19]		X[19]	X[19]	
ECG	X[7,20]	X[20]				X[20]		X[20]		
Physical examination	X[7]							X		

Cycle/Visit:	Screening	Cycle 1				Subsequent Cycles[1]		EOT[2]	Safety Follow-up	Follow-up Assessments (every 90 ± 14 days) via telephone
Day: / Procedure:	-21 to -1	1	2[3]	8[4]	15	Cycle n, Day 1	Cycle 2, Day 2[3]		30 + 7 days	
Symptom-directed physical examination		X			X	X			X	
Vital signs, height, and weight[21]	X[7]	X		X[3]	X	X		X	X	
ECOG performance status	X					X		X		
Concomitant medications	X	X		X[3]	X	X		X	X	
Adverse event monitoring	X	X		X[3]	X	X		X	X[22]	X[22]
Pembrolizumab study treatment administered[23]		X				X				
Niraparib study treatment dispensed/collected[24]		X[25]				X[25]		X		
Survival assessment, including new malignancy information										X
Sample collection (whole blood) for cytogenetic analysis	X[26]							X[26]		
Bone marrow aspirate and biopsy and sample collection (whole blood) for cytogenetic analysis		X[27]								

Abbreviations: AE = adverse event; CBC = complete blood count; CT = computed tomography; ECG = electrocardiogram; ECI = event of clinical interest; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; irRECIST = immune-related RECIST; IV = intravenous; MDS = myelodysplastic syndrome; MRI = magnetic resonance imaging; OC = ovarian cancer; PK = pharmacokinetics; RECIST = Response Evaluation Criteria in Solid Tumors; RP2D = recommended Phase 2 dose; SAE = serious adverse event; TNBC = triple-negative breast cancer.

[1] Treatment cycles are 21 days long, with visits on Day 1 of each cycle beyond Cycle 1 unless otherwise specified. Visits for subsequent cycles continue every 21 days (± 3 days) until study treatment discontinuation.

[2] EOT visit should be completed within 7 days of the last dose of study drug.

[3] Required for Phase 1 patients only.

[4] Patients in Phase 1 are required to have an in-clinic visit on Day 8 with CBC done at the study center's laboratory**.** For patients in Phase 2, collection of blood for the Cycle 1/Day 8 CBC may be done at the study center's laboratory or at a laboratory local to the patient, if approved by the Principal Investigator as an

adequate laboratory. The laboratory must have the capability to provide results to the Principal Investigator electronically or by fax within 24 hours of blood collection.

[5] For patients who do not have archival tissue, tissue from a fresh biopsy must be obtained prior to study treatment initiation. See the Study Manual for details on sample collection and processing.

[6] In patients who consent to serial biopsies, fresh tumor sample is to be obtained at screening, 1 to 3 days before or on C3D1 prior to pembrolizumab infusion, and when possible, at the time of disease progression. See the Study Manual for details on sample collection and processing. The serial biopsies at different time points should be on the same lesion preferably. A core biopsy is recommended; if an excisional or incisional biopsy is to be performed, it must be conducted on a non-target lesion. If a patient has had a biopsy within 12 weeks prior to entering screening, that biopsy may be accepted as the screening biopsy.

[7] Standard of care tests/procedures, including biopsy, radiographic scans, laboratory assessments (fasting glucose at baseline), ECG, physical examination, vital signs, height, and weight, performed prior to the patient signing the informed consent form can be used as part of the screening assessments as long as the tests/procedures meet the protocol-required timelines (ie, within 21 days of first dose for these procedures with the exception of the biopsy, which may have been conducted within 12 weeks of first dose, and pregnancy test, which must be conducted within 72 hours of first dose) and any relevant guidelines (eg, diagnostic quality for scans).

[8] Required on Day 1 of Cycle 2 only.

[9] Blood samples are to be obtained for niraparib and major metabolite M1, pembrolizumab PK assessments; see Table 8 and Table 9 for the detailed schedule.

[10] Tumor assessment per RECIST and irRECIST via CT or MRI (chest, abdomen, and pelvis [brain, only if clinically indicated]) required at screening, every 9 weeks (63 ±7 days) from Cycle 1/Day 1 for the first year, and then every 12 weeks (84 ±7 days) until progression; at the time of progression, a final follow up set of images is required if not done within the last 4 weeks. The same modality (CT or MRI) should be used throughout the study for a given patient. If the chest (OC patients only) or brain (OC and TNBC patients) CT/MRI is clear at screening, repeat imaging of these areas is not required in the absence of clinical indication requiring follow-up. Positron emission tomography/CT may be used according to RECIST v1.1 guidelines. Bone scans should be conducted per standard of care. Timing of images will not be delayed for treatment interruptions, and tumor assessment should occur according to this schedule regardless of whether study treatment is interrupted. If a patient discontinues treatment for a reason other than progression or death, withdrawal of consent, or loss to follow-up, scans and CA-125 testing (OC patients only) should continue at the specified intervals.

[11] May be done within 24 hours prior to the visit.

[12] May be done at the study center's local laboratory or at a laboratory local to the patient if the laboratory is included on FDA Form 1572.

[13] If dose interruption or modification is required at any point on study because of hematologic toxicity, twice-weekly (thrombocytopenia or neutropenia) or once weekly (anemia) blood draws (CBC) will be monitored until the AE resolves, and to ensure safety of the new dose, weekly blood draws for CBC will also be required for a subsequent 3 week cycle after the AE has been resolved to the specified levels, after which monitoring every 3 weeks may resume.

[14] If screening laboratory testing (CBC, serum chemistry, CA-125, urinalysis) is performed within 72 hours of first dose of study treatment on Day 1, repeat testing is not required.

[15] Serum chemistry to be conducted on Day 90 post-treatment (or to a minimum of 30 days post-treatment if the patient starts alternate anticancer therapy) to assess for possible ECI (see Section 6.1.6). The assessment may be done at the study center's laboratory or at a laboratory local to the patient, if approved by the Principal Investigator as an adequate laboratory. This should be the same laboratory as conducted any Cycle 1/Day 8 CBC samples.

[16] Required for Phase 1 patients only. Required on Day 1 of Cycle 2 and Cycle 3 only.

[17] Negative serum pregnancy test required within 72 hours prior to first dose of study treatment on Day 1 for females of childbearing potential; urine pregnancy test conducted every 3 cycles for duration of study (ie, Cycle 4, Cycle 7, etc.) and at the 30-day safety follow-up visit. Pregnancy status must be determined 120 days post treatment.

[18] If a patient discontinues treatment for a reason other than progression or death, withdrawal of consent, or loss to follow-up, CA-125 testing (OC patients only) should continue at the intervals specified for tumor assessments.

[19] Blood samples for TSH, T3 or FT3, and FT4 are to be collected at screening, every 6 weeks from C1D1, and at EOT. Blood samples for TSH, T3 or FT3, and FT4 to be collected at 30-day post-treatment safety follow-up only if assessment is clinically indicated.

[20] Patients will undergo ECG monitoring as per Table 8 and Table 9.

[21] Vital signs include blood pressure, pulse, and temperature. Height obtained at screening only.

[22] AEs are required to be captured through 30 days after cessation of study treatment, SAEs and ECIs (see Section 6.1.6) are required to be captured through 90 days after cessation of study treatment (or to a minimum of 30 days post-treatment if the patient starts alternate anticancer therapy), and any pregnancies that occur within 120 days post-treatment are to be captured.

[23] Administer pembrolizumab once every 21 days (200 mg IV). Pembrolizumab may be administered up to 3 days before or after the scheduled Day 1 of each cycle after Cycle 2 due to administrative reasons.

[24] See Table 10 for details of niraparib administration in Phase 1, and Section 3.1.2.1 for the RP2D of the combination. Niraparib dose may be escalated on or after C3D1 from 200 mg daily to 300 mg daily if hemoglobin ≥ 9 g/dL, platelets ≥ 100,000/µL and neutrophils ≥ 1500/µL for all labs performed during the first two cycles after discussion with Medical Monitor or Designee.

[25] Niraparib dose administered upon completion of pembrolizumab infusion.

