1.0 Statistical Analysis Plan

Sponsor:	TESARO, Inc.
Protocol No:	3000-PN162-01-001, Amendment 2
PRA Project Id:	TSRNIRPD-NIRPD1
Version No.:	Protocol v3.0

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
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SAP No.	Final v2.0

2.0 Approvals

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3.0 Purpose

The statistical analysis plan (SAP) describes the statistical methods to be used during the reporting and analyses of data collected under TESARO Inc. Protocol 3000-PN162-01-001.

4.0 Scope

This plan is a living document that will be created during the trial start-up. SAP 1 will be drafted within three months of final CRF, and maintained throughout the lifecycle of the trial, an email approval of SAP 1 from the sponsor is sufficient to start programming activities. The SAP 2 will be finalized prior to database lock. SAP 2 will require sign off from the PRA Project Manager and the sponsor.
The SAP outlines the following:

- Study objectives
- Study design
- Variables analyzed and analysis sets
- Applicable study definitions
- Statistical methods regarding important protocol deviations, study treatment exposure, efficacy analysis, concomitant medications, adverse events handling and laboratory data.

5.0 Introduction

This SAP describes the statistical methods to be used during the reporting and analyses of data collected under TESARO, Inc. Protocol 3000-PN162-01-001.

This SAP should be read in conjunction with the study protocol and case report form (CRF). This version of the plan has been developed using the protocol dated 01-MAR-2017 (Amendment 2) and CRF dated 31-MAY-2018. Any further changes to the protocol or CRF may necessitate updates to the SAP.

The SAP is to be developed in two stages. The purpose is to "finalize" an SAP so that we can start programming earlier in the process. A final version of the SAP, known as SAP 2, will be issued for sponsor approval prior to database lock. Chances made to the SAP after database lock will be documented in the Clinical Study Report.

5.1 Changes from Protocol

The protocol describes a per-protocol population for use in evaluation of supportive analyses of efficacy. This population will not be used in this SAP.

The protocol defined evaluation of irRECIST endpoints (objective response rate, duration of response, disease control rate and progression free survival). These endpoints were not consistently collected across all patients and therefore cannot formally be evaluated. All collected data will be listed. In addition, for patients who received study treatment for ≥28 days beyond radiological progression per RECIST v1.1 and who have post-progression tumor assessments, the irRECIST evaluations will be listed along-side the RECIST v1.1 evaluations, as available.

The relationship between cytogenetic abnormalities and safety parameters was to be evaluated per protocol, however this was not done since there is no cytogenetic abnormality assessment.

6.0 Study Objectives

6.1 Phase 1

6.1.1 Primary Objectives

- To evaluate dose-limiting toxicities (DLTs) of combination treatment with niraparib and pembrolizumab during the first cycle of treatment.
- To establish a recommended Phase 2 dose (RP2D) and schedule.

6.1.2 Secondary Objectives

- To evaluate the safety and tolerability of combination treatment with niraparib and pembrolizumab using Common Terminology Criteria for Adverse Events (CTCAE, v.4.03)
- To evaluate the pharmacokinetics (PK) of niraparib and associated major metabolite M1 during combination treatment.

6.2 Phase 2

6.2.1 Primary Objective:

- 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.

6.2.2 Secondary Objective:

- 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 v1.1 (irRECIST);
  − Duration of response (DOR) by RECIST v1.1 and 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).
- To evaluate the PK of niraparib and associated major metabolite M1 during combination treatment.

6.2.3 Exploratory Objectives

- 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) score with other immune-related biomarkers and with efficacy outcomes.

7.0 Study Design

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.

The study will be conducted in 2 parts. The Phase 1 portion of the study will be a dose-escalation evaluation to determine the recommended Phase 2 dose (RP2D) and schedule of niraparib to be administered in combination with the recommended dose of pembrolizumab to be used in the Phase 2 portion.

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. 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.

The following are 4 dose levels/schedules planned for the Phase 1 of the study; each cohort will contain 6 patients but may be expanded to 12 patients:

- 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.
- 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.