[26] Blood samples collected at screening and EOT will be stored for evaluation if the Sponsor's medical monitor finds evaluation necessary for assessing niraparib-related risk for MDS/AML (eg, the patient develops MDS/AML). Mutation profile before and after study treatment will be compared to determine whether any mutations were present prior to study treatment. Additional details on sample collection and analysis are in the Study Manual.

[27] It is strongly recommended that any suspected MDS/AML case reported while a patient is receiving treatment or being followed for post-treatment assessments be referred to a local hematologist, who must perform bone marrow aspirate and biopsy testing. A whole blood sample will also be collected for cytogenetic analysis (mutations of select myeloid-associated genes). Testing completed as part of standard of care is sufficient as long as the methods are acceptable to the Sponsor's medical monitor. The study site must receive a copy of the hematologist's report of aspirate/biopsy findings, which must include a classification according to WHO criteria, [(64)] and other sample testing results related to MDS/AML.

Table 7 Schedule of Events - Phase 2 Only

Cycle/Visit:	Screening	Cycle 1			Subsequent Cycles[1]	EOT[2]	Safety Follow-up	Follow-up Assessments (every 90 ± 14 days) via telephone
Day:	-21 to -1	1	8[3]	15	Cycle n, Day 1		30 + 7 days	
Procedure:								
Informed consent	X							
Inclusion/exclusion criteria review	X	X						
Demographics	X							
Medical, surgical, cancer, and medication history	X							
Archival tissue[4]	X							
Optional serial tumor biopsy[5]	X [5,6]				X[5]	X[5]		
Blood sample for exploratory biomarkers		X			X[7]	X		
Blood sample for PK[8]		X			X			
Tumor assessment (RECIST and irRECIST)	X[6,9]				X[9]	X[9]	X[9]	X[9]
Laboratory assessments:					X[10]		X[11]	
CBC[12]	X[6]	X[13]	X[3]	X	X	X	X	
Serum chemistry	X[6]	X[13]		X	X	X	X	X[14]
Coagulation	X[6]							
Pregnancy test	X[6,15]				X[15]		X[15]	X[15]
Serum CA-125 (OC patients only)	X[6]	X[13]			X	X[16]	X[16]	
Urinalysis	X[6]	X[13]			X	X	X	
TSH, T3 or FT3, and FT4	X[6,17]				X[17]	X[17]	X[17]	
ECG	X[6,18]	X[18]			X[18]	X[18]		
Physical examination	X[6]					X		
Symptom-directed physical examination		X		X	X		X	

Cycle/Visit:	Screening	Cycle 1			Subsequent Cycles[1]	EOT[2]	Safety Follow-up	Follow-up Assessments (every 90 ± 14 days) via telephone
Day:	-21 to -1	1	8[3]	15	Cycle n, Day 1		30 + 7 days	
Procedure:								
Vital signs, height, and weight[19]	X[6]	X		X	X	X	X	
ECOG performance status	X				X	X		
Concomitant medications	X	X		X	X	X	X	
Adverse event monitoring	X	X		X	X	X	X[20]	X[20]
Pembrolizumab study treatment administered[21]		X			X			
Niraparib study treatment dispensed/collected[22]		X[23]			X[23]	X		
Survival assessment, including new malignancy information								X
Sample collection (whole blood) for cytogenetic analysis	X[24]					X[24]		
Bone marrow aspirate and biopsy and sample collection (whole blood) for cytogenetic analysis		X[25]						

Abbreviations: AE = adverse event; CBC = complete blood count; CT = computed tomography; ECG = electrocardiogram; ECI = event of clinical interest; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; irRECIST = immune-related RECIST; IV = intravenous; MDS = myelodysplastic syndrome; MRI = magnetic resonance imaging; OC = ovarian cancer; PK = pharmacokinetics; RECIST = Response Evaluation Criteria in Solid Tumors; RP2D = recommended Phase 2 dose; SAE = serious adverse event; TNBC = triple-negative breast cancer.

[1] Treatment cycles are 21 days long, with visits on Day 1 of each cycle beyond Cycle 1 unless otherwise specified. Visits for subsequent cycles continue every 21 days (± 3 days) until study treatment discontinuation.

[2] EOT visit should be completed within 7 days of the last dose of study drug.

[3] For patients in Phase 2, collection of blood for the Cycle 1/Day 8 CBC may be done at the study center's laboratory or at a laboratory local to the patient, if approved by the Principal Investigator as an adequate laboratory. The laboratory must have the capability to provide results to the Principal Investigator electronically or by fax within 24 hours of blood collection.

[4] For patients who do not have archival tissue, tissue from a fresh biopsy must be obtained prior to study treatment initiation. See the Study Manual for details on sample collection and processing.

[5] In patients who consent to serial biopsies, fresh tumor sample is to be obtained at screening, 1 to 3 days before or on C3D1 prior to pembrolizumab infusion, and when possible, at the time of disease progression. See the Study Manual for details on sample collection and processing. The serial biopsies at different time points should be on the same lesion preferably. A core biopsy is recommended; if an excisional or incisional biopsy is to be performed, it must be conducted on a non-target lesion. If a patient has had a biopsy within 12 weeks prior to entering screening, that biopsy may be accepted as the screening biopsy.

[6] Standard of care tests/procedures, including biopsy, radiographic scans, laboratory assessments (fasting glucose at baseline), ECG, physical examination, vital signs, height, and weight, performed prior to the patient signing the informed consent form can be used as part of the screening assessments as long as the

tests/procedures meet the protocol-required timelines (ie, within 21 days of first dose for these procedures with the exception of the biopsy, which may have been conducted within 12 weeks of first dose, and pregnancy test, which must be conducted within 72 hours of first dose) and any relevant guidelines (eg, diagnostic quality for scans).

[7] Required on Day 1 of Cycle 2 only.

[8] Blood samples are to be obtained for niraparib and and major metabolite M1, pembrolizumab PK assessments; see Table 8 and Table 9 for the detailed schedule.

[9] Tumor assessment per RECIST and irRECIST via CT or MRI (chest, abdomen, and pelvis [brain, only if clinically indicated]) required at screening, every 9 weeks (63 ±7 days) from Cycle 1/Day 1 for the first year, and then every 12 weeks (84 ±7 days) until progression; at the time of progression, a final follow up set of images is required if not done within the last 4 weeks. The same modality (CT or MRI) should be used throughout the study for a given patient. If the chest (OC patients only) or brain (OC and TNBC patients) CT/MRI is clear at screening, repeat imaging of these areas is not required in the absence of clinical indication requiring follow-up. Positron emission tomography/CT may be used according to RECIST v1.1 guidelines. Bone scans should be conducted per standard of care. Timing of images will not be delayed for treatment interruptions, and tumor assessment should occur according to this schedule regardless of whether study treatment is interrupted. If a patient discontinues treatment for a reason other than progression or death, withdrawal of consent, or loss to follow-up, scans and CA-125 testing (OC patients only) should continue at the specified intervals.

[10] May be done within 24 hours prior to the visit.

[11] May be done at the study center's local laboratory or at a laboratory local to the patient if the laboratory is included on FDA Form 1572.

[12] If dose interruption or modification is required at any point on study because of hematologic toxicity, twice-weekly (thrombocytopenia or neutropenia) or once weekly (anemia) blood draws (CBC) will be monitored until the AE resolves, and to ensure safety of the new dose, weekly blood draws for CBC will also be required for a subsequent 3 week cycle after the AE has been resolved to the specified levels, after which monitoring every 3 weeks may resume.

[13] If screening laboratory testing (CBC, serum chemistry, CA-125, urinalysis) is performed within 72 hours of first dose of study treatment on Day 1, repeat testing is not required.

[14] Serum chemistry to be conducted on Day 90 post-treatment (or to a minimum of 30 days post-treatment if the patient starts alternate anticancer therapy) to assess for possible ECI (see Section 6.1.6). The assessment may be done at the study center's laboratory or at a laboratory local to the patient, if approved by the Principal Investigator as an adequate laboratory. This should be the same laboratory as conducted any Cycle 1/Day 8 CBC samples.

[15] Negative serum pregnancy test required within 72 hours prior to first dose of study treatment on Day 1 for females of childbearing potential; urine pregnancy test conducted every 3 cycles for duration of study (ie, Cycle 4, Cycle 7, etc.) and at the 30-day safety follow-up visit. Pregnancy status must be determined 120 days post treatment.

[16] If a patient discontinues treatment for a reason other than progression or death, withdrawal of consent, or loss to follow-up, CA-125 testing (OC patients only) should continue at the intervals specified for tumor assessments.

[17] Blood samples for TSH, T3 or FT3, and FT4 are to be collected at screening, every 6 weeks from C1D1, and at EOT. Blood samples for TSH, T3 or FT3, and FT4 to be collected at 30-day post-treatment safety follow-up only if assessment is clinically indicated.

[18] Patients will undergo ECG monitoring as per Table 8 and Table 9.

[19] Vital signs include blood pressure, pulse, and temperature. Height obtained at screening only.

[20] AEs are required to be captured through 30 days after cessation of study treatment, SAEs and ECIs (see Section 6.1.6) are required to be captured through 90 days after cessation of study treatment (or to a minimum of 30 days post-treatment if the patient starts alternate anticancer therapy), and any pregnancies that occur within 120 days post-treatment are to be captured.

[21] Administer pembrolizumab once every 21 days (200 mg IV). Pembrolizumab may be administered up to 3 days before or after the scheduled Day 1 of each cycle after Cycle 2 due to administrative reasons.

[22] See Table 11 for details of niraparib administration in Phase 2. See Section 3.1.2.1 for the RP2D of the combination. Niraparib dose may be escalated on or after C3D1 from 200 mg daily to 300 mg daily if hemoglobin ≥ 9 g/dL, platelets ≥ 100,000/µL and neutrophils ≥ 1500/µL for all labs performed during the first two cycles after discussion with Medical Monitor or Designee.

[23] Niraparib dose administered upon completion of pembrolizumab infusion.

[24] Blood samples collected at screening and EOT will be stored for evaluation if the Sponsor's medical monitor finds evaluation necessary for assessing niraparib-related risk for MDS/AML (eg, the patient develops MDS/AML). Mutation profile before and after study treatment will be compared to determine whether any mutations were present prior to study treatment. Additional details on sample collection and analysis are in the Study Manual.

[25] It is strongly recommended that any suspected MDS/AML case reported while a patient is receiving treatment or being followed for post-treatment assessments be referred to a local hematologist, who must perform bone marrow aspirate and biopsy testing. A whole blood sample will also be collected for cytogenetic analysis (mutations of select myeloid-associated genes). Testing completed as part of standard of care is sufficient as long as the methods are acceptable to the Sponsor's medical monitor. The study site must receive a copy of the hematologist's report of aspirate/biopsy findings, which must include a classification according to WHO criteria, (64) and other sample testing results related to MDS/AML.

Table 8 Pharmacokinetic Sampling and Electrocardiogram Schedule – Phase 1

Visit/Cycle:	Screen	Cycle 1					Cycle 2			Cycle 4		Cycle 8		EOT
Study Day:	-21 to -1	1		2	8	15	1		2	1		1		
Assessment: / Time Point:	ECG	ECG	Blood	Blood	Blood	Blood	ECG	Blood	Blood	ECG	Blood	ECG	Blood	ECG
Anytime	X													X
Pre Niraparib dose[a]		X	X				X	X		X	X	X	X	
Post Niraparib dose														
1 hr (±5 min)			X					X						
2 hr (±5 min)		X	X				X	X			X[b]		X[b]	
4 hr (±5 min)			X					X						
6 hr (±5 min)			X					X						
8 hr (±10 min)			X					X						
24 hr (±30 min)				X					X					
Pre Pembrolizumab infusion[c]			X					X			X		X	
Post Pembrolizumab infusion[d]														
30 min (±5 minutes)			X										X	
24 hrs (±30 minutes)				X										
168 hrs (±2 hours)					X									
336 hour (±4 hours)						X								

Abbreviations: ECG = electrocardiogram; EOT = end of treatment; hr = hour; min = minute

[a] To be obtained within 30 minutes of niraparib dose; ECG should be conducted prior to blood draws.

[b] Sample to be obtained 2 hours ±15 minutes post niraparib dose.

[c] To be obtained within 30 minutes (±5 minutes) before the start of infusion of pembrolizumab; samples will only be analyzed to understand any AE in an individual patient.

[d] Samples will only be analyzed to understand an AE in an individual patient. Times are relative to the end of the infusion.

Table 9 Pharmacokinetic Sampling and Electrocardiogram Schedule – Phase 2

Visit/Cycle:	Screen (Days -21 to -1)	Cycle 1/Day 1		Cycle 2/Day 1		Cycle 4/Day 1		Cycle 8/ Day 1		EOT
Assessment: / Time Point:	ECG	ECG	Blood	ECG	Blood	ECG	Blood	ECG	Blood	ECG
Anytime	X									X
Pre Niraparib dose[a]		X	X	X	X	X	X	X	X	
Post Niraparib dose										
2 hr (±15 min)		X	X	X	X		X		X	

Abbreviations: ECG = electrocardiogram; EOT = end of treatment; hr = hour; min = minute

[a] To be obtained within 30 minutes of niraparib dose; ECG should be conducted prior to blood draws.

Table 10 Niraparib Administration – Phase 1

Cycle	1					
Day	**1**	**7**	**8**	**14**	**15**	**21**
Niraparib 200 mg QD PO (Dose Level 1)[a]	X----------	----------	----------	----------	----------	----------X
Niraparib 300 mg QD PO (Dose Level 2)[a]	X----------	----------	----------	----------	----------	----------X
Niraparib 200 or 300 mg QD PO (Dose Level -1)[a] [b]	X----------	----------	----------	----------X		
Niraparib 200 or 300 mg QD PO (Dose Level -2)[a] [b]	X----------	----------X				

Abbreviations: PO = oral; QD = once daily

[a] For all dose levels, niraparib will be administered during Cycle 1 in combination with pembrolizumab (200 mg IV on Day 1 of the 21-day cycle).

[b] Schedule of niraparib administration will be determined by agreement between Investigators and Sponsor (see Section 9.12).

Table 11 Niraparib Administration – Phase 2

Cycle	**N**[a]
Day	**1 to 21**
Niraparib 200 mg QD PO Phase 2	X

Abbreviations: PO = oral; QD = once daily

[a] The RP2D to be implemented in the Phase 2 portion of this study is niraparib 200 mg/day PO on days 1-21 and pembrolizumab 200 mg IV on day 1 of each 21-day cycle; niraparib dose may be escalated on or after C3D1 from 200 mg daily to 300 mg daily if hemoglobin ≥ 9 g/dL, platelets ≥ 100,000/µL and neutrophils ≥ 1500/µL for all labs performed during the first two cycles after discussion with Medical Monitor or Designee.

7.2. Procedures by Visit

7.2.1. Screening (Day -21 to Day -1)

Standard of care tests/procedures, including laboratory assessments, ECG, physical examination, vital signs, height, and weight, performed prior to the patient signing the informed consent form can be used as part of the screening assessments as long as the tests/procedures meet the protocol-required timelines (ie, within 21 days of first with the exception of the pregnancy test which must be conducted within 72 hours of first dose). Note that source documents must clearly identify the standard of care tests/procedures that are used for screening and the results of these tests/procedures must be entered in the eCRF.

At screening, the following procedures/tests will be performed:

- Obtain written informed consent
  - A single study ICF will be signed before any study procedures
- Inclusion/exclusion criteria review
- Demographics
- Medical/surgical/cancer/medication history
- Archival tumor sample for biomarker testing
  - For patients who do not have archival tissue, tissue from a fresh biopsy must be obtained prior to study treatment initiation. See the Study Manual for details on sample collection and processing.
- Optional tumor biopsy for biomarker testing
  - For patients who consented to serial biopsies. See the Study Manual for details on sample collection and processing. If a patient has had a biopsy within 12 weeks prior to entering screening, that biopsy may be accepted in lieu of the screening biopsy.
- Sample collection (whole blood) for cytogenetic analysis.
- Tumor assessment (CT/MRI) for determination of measurable disease (RECIST v1.1)
  - Chest, abdomen, and pelvis (brain, if clinically indicated) CT (preferred method) or MRI (if clinically indicated). If the chest (applies to OC patients only) and/or brain (applies to OC and TNBC patients) CT/MRI is clear at screening, repeat imaging is not required in the absence of clinical indication requiring follow-up. Positron emission tomography (PET)/CT may be used according to RECIST v1.1 guidelines.
  - Scans performed prior to informed consent as part of routine clinical management are acceptable for use as initial tumor imaging if they are of diagnostic quality and are performed within 21 days prior to first dose date.
- Bone scans performed per standard of care.