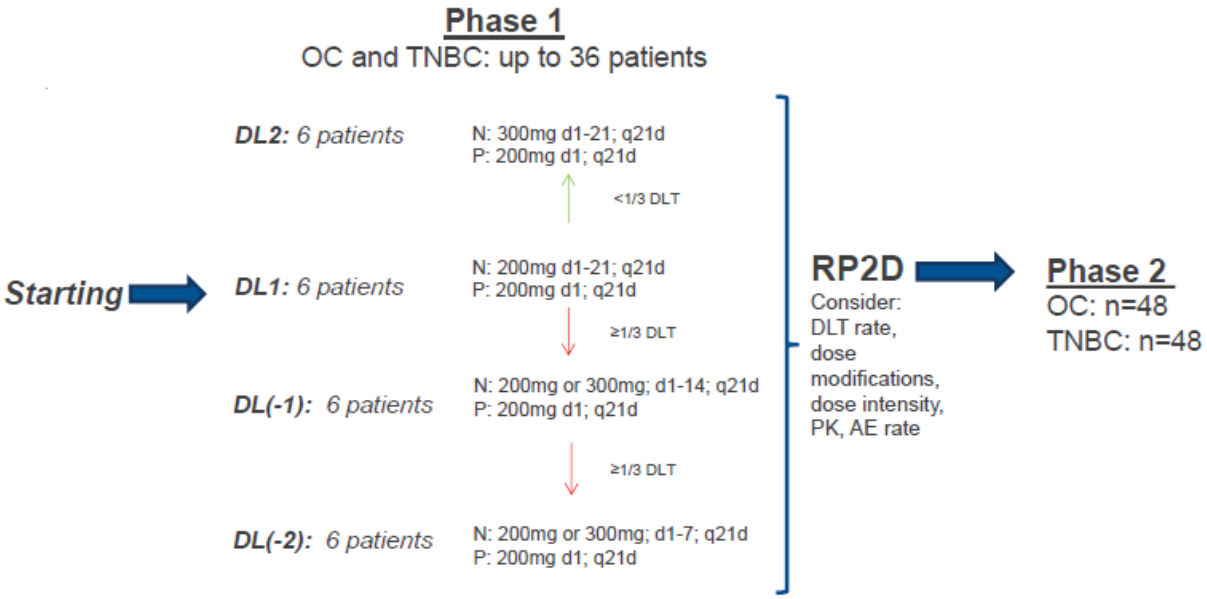
The Phase 2 portion of the study will commence after the RP2D is determined during the Phase 1 portion. Two cohorts of approximately 48 patients each with advanced TNBC or OC will be evaluated.

Patients in this phase of the study will receive the RP2D of niraparib in combination with pembrolizumab 200 mg IV on Day 1 of each 21-day cycle.

In Phase 2, pembrolizumab will be administered 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. Niraparib is administered as a daily dose. On day 1 of each cycle, niraparib dose will be administered upon completion of pembrolizumab infusion. The RP2D of the combination will be based on the results in Phase 1.

Combination pembrolizumab/niraparib treatment may continue for up to 2 years unless specific withdrawal criteria are met (Section 4.3 of the protocol). Continued treatment with niraparib beyond 2 years may be considered following discussion between the Sponsor and Investigator. Figure 1 describes the study schema. The schedule of events is added in the appendix of section 19.0.

Figure 1: Study Schema



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.

7.1 Sample Size Considerations

A total sample size of approximately 18 patients is estimated for the Phase 1 portion of the study to provide initial comparison of the incidence of DLTs and safety profiles of the combination treatment between dose schedules in each patient population. More patients could be enrolled (e.g., 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.

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

7.2 Randomization

Not applicable, as this is a single-arm study and Phase 2 is conducted in two cohorts.

8.0 Study Variables and Covariates

8.1 Primary Variables

Phase 1

- DLTs of combination treatment during the first treatment cycle

- MTD defined as the highest dose of niraparib with DLTs observed in less than one-third of patients (i.e., < 2 of 6 patients or < 4 of 12 patients) during Cycle 1 of combination treatment.
- RP2D - defined as the greatest dose intensity and regimen of niraparib that can be safely combined with the recommended dose and regimen of pembrolizumab

Phase 2

- ORR for combination treatment with pembrolizumab and niraparib using RECIST v1.1 criteria based on the investigator assessment.

8.2 Secondary Variables

8.2.1 **Efficacy**

- ORR for combination treatment with pembrolizumab and niraparib using irRECIST criteria.
- Duration of Response (DOR) per RECIST v1.1
- Duration of Response (DOR) per irRECIST
- Disease Control Rate per RECIST v1.1
- Disease Control Rate (DCR) per irRECIST
- Progression Free Survival (PFS) per RECIST v1.1
- Progression Free Survival (PFS) per irRECIST
- Overall Survival (OS)

Protocol specified irRECIST endpoints were not consistently collected across all patients and therefore cannot formally be evaluated using standard summaries. irRECIST timepoint assessments will be listed, as available.