- Laboratory assessments:
  - Serum pregnancy test for women of childbearing potential within 72 hours of first dose of study treatment
  - CBC
  - Serum chemistry
  - TSH, T3 or FT3, and FT4
  - Coagulation
  - Serum CA-125 (OC patients only)
  - Urinalysis
- ECG
- Physical examination
- Vital signs (BP, pulse, and temperature) and weight
- Height
- ECOG performance status
- Concomitant medications
- AE monitoring

7.2.2. Cycle 1/Day 1

- Inclusion/exclusion criteria review
- Laboratory assessments (if screening assessments were performed within 72 hours of Day 1, repeat testing is not required):
  - CBC
  - Serum chemistry
  - Serum CA-125 (OC patients only)
  - Urinalysis
- Symptom-directed physical examination
- Vital signs (BP, pulse, and temperature) and weight
- Concomitant medications
- AE monitoring
- Blood sample to be obtained predose for exploratory biomarkers
- Pembrolizumab study treatment administered after other visit procedures are completed

- Blood samples for pembrolizumab PK assessment
  - **Phase 1 patients only**: Blood samples will be obtained predose (within 30 minutes) and within 30 minutes (±5 minutes) after the end of the pembrolizumab infusion.
- Niraparib first dose administered in clinic after completion of pembrolizumab infusion
- ECG
  - ECG monitoring to be conducted prior to the niraparib dose and 2 hours postdose. ECGs should be performed prior to PK blood draws.
- Blood samples for niraparib and M1 PK assessment
  - **Phase 1 patients only**: Patients at each dose level will undergo intensive niraparib and M1 PK evaluation with blood samples obtained at 0 (predose within 30 minutes) and at 1, 2, 4, and 6 hours (±5 minutes), and 8 hours (±10 minutes) postdose.
  - Phase 2 patients: Blood samples for niraparib and M1 PK will be obtained at 0 (predose within 30 minutes) and 2 hours (±15 minutes) postdose.

7.2.3. Cycle 1/Day 2 (Phase 1 Patients Only)

- Blood samples for pembrolizumab PK assessment
  - **Phase 1 patients only**: Obtain blood sample 24 hours (±30 minutes) after the end of the pembrolizumab infusion.
- Blood sample for niraparib PK and M1 assessment
  - **Phase 1 patients only**: Obtain blood sample 24 hours (±30 minutes) postdose following the Cycle 1, Day 1 dose.

7.2.4. Cycle 1/Day 8

For Phase 1 patients, visit to be conducted at the study site to include:

- Vital signs (BP, pulse, and temperature) and weight
- Blood samples for pembrolizumab PK assessment obtained 168 hours (±2 hours) Day 8) after the end of the pembrolizumab infusion.
- CBC
- Concomitant medications
- AE monitoring

For Phase 2 patients:

- CBC: may be done at the study center's local laboratory or at a laboratory local to the patient, if approved by the Principal Investigator as an adequate laboratory. The

laboratory must have the capability to provide results to the Principal Investigator electronically or by fax within 24 hours of blood collection.

7.2.5. Cycle 1/Day 15

- Laboratory assessments:
  - CBC
  - Serum chemistry
  - Coagulation (**Phase 1 patients only**)
- Symptom-directed physical examination
- Vital signs (BP, pulse, and temperature) and weight
- **Phase 1 patients only**: Blood samples for pembrolizumab PK will be obtained 336 hours (±4 hours) (Day 15) after the end of the pembrolizumab infusion.
- Concomitant medications
- AE monitoring

7.2.6. Day 1, Subsequent Cycles

- Tumor assessment (RECIST v1.1 and irRECIST)
  - Conduct radiographic evaluations of chest (all TNBC patients and OC patients with abnormal screening assessment or clinical indication), abdomen, pelvis, and brain (if abnormal at screening or clinical indication). The first on-study imaging assessment should be performed at 9 weeks (63 ±7 days) from the date of first dose of study treatment; in the case of PD, a confirmatory image will be required 4 weeks later (eg, 13 weeks [91 ±7 days]) (see Section 6.3.1.4). Subsequent tumor imaging should be performed every 9 weeks (63 ±7 days) or more frequently if clinically indicated and at the time of suspected disease progression. After 1 year of radiographic assessments, patients will have imaging performed every 12 weeks (84 ±7 days). Imaging should not be delayed for delays in cycle starts or extension of combination treatment cycle intervals. The same modality (ie, CT or MRI) should be used for a given patient throughout the study. PET/CT may be used according to RECIST v1.1 guidelines.
  - Patients with CR or PR should have the response confirmed by a repeat tumor imaging assessment performed at the earliest 4 weeks after the first indication of response, or at the next scheduled scan (ie, 9 weeks later), whichever is clinically indicated.
- Bone scans performed per standard of care.
- Laboratory assessments: may be done within 24 hours prior to the visit
  - CBC
  - Serum chemistry

  - Coagulation (**Phase 1 patients only; Day 1 of Cycles 2 and 3 only**)
  - TSH, T3 or FT3, and FT4 (every 6 weeks)
  - Serum CA-125 (OC patients only)
  - Urinalysis
- Urine pregnancy test for females of childbearing potential conducted every 3 cycles for duration of study (ie, Cycle 4, Cycle 7, etc.). Symptom-directed physical examination
- Vital signs (BP, pulse, and temperature) and weight
- ECOG performance status
- Blood sample to be obtained prior to study treatment for exploratory biomarkers on Day 1 of Cycle 2 only
- Pembrolizumab study treatment administered after other visit procedures are completed
- Blood samples for pembrolizumab PK assessment
  - **Phase 1 patients (Cycles 2, 4, and 8 only)**: Blood samples will be obtained predose (within 30 minutes). An additional sample will be obtained within 30 minutes after the end of the pembrolizumab infusion in Cycle 8.
- Niraparib dose administered in clinic after completion of pembrolizumab infusion
- ECG
  - Patients will undergo ECG monitoring on Cycle 2/Day 1 prior to the niraparib dose and 2 hours postdose and on Cycle 4/Day 1 and Cycle 8/Day 1 predose. ECGs should be performed prior to PK blood draws.
- Blood samples for niraparib and M1 PK assessment
  - **Phase 1 patients (Cycle 2 only)**: Patients at each dose level will undergo intensive niraparib and M1 PK evaluation with blood samples obtained at 0 (predose within 30 minutes) and at 1, 2, 4, and 6 hours (±5 minutes), and 8 hours (±10 minutes) postdose.
  - **Phase 1 patients (Cycles 4 and 8 only)**: Blood samples for niraparib and M1 PK will be obtained at 0 (predose within 30 minutes) and 2 hours (±15 minutes) postdose.
  - Phase 2 patients (Cycles 2, 4, and 8 only): Blood samples for niraparib and M1 PK will be obtained at 0 (predose within 30 minutes) and 2 hours (±15 minutes) postdose.
- Optional tumor biopsy for biomarker testing
  - Sample to be obtained 1 to 3 days before or on Cycle 3/Day 1 prior to pembrolizumab infusion. See the Study Manual for details on sample collection and processing.

- Concomitant medications
- AE monitoring

7.2.7. Cycle 2, Day 2 (Phase 1 Patients Only)

- Blood sample for niraparib and M1 PK assessment
  - **Phase 1 patients only**: Obtain blood sample 24 hours (±30 minutes) postdose following the Cycle 2, Day 1 dose.

7.2.8. End of Treatment (within 7 days of last dose)

- Optional fresh tumor sample
  - If possible, sample to be obtained at the time of disease progression. See the Study Manual for details on sample collection and processing.
- Sample collection (whole blood) for cytogenetic analysis.
- Tumor assessment (RECIST and irRECIST)
  - A final set of radiographic images is required at the time of disease progression, if not done within the last 4 weeks.
  - If a patient discontinues treatment for a reason other than progression or death, withdrawal of consent, or loss to follow-up, radiographic scans/images and CA-125 testing (OC patients only) should continue every 9 weeks (63 ±7 days) through 1 year and every 12 weeks (84 ±7 days) thereafter.
- ECG
- Laboratory assessments:
  - CBC
  - Serum chemistry
  - TSH, T3 or FT3, and FT4
  - Serum CA-125 (OC patients only)
  - Urinalysis
- Physical examination
- Vital signs (BP, pulse, and temperature) and weight
- ECOG performance status
- Concomitant medications
- AE monitoring
- Niraparib study treatment collected

7.2.9. Safety Follow-up (30 days [+ 7 days] Post-treatment)

- Tumor assessment (RECIST and irRECIST) and serum CA-125 (OC patients only)
  - Patients who discontinue treatment for reasons other than disease progression, death, withdrawal of consent, or loss to follow-up will be followed for disease assessments, including radiographic scans and CA-125 testing (OC patients only), per the specified schedule.
- Symptom-directed physical examination
- Laboratory assessments: may be done at the study center's local laboratory or at a laboratory local to the patient if the laboratory is included on FDA Form 1572:
  - CBC
  - Serum chemistry
  - TSH, T3 or FT3, and FT4 (only if clinically indicated)
  - Serum CA-125 (OC patients only)
  - Urine pregnancy test
  - Urinalysis
- Vital signs (BP, pulse, and temperature) and weight
- Concomitant medications
- AE monitoring – AEs are required to be captured through 30 days after cessation of study treatment, SAEs, and ECI (see Section 6.1.6) are required to be captured through 90 days after cessation of study treatment (or to a minimum of 30 days post-treatment if the patient starts alternate anticancer therapy), and any pregnancies that occur within 120 days post-treatment are to be captured.

7.2.10. Follow-up Assessments

- Tumor assessment (RECIST and irRECIST) and serum CA-125 (OC patients only)
  - Patients who discontinue treatment for reasons other than disease progression, death, withdrawal of consent, or loss to follow-up will be followed for disease assessments, including radiographic scans and CA-125 testing (OC patients only), per the specified schedule.
- Serum chemistry to be conducted on Day 90 post-treatment (or to a minimum of 30 days post-treatment if the patient starts alternate anticancer therapy) to assess for possible ECI (see Section 6.1.6). The assessment may be done at the study center's laboratory or at a laboratory local to the patient, if approved by the Principal Investigator as an adequate laboratory. This should be the same laboratory as conducted any Cycle 1/Day 8 CBC samples (see Section 7.2.4).
- AE monitoring – SAEs and ECI (see Section 6.1.6) are required to be captured through 90 days after cessation of study treatment (or to a minimum of 30 days post-treatment if the patient starts alternate anticancer therapy)

- Subsequent anti-cancer therapy information are required to be captured through post-treatment if the patient starts alternate anticancer therapy
- Pregnancy status assessed (through Day 120 post-treatment)
- Survival/new malignancy assessment
  - Patients will be followed by telephone every 90 days for survival status and the occurrence of any new malignancies

7.2.11. Unscheduled Assessments

- For any patient diagnosed with MDS/AML while on study, a bone marrow aspirate and biopsy and sample collection (whole blood) for cytogenetic analysis. See Section 6.1.8 for details.

8. STATISTICAL METHODS

Details of the statistical analyses presented below will be provided in the study's statistical analysis plan (SAP). A change to the data analysis methods described in the protocol will require a protocol amendment only if it alters a principal feature of the protocol. The SAP will be finalized prior to database lock. Any changes to the methods described in the plan will be described and justified in the final clinical study report.

8.1. Study Populations

Three analysis populations will be defined as follows:

- Safety Population: All patients who receive any amount of study drug. The assessment of DLTs in Phase 1 will include only those patients completing the first cycle of therapy, unless the patient discontinued study drug due to a DLT.
- Full Analysis Set (FAS): All patients who receive any amount of study drug. The primary analysis of efficacy endpoints will be performed on the FAS population.
- Per-Protocol Population: All patients who receive at least two cycles of study drug, have protocol-required post-baseline disease assessments and have no major protocol violations that would impact efficacy evaluations. Supportive analyses of efficacy endpoints will be performed on the per-protocol population.

8.2. Demographics, Medical History, Baseline Characteristics, and Concomitant Medications

Demographics, baseline characteristics, and medical history information will be summarized by dose level for Phase 1, and by indication for Phase 2, for the Safety population using descriptive statistics. No formal statistical comparisons will be performed.

Demographic, baseline characteristics, and medical history data for each patient will be provided in data listings.

8.3. Safety Analyses

The following key safety parameters will be evaluated by study phase, pooled dose schedule across phases, by disease type, and overall, unless noted otherwise:

- Dose-limiting toxicities during the first cycle (ie, during the first 21 days of treatment, ie, Cycle 1/Day 1 through Cycle 1/Day 21) for Phase 1
- Incidence of TEAEs during the first cycle compared to the second and subsequent cycles
- Incidence of TEAEs occurring while patients are on treatment or up to 30 days after the last dose of study drug
- Incidence of SAEs and ECI occurring while patients are on treatment or up to 90 days after the last dose of study drug
- Incidence of any new malignancies

- Changes in clinical laboratory parameters (hematology, chemistry, thyroid function, coagulation, urinalysis), vital signs, ECOG performance status, ECG parameters, physical examinations, and usage of concomitant medications

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding system and displayed in tables and data listings using system organ class and preferred term. Analyses of AEs will be performed for those events that are considered treatment-emergent, where treatment-emergent is defined per protocol as any AE with onset beginning at the day of first administration of study drug, throughout the treatment period until 30 days after the last dose of study drug, any SAE or ECI that occurs through 90 days after cessation of study treatment (or to a minimum of 30 days post-treatment if the patient starts alternate anticancer therapy), or any event that was present at baseline but worsened in intensity or was subsequently considered drug-related by the Investigator through the end of the study. DLTs will be tabulated by dose level in Phase 1.

The number and percentage of patients with any TEAE, with any TEAE assessed by the Investigator as related to treatment (definite, probable, or possible relationship), and with any SAE will be summarized by treatment group and overall. In these tabulations, each patient will contribute only once (ie, the most related occurrence or the most intense occurrence) to each of the incidence rates in the descriptive analysis, regardless of the number of episodes. No formal hypothesis-testing analysis of AE incidence rates will be performed.

The occurrence of and reasons for any requirement for dose interruption or modification will be tabulated, and distinguished as to presumptive causality from niraparib or pembrolizumab, if known.

All AEs occurring on-study will be listed in patient data listings. By-patient listings also will be provided for the following: patient deaths, SAEs, and AEs leading to withdrawal.

8.4. Pharmacokinetic Analyses

All patients who receive at least 1 dose of study drug and have measureable drug concentrations will be included in PK analyses.

Non-compartmental methods will be used to evaluate the PK characteristics of niraparib and its major metabolite M1, and pembrolizumab as appropriate. Pharmacokinetic parameters to be determined will include AUC, AUC_{ss}, C_{min}, C_{max}, CL/F, V_z/F, $C_{min,ss}$, and $C_{max,ss}$. Plasma concentrations and PK parameter estimates will be presented using descriptive statistics by dose level.

8.5. Post-Treatment Analyses

Descriptive summary statistics will be used to summarize post-treatment data (ie, any new occurrence of MDS/AML).

8.6. Efficacy Analyses

All efficacy endpoints will be summarized on the Phase 2 population by disease type; in addition, data may be pooled for patients in Phase 1 and Phase 2, by disease type. All analyses will include summary statistics, including number and percentage for categorical variables and

number of patients, mean, standard deviation, median, minimum, and maximum for continuous variables. Two-sided exact 90% confidence intervals (CIs) based on the Clopper-Pearson method [67] will be provided where appropriate. Time-to-event analyses will be performed using Kaplan-Meier (KM) methods. Comparisons in the Phase 1 portion of the study will be made using descriptive statistics. As the Phase 2 portion of the study is single-arm, any statistical analysis to be performed among subgroups is for descriptive and future study purposes.