8.2.2 **Safety**

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All treatment emergent adverse events including serious and non-serious will be collected. Severity will be assessed based on CTCAE (v 4.03) grades. The reported events will be assessed for causal relationship to study drugs. Events of clinical interest for pembrolizumab and niraparib will also be collected.

The following additional safety information will be collected.

- Changes in clinical laboratory values (hematology, chemistry, coagulation, thyroid function, urinalysis)
- Vital signs
- ECG's
- Physical examination findings
- Concomitant medications

8.2.3 Exploratory Endpoints

The relationship between cytogenetic abnormalities and safety parameters was to be evaluated per protocol, however this was not done since there is no cytogenetic abnormality assessment.

8.3 Pharmacokinetic Variables

The pharmacokinetic analysis set will consist of all patients with sufficient data to enable estimation of at least one PK parameter listed below.
The following PK parameters will be calculated for niraparib and major metabolite M1 for Phase 1 using standard non-compartmental methods in Phoenix® WinNonlin® (WNL) (Pharsight Corporation, Version 6.3 or higher):

Table 1: PK parameters

Parameter	Description	SAS Programming Notes
C_{max}	Observed maximum concentration during the dosing interval.	C_{max} from WNL
C_{min}	Observed minimum concentration during the dosing interval	C_{min} from WNL
T_{max}	Time of the maximum observed concentration.	T_{max} from WNL
$AUC_{(0-24)}$	Area under the plasma concentration-time curve from time 0 to 24 hours. This parameter will be calculated for Phase 1, Cycle 1 and Cycle 2	$AUC_{(0-24)}$ from WNL (partial area)
$AUC_{(0-last)}$	Area under the concentration-time curve between time zero (predose) and time of last quantifiable concentration.	AUC_{last} from WNL
$AUC_{(0-tau)}$; $AUC_{(0-tau)\ ss}$	Area under the plasma concentration-time curve during a dosing interval. This parameter will be calculated after a single dose and after multiple doses at steady state based on available data	AUC_{tau} from WNL where tau is equal to XX hr
AR	The accumulation ratio will be calculated as the exposure at steady state within tau divided by the first dose exposure within tau.	$AUC_{(0-tau)\ ss}$ / $AUC_{(0-tau)}$
$AUC_{(0-inf)}$	Area under the concentration-time curve between time zero (predose) extrapolated to infinity. AUC_%Extrap_obs ≤ 20% or R^2 > 0.70 is required to retain AUC_{inf} This parameter will be calculated for Phase 1, Cycle 1 only	AUC_{INF}_obs from WNL If AUC_%Extrap_obs > 20% or Rsq_{adj} ≤ .70 then parameter will not be reported.
CL/F	Apparent clearance calculated as CL = Dose/AUC_{inf} Percent extrapolation less than or equal to 20% and r2 greater than 0.70 is required to retain CL/F.	Cl_F_obs from WNL If AUC_%Extrap_obs >20% or Rsq ≤ .70 then parameter is deleted
V_z/F	Apparent volume of distribution as Vz/F = (CL/F)/λz Percent extrapolation less than or equal to 20% and r2 greater than 0.70 is required to retain Vz/F.	V_z_F_obs from WNL If AUC_%Extrap_obs >20% or Rsq ≤ .70 then parameter is deleted

General statistics will be summarized for both Phase 1 and sparse data in Phase 2.
PK analysis will use actual times as recorded on the CRF. If actual times are missing, nominal times may be used with sponsor approval.
Concentrations are used as supplied by the analytical laboratory for PK analysis. The units of concentration and resulting PK parameters, with amount or concentration in the unit, will be presented as they are received from the analytical laboratory. Concentration values that are below the level of quantification (BLQ) will be set to zero, with defined exceptions as follows: any embedded BLQ value (between 2 quantifiable concentrations) and BLQ values following the last quantifiable concentration in a profile will be set to missing for the purposes of PK analysis.
If there are late quantifiable concentration values following 2 BLQ concentration values in the apparent terminal phase, these values will be evaluated. If these values are considered to be anomalous, they will be set to missing. If an entire concentration-time profile is BLQ, the profile will be excluded from the PK analysis. If concentration values at the beginning of the profile (i.e. pre-dose) are missing, these values may be set to zero with sponsor approval.

8.3.1 Presentation of Pharmacokinetic Concentrations

- The following rules will be applied if there are values that are below the lower limit of quantification (BLQ) or if there are missing values (e.g., no result [NR]) in a plasma concentration data series to be summarized.
    - For the calculation of summary statistics, BLQ values will be set to zero.
    - Where there is NR, these will be set to missing.
- If all the values are BLQ, then the arithmetic mean, arithmetic SD, median, min and max will be presented as zero and the geometric mean and geometric CV% will be denoted as not calculated (NC).
- If the value of any descriptive statistic calculation is BLQ, these will be presented as zero and the geometric mean and geometric CV% will be denoted as NC.

9.0 Definitions

Age:
The age collected at time of screening, presented in whole years.

Age Group:
There will be three age groups summarized in the demographics tables: <65 years old, ≥65-<75 years old and ≥ 75 years old.

Baseline:
Unless otherwise specified, baseline is the last measurement taken on or prior to first dose of pembrolizumab or niraparib, whichever is earlier (baseline can be the same date as first dose, given the measurement is expected prior to first dose, otherwise consider both time and date of dosing (if time is available for both).

Best Overall Response (BOR) per RECIST v1.1 - Confirmed:
The best overall response (BOR) according to RECIST v1.1 will be assessed based on reported overall timepoint responses at different evaluation time points from the first dose date until documented disease progression, according to the following rules:

- CR = at least two determinations of CR at least 4 weeks apart with no evidence of progression between the two determinations.
- PR = at least two determinations of PR or better at least 4 weeks apart before progression (and not qualifying for a CR).
- SD= at least one SD assessment (or better) ≥ 28 days after the baseline scan and before progression (and not qualifying for a CR or PR).
- PD= progression after baseline.

Only tumor assessments performed before the start of any further anti-cancer treatment will be considered in the assessment of BOR. Clinical deterioration will not be considered as documented disease progression.

Best Overall Response (BOR) per RECIST v1.1 Without Confirmation Requirements: The best overall response (BOR) according to RECIST v1.1 without confirmation requirements will be assessed based on reported overall timepoint responses at different evaluation time points from the first dose date until documented disease progression, according to the following rules:

- Confirmed CR = at least two determinations of CR at least 4 weeks apart with no evidence of progression between the two determinations.
- Unconfirmed CR = at least one determinations of CR and not followed by another CR meeting the requirement for confirmation.
- Confirmed PR = at least two determinations of PR or better at least 4 weeks apart before progression (and not qualifying for a CR).
- Unconfirmed PR = at least one determinations of PR before progression (and not qualifying for a CR), and not followed by another PR meeting the requirement for confirmation.
- SD= at least one SD assessment after baseline and before progression [and not qualifying for any type of CR or PR above (confirmed or unconfirmed)].
- PD= progression after baseline.

Only tumor assessments performed before the start of any further anti-cancer treatment will be considered in the assessment of BOR. Clinical deterioration will not be considered as documented disease progression.

Body Mass Index (BMI):
Calculated at each visit and is equal to the weight (in kg)/ [height at screening (in m)^2].

Clinical Benefit Rate at 18 weeks (CBR18)
The clinical benefit rate at 18 weeks is the proportion of patients in the analysis population who achieved confirmed CR or PR, or achieved SD ≥18 weeks without evidence of radiologic progression prior to this point. A seven day window will be used to accommodate scan timing, thereby considering any SD, PR or CR beyond 17 weeks (ie, ≥119 days). Patients who are ongoing treatment who have not reached the timepoint of interest will not be included in the denominator.

Corrected QT Interval (QTcF):

QTcF is defined as corrected QT interval with Fridericia's correction formula: $QTcF=QT/(RR)^{1/3}$, where QT is the heart rate interval, measured in milliseconds and RR is the interval from the onset of one QRS complex to the onset of the next QRS complex, measured in seconds.

Disease Control Rate (DCR) per RECIST v1.1:
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. DCR will be assessed requiring confirmation and without confirmation requirements.