8.6.1. Primary Efficacy Parameter

The primary efficacy endpoint will be ORR, defined as the achievement of CR or PR using RECIST (v1.1), as assessed by the Investigator. Point estimates and 1-sided 95% CI, corresponding to the specifications of the sample size calculation will be provided. The primary analysis will be performed for each patient cohort and no multiplicity adjustment will be made since separate inferences will be drawn for each cohort.

8.6.2. Secondary Efficacy Parameter(s)

Objective response rate as assessed by the Investigator using irRECIST will be assessed as a secondary endpoint.

Disease control rate will be assessed as a secondary endpoint and is defined as the proportion of patients achieving best overall response of CR, PR, or SD as assessed by the Investigator per RECIST v1.1 and irRECIST, with point estimates and 2-sided 90% CIs.

Duration of response, PFS and OS will be presented through use of summary statistics using KM methods, to include 25th, 50th (median), and 75th percentiles and associated 2-sided 95% CIs, number of events and number of censored observations. DOR and PFS will be defined by both RECIST v1.1 and irRECIST criteria, based on the date of PD that will be used to determine duration, and will be analyzed separately by both criteria.

8.7. Biomarker Analyses

For each patient in the study, blood and tumor samples will be prospectively collected, evaluated and archived to support exploratory biomarker analysis. PD-L1 expression (retrospective analysis), HRD score, immune cell infiltrates, and other exploratory biomarkers will be correlated with response.

8.8. Probability of Dose Escalation

Based on the dose escalation schema planned for the Phase 1 portion of the study as outlined in Section 3.1.2, the following decision rules will be used to determine if a dose is or is not increased:

Table 12 Dose Escalation Decision Rules

First 6 Patients		Second 6 Patients		Decision
Number of Hematologic DLTs	Number of Non-hematologic DLTs	Number of Hematologic DLTs	Number of Non-hematologic DLTs	
0	0	NA	NA	Escalate
1	0	NA	NA	Escalate
0	1	NA	NA	Escalate
1	1	0	0	Escalate
1	1	1	0	Escalate
1	1	0	1	Escalate
0	2	0	0	Escalate
0	2	1	0	Escalate
0	2	0	1	Escalate
2	Any	NA	NA	Decrease dose

Abbreviations: DLT = dos-limiting toxicity; NA = not applicable; second 6 patients are not required to be enrolled.

To model the probabilities of dose escalation given various rates of true hematological and non-hematological DLTs, let X = number of hematological DLTs observed and Y = number of non-hematological DLTs observed. Then the joint distribution of (X,Y) is multinomial (trinomial) with parameters: N = number of patients evaluated, PH = true probability of a hematological DLT, and PN = true probability of a non-hematological DLT. There are 2 probabilities to calculate. First, the probability of escalation based on the first 6 patients enrolled. Second is the conditional probability of escalation based on the second 6 patients enrolled, given (X,Y) = (1,1) or (0,2) in the first 6 patients. The probability of dose escalation is the sum of these 2 probabilities. It is assumed that a given patient cannot have more than 1 DLT, and that hematologic DLTs take precedence over non-hematologic DLTs. The following graph presents the probabilities of dose escalation for ranges of true rates of DLTs, where it is assumed the true rates will be approximately 18% (range 12-24%) for hematologic DLTs and 5% (range 3-7%) for non-hematologic DLTs.

As shown in Figure 2, the probability of dose escalation decreases as the DLT rate increases, as expected. Over the restricted range of DLT rates, the probabilities are close to a linear relationship as the true DLT rates increase.

Figure 2 Probability of Dose Escalation in a 6 + 6 Design

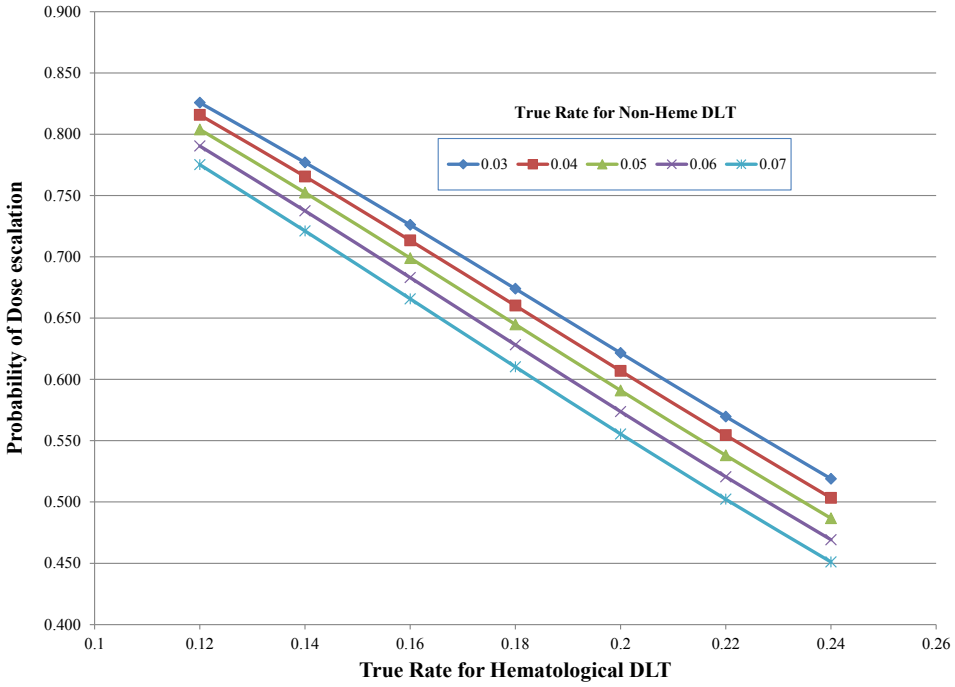
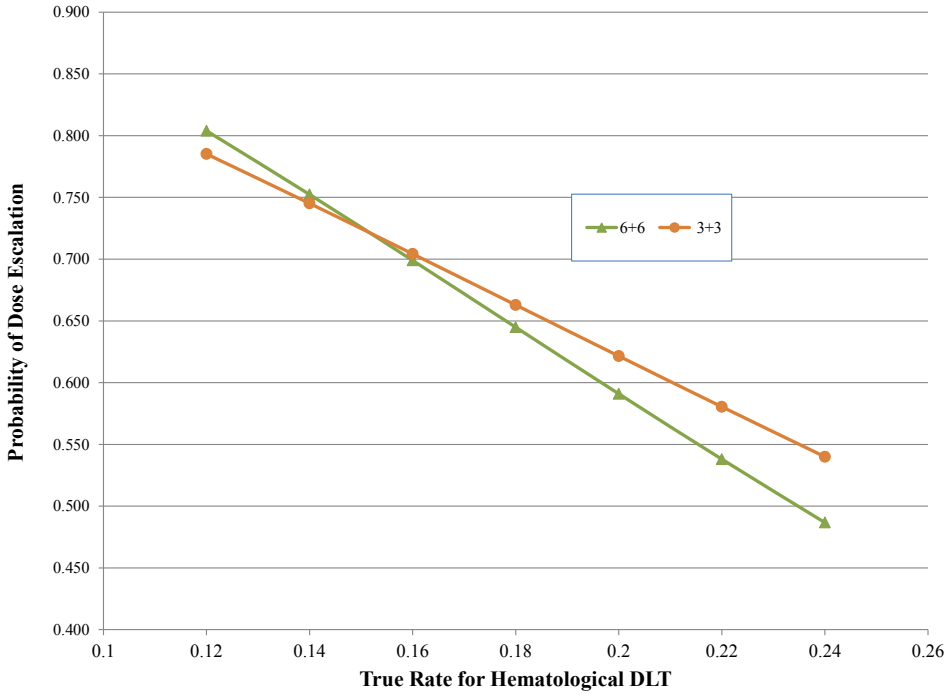


Figure 3 shows the probability of dose escalation for a standard 3+3 escalation design, contrasted with the 6 + 6 design, at the fixed rate of 0.05 for non-hematologic DLTs (the anticipated rate). As can be seen, the protocol-specified 6 + 6 design has a similar probability of escalation as the 3+3 design, and is, in fact, somewhat more conservative for hematologic DLT rates >0.15.

Figure 3 Probability of Dose Escalation in a 6 + 6 Design versus 3 + 3 Design at a Fixed Rate of 0.05 for Non-hematologic DLTs



8.9. Interim Analyses

To minimize the risk of exposing patients to an ineffective treatment, a series of response assessments will be performed when 6, 12, and18 of 48 Phase 2 patients from each cancer type have at least 2 post-baseline tumor assessments. A formal decision regarding futility, which could result in stopping the study early, will be conducted separately for the TNBC and OC cohorts and will only be made from the analysis of 24 patients within each cohort. The earlier response assessments, however, will inform the conduct of the formal interim analysis as follows: If no responder is observed in all three response assessments from 6, 12, and 18 patients, then enrollment will be suspended after 24 patients have been enrolled, and no further patients will be enrolled until the result of the formal interim analysis of 24 patients is known. If ≥1 responder is observed in any single response assessment from 6, 12, or 18 patients, then enrollment will not be curtailed. The decision rule regarding the formal interim analysis at N=24 is as follows: If there are fewer than 3 responders out of 24, enrollment may be closed and the corresponding cohortmay be stopped for futility. Otherwise, the study will continue to the planned enrollment of 48 patients.

8.10. Determination of Sample Size

Phase 1: In the Phase 1 portion of this study, 14 patients with advanced TNBC or OC were enrolled in Dose Level 1 or Dose Level 2. Twelve patients were eligible for DLT evaluation. In Dose Level 1, 1 of 6 DLT-eligible patients experienced multiple DLTs including Grade3 anemia, Grade 4 neutropenia, and Grade 4 thrombocytopenia. In Dose Level 2, 1 of 6 DLT-eligible patients experienced 1 DLT, Grade 4 thrombocytopenia; an additional patient experienced an

adverse event that was deemed to be a DLT-equivalent; the patient had epistaxis on C1D17 and Grade 4 thrombocytopenia on C2D1.

Phase 2: A total of approximately 96 evaluable patients (approximately 48 patients in each tumor type) will be enrolled to ensure understanding of the activity of the combination treatment With 48 patients treated in each cohort, observed 12 responses (CR and/or PR) at the final analysis will rule out a 15% response rate. The study has approximately 82%/94% power for each cohort to rule out a ≤15% ORR (null hypothesis) when the true ORR is 30%/35% at the 10% type I error rate (two-sided).

The following table shows the two-sided 90% CI for ORR based on 48 subjects for different observed response rates.

Number of Observed Responses	ORR Estimate	90% CI for ORR
8	16.7%	(8.6%, 28.1%)
10	20.8%	(11.8%, 32.8%)
12	25.0%	(15.1%, 37.3%)
14	29.2%	(18.6%, 41.8%)
16	33.3%	(22.2%, 46.1%)

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

9. ETHICAL, LEGAL, AND ADMINISTRATIVE ASPECTS

9.1. Data Quality Assurance

The Sponsor (or designee) will conduct a study initiation visit to verify the qualifications of the Investigator, inspect the facilities, and inform the Investigator of responsibilities and procedures for ensuring adequate and correct documentation.

The Investigator must prepare and maintain adequate and accurate records of all observations and other data pertinent to the clinical study for each study participant. Frequent communication between the clinical site and the Sponsor is essential to ensure that the safety of the study is monitored adequately. The Investigator will make all appropriate safety assessments on an ongoing basis. The Sponsor's Medical Monitor may review safety information as it becomes available throughout the study.

All aspects of the study will be carefully monitored with respect to GCP and standard operating procedures for compliance with applicable government regulations. The Study Monitor will be an authorized individual designated by the Sponsor. The Study Monitor will have access to all records necessary to ensure integrity of the data and will periodically review the progress of the study with the Principal Investigator.

9.2. Access to Source Data/Documents

An electronic data capture system to manage data collection will be utilized during this study. The electronic data capture system is a software tool designed to ensure quality assurance and facilitate data capture during clinical studies. The system is fully compliant with Code of Federal Regulations 21 Part 11.

The Investigator will ensure the accuracy, completeness, and timeliness of the data reported to the Sponsor. Data collection processes and procedures will be reviewed and validated to ensure completeness, accuracy, reliability, and consistency. A complete audit trail will be maintained of all data changes. The Investigator or designee will cooperate with the Sponsor's representative(s) for the periodic review of study documents to ensure the accuracy and completeness of the data capture system at each scheduled monitoring visit.

Electronic consistency checks and manual review will be used to identify any errors or inconsistencies in the data. This information will be provided to the respective study sites by means of electronic or manual queries.

The Investigator or designee will prepare and maintain adequate and accurate study documents (medical records, ECGs, AE, and concomitant medication reporting, raw data collection forms, etc.) designed to record all observations and other pertinent data for each patient receiving study treatment.

The Investigator will allow Sponsor representatives, contract designees, authorized regulatory authority inspectors, and the IRB/IEC to have direct access to all documents pertaining to the study.

9.3. Archiving Study Documents

Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study, and retained according to the appropriate regulations. According to International Conference on Harmonisation (ICH) guidelines, essential documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the study treatment.

9.4. Good Clinical Practice

This study will be conducted in accordance with the ICH for good clinical practices (GCPs) and the Declaration of Helsinki (Version 2008). The clinical study will also be carried out in accordance with national and local regulatory requirement(s).

9.5. Informed Consent

Before each patient is enrolled in the clinical study, written informed consent will be obtained from the patient according to the regulatory and legal requirements of the participating country. As part of this procedure, the Investigator must explain orally and in writing the nature, duration, and purpose of the study, and the action of the study treatment in such a manner that the patient is aware of the potential risks, inconveniences, or AEs that may occur. The patient should be informed that he or she is free to withdraw from the study at any time. The patient will receive all information that is required by regulatory authorities and ICH guidelines. The Investigator or designee will provide the Sponsor with a copy of the IRB/IEC-approved ICF prior to the start of the study.

The ICF must be signed and dated; one copy will be given to the patient and the Investigator will retain a copy as part of the clinical study records. The Investigator will not undertake any investigation specifically required for the clinical study until written consent has been obtained. The terms of the consent and when it was obtained must also be documented.

If a protocol amendment is required, then the ICF may need to be revised to reflect the changes to the protocol. If the ICF is revised, it must be reviewed and approved by the responsible IRB/IEC and signed by all patients subsequently enrolled in the clinical study as well as those currently enrolled in the clinical study.

9.6. Protocol Approval and Amendment

Before the start of the study, the study protocol and/or other relevant documents will be approved by the IEC/IRB/Competent Authorities, in accordance with local legal requirements. The Sponsor must ensure that all ethical and legal requirements have been met before the first patient is enrolled in the study.

This protocol is to be followed exactly. To alter the protocol, amendments must be written, receive approval from the appropriate personnel, and receive IRB/IEC/Competent Authority approval prior to implementation (if appropriate). In the United States, following approval, the protocol amendment(s) will be submitted to the IND under which the study is being conducted.

Administrative changes (not affecting the patient benefit/risk ratio) may be made without the need for a formal amendment. All amendments will be distributed to all protocol recipients, with appropriate instructions.

9.7. Patient Confidentiality and Data Protection

All clinical study findings and documents will be regarded as confidential. Study documents (protocols, IBs, and other material) will be stored appropriately to ensure their confidentiality. The Investigator and members of his/her research team (including the IRB/IEC) must not disclose such information without prior written approval from the Sponsor, except to the extent necessary to obtain informed consent from patients who wish to participate in the study or to comply with regulatory requirements.

The anonymity of participating patients must be maintained. Patients will be specified on study documents by their enrollment number or birth date, not by name. Documents that identify the patient (eg, the signed informed consent document) must be maintained in confidence by the Investigator.

9.8. Study Monitoring

Monitoring and auditing procedures approved by the Sponsor will be followed in order to comply with GCP guidelines. On-site checking of the eCRFs for completeness and clarity, cross-checking with source documents, and clarification of administrative matters will be performed.

The study will be monitored by the Sponsor or its designee. Monitoring will be done by personal visits from a representative of the Sponsor (site monitor) who will review the eCRFs and source documents. The site monitor will ensure that the investigation is conducted according to protocol design and regulatory requirements by frequent site visits and by communications (letter, telephone, and fax).

All unused study treatment and other study materials will be returned to the Sponsor after the clinical phase of the study has been completed.