Duration of Response (DOR) per RECIST v1.1:
DOR is applicable to patients that achieve either CR/PR per RECISTv1.1 and is defined as time from the first assessment of CR/PR until the date of the first occurrence of PD, or until the date of death. Follow Table 2 for censoring rules of DOR. DOR will be assessed for both confirmed responses only and for responses without confirmation requirements.

$$DOR\ (months) = \frac{\text{Date of PD/Death/Censoring} - \text{ Date of First recorded CR or PR } + 1}{30.4375}$$

Last Known Contact Date:
The date of last known contact date will be derived for patients not known to have died at the analysis cut-off using the latest complete date among the following:

- Patient assessment dates (blood draws [laboratory, PK], vital signs, performance status, ECG, tumor assessments, ECOG, tumor measurement, or tumor biopsy dates)
- Start and end dates of anti-cancer therapies administered after study treatment discontinuation.
- AE start and end dates
- Last date of contact collected on the 'Survival information' eCRF (do not use date of survival follow-up assessment unless status is 'alive')
- Study treatment start and end dates
- Date of discontinuation on disposition eCRF pages (do not use if reason for discontinuation is lost to follow-up).

Only dates associated with actual examinations of the patient will be used in the derivation. Dates associated with a technical operation unrelated to patient status such as the date a blood sample was processed will not be used. Assessment dates after the cut-off date will not be applied to derive the last contact date, if applicable.

Objective Response Rate (ORR) per RECIST v1.1:
ORR will be assessed using tumor data recorded by the Investigator, and the denominator will be based on all patients in the defined analysis population.
The ORR is the proportion of patients who achieved best overall response of CR (complete response) or PR (partial response). ORR will be assessed requiring confirmation and without confirmation requirements. When confirmation is required, the objective responses should be confirmed by a repeat tumor imaging assessment, at least 4 weeks apart, per RECIST v1.1. Each patient will have an objective response status (0: OR=no; 1: OR=yes).

Overall Response:
Overall tumor response assessment at each time point is a combination of target lesions, non-target lesions and new lesions assessed by the investigator following the guidelines presented specified in RECIST v1.1. The response evaluation criteria per RECIST v1.1 are presented in Appendix D of the protocol.

Overall Survival (OS):
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. Patients last known to be alive will be censored at date of last known contact.

$$OS(months) = \frac{\text{Date of Death/Censoring} - \text{Date of First Dose} + 1}{30.4375}$$

Progression-Free Survival Time (PFS) per RECIST v1.1:
Progression-free survival will be assessed as a secondary endpoint and is defined as the time from first dose of study treatment to the earlier date of assessment of progression or death by any cause in the absence of progression based on the time of first documentation of disease progression per RECIST v1.1.
Censoring rules for PFS events follow the guidelines presented in Table 2.

$$PFS(months) = \frac{\text{Date of PD/Death/Censoring} - \text{Date of First Dose} + 1}{30.4375}$$

Table 2: Censoring Rules for PFS and DOR.

Scenario	Date of event/censoring	Outcome
No baseline assessment or no post-baseline assessment	First dose date	Censored [a]
Progression or death ≤ 18 weeks after last tumor assessment or ≤ 18 weeks after first dose date	Date of progression or death	Event
Progression or death > 18 weeks after the last tumor assessment	Date of last adequate assessment	Censored
No progression	Date of last adequate assessment	Censored
New anticancer therapy given (excluding radiation therapy)	Date of last adequate assessment before anticancer therapy given	Censored

[a] However if the patient dies ≤18 weeks after first dose date the death is an event with date on death date

Study Treatments:
Study treatments are niraparib and pembrolizumab.

Treatment Cycle:
Cycles will be identified in the visit label in the clinical database associated with dosing records.

Treatment Emergent Adverse Event (TEAE):
All AEs were 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 were monitored through 90 days after the last dose of study treatment (or to a minimum of 30 days post-treatment if the patient started alternate anticancer therapy). All AEs and SAEs experienced by a patient,

irrespective of the suspected causality, were to be monitored until the AE or SAE was resolved, any abnormal laboratory values had returned to baseline or normal levels, until there was a satisfactory explanation for the changes observed, until the patient was lost to follow-up, or until the patient died. Per protocol (Section 6.1.1), a treatment emergent adverse event was defined as any new AE that began, or any preexisting condition that worsens in severity after at least 1 dose of study treatment has been administered. For analysis, TEAE's are AE's with the onset date beginning on or after the day of first administration of either study treatment. It is expected that data cleaning activities will ensure collection of all reportable events in the clinical database. An AE with completely missing onset and stop dates, or with the onset date missing and a stop date later than the first dose date of either study treatment, will be considered to be treatment emergent.