9.9. Audits and Inspections

Regulatory authorities, the IRB/IEC, and/or the Sponsor's clinical quality assurance group, or its designee, may request access to all source documents, eCRFs, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the Investigator, who must provide support at all times for these activities.

9.10. Ethical Considerations

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki. The IRB/IEC will review all appropriate study documentation in order to safeguard the rights, safety, and well-being of the patients. The study will only be conducted at sites where IRB/IEC approval has been obtained. The protocol, Investigator Brochure, informed consent, advertisements (if applicable), written information given to the patients, safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC by the Investigator.

9.11. Publication Policy

Information regarding publication of study results is contained in the Clinical Trial Agreement for this study.

9.12. Study Committee

A Study Committee comprised of Investigators and Sponsor representatives will be established to provide review and assessment of the study data on an ongoing basis and to safeguard the interest and safety of the participating patients in the study. The details on membership, key responsibilities, and corresponding procedures are provided in the Study Committee charter.

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APPENDIX A. ASCO TNBC GUIDANCE 2010[70]

American Society of Clinical Oncology/College of American Pathologists Guideline Recommendations for Immunohistochemical Testing of Estrogen and Progesterone Receptors in Breast Cancer

Recommendations.—The Panel recommends that ER and PgR status be determined on all invasive breast cancers and breast cancer recurrences. A testing algorithm that relies on accurate, reproducible assay performance is proposed. Elements to reliably reduce assay variation are specified. It is recommended that ER and PgR assays be considered positive if there are at least 1% positive tumor nuclei in the sample on testing in the presence of expected reactivity of internal (normal epithelial elements) and external controls.

APPENDIX B. DRUGS KNOWN TO INHIBIT OR INDUCE CYP1A2 OR ARE SUBSTRATES OF CYP1A2

Inhibitors of CYP1A2		
Strong ≥ 5-fold increase in AUC or > 80% decrease in CL	**Moderate** ≥ 2 but < 5-fold increase in AUC or 50%-80% decrease in CL	**Weak** ≥ 1.25 but < 2-fold increase in AUC or 20**%**-50% decrease in CL
Ciprofloxacin, enoxacin, fluvoxamine	Methoxsalen, mexiletine, oral contraceptives, phenylpropanolamine, thiabendazole, vemurafenib, zileuton	Acyclovir, allopurinol, caffeine, cimetidine, Daidzein, disulfiram, Echinacea, famotidine, norfloxacin, propafenone, propranolol, terbinafine, ticlopidine, verapamil
Inducers of CY1A2		
Strong 80% decrease in AUC	**Moderate** 50%-80% decrease in AUC	**Weak** 20%-50% decrease in AUC
	Montelukast, phenytoin, smokers versus non-smokers	Moricizine, omeprazole, phenobarbital
Substrates of CYP1A2		
Sensitive substrates[a]		**Substrates with narrow therapeutic range**[b]
Alosetron, caffeine, duloxetine, melatonin, ramelteon, tacrine, tizanidine		Theophylline, tizanidine, warfarin

Abbreviations: AUC = area under the curve; CL = clearance.
Source: [68]

[a] Sensitive CYP substrates refers to drugs whose plasma AUC values have been shown to increase 5-fold or higher when coadministered with a known CYP inhibitor or AUC ratio in poor metabolizers vs. extensive metabolizers is greater than 5-fold.

[b] CYP substrates with narrow therapeutic range refers to drugs whose exposure-response relationship indicates that small increases in their exposure levels by the concomitant use of CYP inhibitors may lead to serious safety concerns (eg, Torsades de Pointes).

APPENDIX C. DRUGS THAT ARE SUBSTRATES OR INHIBITORS OF P-GLYCOPROTEIN

Substrates	**Inhibitors**
Aliskiren	Amiodarone
Ambrisentan	Azithromycin
Colchicine	Captopril
Dabigatran etexilate	Carvedilol
Digoxin	Clarithromycin
Everolimus	Conivaptan
Fexofenadine	Cyclosporine
Imatinib	Diltiazem
Lapatinib	Dronedarone
Maraviroc	Erythromycin
Nilotinib	Felodipine
Posaconazole	Itraconazole
Ranolazine	Ketoconazole
Saxagliptin	Lopinavir and Ritonavir
Sirolimus	Quercetin
Sitagliptin	Quinidine
Talinolol	Ranolazine
Tolvaptan	Ticagrelor
Topotecan	Verapamil

Source: [68]

APPENDIX D. RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST), V1.1

Response Criteria by RECIST v1.1

Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Table 13 RECIST Response for Patients with Measurable Disease (ie, Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	> 4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	> 4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	documented at least once > 4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

Abbreviations: CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease
* See RECIST v1.1 publication [65] for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.
Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment.

Table 14 RECIST Response for Patients with Non-Measurable Disease (ie, Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

Abbreviations: CR = complete response; PD = progressive disease
*'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

APPENDIX E. IMMUNE-RELATED RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (irRECIST)

Immune-related RECIST will be used by local site Investigators to assess tumor response and progression and make treatment decisions.

Table 15 provides a high-level summary of the imaging procedures and treatment decisions to be made based on evidence of progression of disease per RECIST v1.1. See also details provided in Section 6.3.1.4.

Table 15 Imaging and Treatment after First Radiologic Evidence of Progressive Disease

Timing of Imaging	Clinically Stable		Clinically Unstable	
	Tumor Imaging	Treatment	Tumor Imaging	Treatment
1st radiologic evidence of PD	Repeat imaging at ≥ 4 weeks at site to confirm PD	May continue study treatment at the local site Investigator's discretion while awaiting confirmatory tumor imaging	Repeat imaging at ≥ 4 weeks to confirm PD per physician discretion only	Discontinue treatment
Repeat tumor imaging confirms PD	No additional imaging required	Discontinue treatment	No additional imaging required	N/A
Repeat tumor imaging shows SD, PR or CR	Continue regularly scheduled imaging assessments	Continue study treatment at the local site Investigator's discretion	Continue regularly scheduled imaging assessments	May restart study treatment if condition has improved and/or clinically stable per Investigator's discretion.

Abbreviations: CR = complete response; irRECIST = immune-related Response Criteria in Solid Tumors; N/A = not applicable; PD = progressive disease; PR = partial response; RECIST = Response Criteria in Solid Tumors; SD = stable disease

APPENDIX F. ASSESSMENT OF RESPONSE IN OVARIAN CANCER BY GYNECOLOGIC CANCER INTERGROUP (GCIG) CRITERIA

Because of the pelvic location of the primary tumor in patients with OC and the frequent occurrence of peritoneal disease, imaging may not always be reliable for documentation of PD in patients with OC. Criteria other than RECIST may be applicable to define PD in these patients. For this protocol, the GCIG criteria for disease progression will also be considered for patients with OC.[66] Based on these criteria, PD may also be determined if at least 1 of the following criteria is met:

1. Additional diagnostic tests (eg, histology/cytology, ultrasound techniques, endoscopy, positron emission tomography) identify new lesions or determine existing lesions qualify for unequivocal PD AND CA-125 progression according to GCIG criteria.
2. Definitive clinical signs and symptoms of PD unrelated to nonmalignant or iatrogenic causes ([a] intractable cancer-related pain; [b] malignant bowel obstruction/worsening dysfunction; or [c] unequivocal symptomatic worsening of ascites or pleural effusion) AND CA-125 progression according to GCIG criteria.

Abnormal CA-125 levels on-study do not represent disease progression; however, they may prompt imaging if clinically indicated. Progressive disease will not be diagnosed in case of CA-125 progression in the absence of at least 1 of the criteria defined above.

The Investigator will describe how PD was diagnosed in the eCRF.

The date of PD is defined as the earliest time point when one of the PD criteria is met. If CT/MRI shows existing (baseline) lesions that only equivocally suggest PD and additional diagnostic tests are required to determine unequivocal PD, the official date of PD will be the date PD was unequivocally determined. Alternatively, with new lesions (except ascites and effusions) that are initially equivocal that are later unequivocally determined, the date of progression will be the date the lesion was initially identified.

APPENDIX G. EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE STATUS

Description	Grade
Fully active, able to carry on all pre-disease performance without restriction.	0
Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature, ie, light house work, office work.	1
Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.	2
Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	3
Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	4

Source: [69]