10.0 Biomarker Definitions

HRR status: Mutational status of Homologous Recombination Repair (HRR) pathway genes: . In this document, HRR status is primarily determined using the Myriad research assay on tumor sample collected prior to enrollment. This test only reports HRR mutational status in the tumor and cannot distinguish germline mutation from somatic mutation. In addition, local germline testing results for BRCA1, BRCA2 were collected from sites when available. Local testing results for other HRR genes, when available, are also included.

- BRCA mutant (BRCA-mut): gBRCA mutant OR tBRCA mutant
  - gBRCA mutant (gBRCA-mut): At least one deleterious or suspected deleterious mutation found in BRCA1 or BRCA2 in local germline testing.
  - tBRCA mutant (tBRCA-mut): At least one deleterious or suspected deleterious mutation found in BRCA1 or BRCA2 in the tumor.
- BRCA wild type (BRCA-wt): tBRCA-wt AND not gBRCA-mut
  - tBRCA wild type (tBRCA-wt): No deleterious or suspected deleterious mutation found in BRCA1 or BRCA2.
- Unknown BRCA status: Not BRCA-mut AND not BRCA-wt
- Other HRR mutant (oHRR-mut): At least one deleterious or suspected deleterious mutation found in one or more of the HRR pathway genes, excluding BRCA1 and BRCA2.
- Other HRR wild type (oHRR-wt): No deleterious or suspected deleterious mutation found in any of the HRR pathway genes, excluding BRCA1 and BRCA2.
- HRR mutant (HRR-mut): BRCA-mut or oHRR-mut.
- HRR wild type (HRR-wt): BRCA-wt AND oHRR-wt.
- Unknown HRR status: No sample tested or failed sample AND not gBRCA mutant

HRD status: Homologous recombination deficiency (HRD) – Dysregulation in the homologous recombination pathway (due to genetic mutations or alterations) leading to cellular genomic instability and an inability to efficiently repair damaged DNA. In this document, HRD status is determined using the Myriad research assay test on tumor sample collected prior to enrollment.

- HRD positive (HRD-pos): Any tumor with an HRD score ≥42, OR BRCA mutant, is considered HRD positive.
- HRD negative (HRD-neg): Any tumor with an HRD score <42, AND not BRCA mutant, is considered HRD negative.
- HRD unknown (HRD-unk): No sample tested or failed sample AND not gBRCA mutant.

PD-L1 status: PD-L1 is one of the ligands that bind to PD-1 on tumor infiltrating T cells and renders the T cells inactive. PD-L1 expression has been used as a biomarker for identifying patients who may benefit from anti-PD1/L1 therapies. In this document, PD-L1 status is determined using the Agilent/DAKO 22C3 immunohistochemistry (IHC) clinical trial assay (CTA) on tumor sample collected prior to enrollment.

- PD-L1 positive (PD-L1-pos): Any tumor with a combined proportion score (CPS) score ≥1. CPS is defined as: (the number of PD-L1 positive tumor and immune cells/the number total tumor cells)*100.
- PD-L1 negative (PD-L1-neg): Any tumor with a combined proportion score (CPS) score <1.
- PD-L1 unknown: No sample tested or failed sample.

11.0 Analysis Sets

11.1 Screening Analysis Set

All patients that signed the informed consent form including screen failures.

11.2 Full Analysis Set

The full analysis set (FAS) will consist of all Phase 2 patients who receive any amount of study treatment. If a patient receives more than one dose level of study treatment, the patient will be classified according to the original dose level received. The primary analysis of efficacy endpoints will be performed on the FAS population.

11.3 Pooled OC Full Analysis Set:

Given the similarities of the Phase 1 and Phase 2 patient population for the ovarian cancer cohort, corresponding efficacy analyses will be provided using the pooled Phase 1 and Phase 2 data. This analysis set will include all OC patients that are treated with any amount of study treatment.

11.4 Safety Analysis Set

The safety analysis set will include all patients who receive any amount of study treatment in Phase 1 or Phase 2. In Phase 1, patients will be evaluated by dose level actually received and tumor type. In Phase 2, patients can be evaluated by tumor type. If a patient receives more than one dose level, the patient will be classified according to the first dose level received. In this non-randomized study, the FAS and the safety analysis set in Phase 2 are identical. The safety analysis set will be used to summarize patient disposition.

11.5 DLT Analysis Set

The DLT analysis set will consist of all Phase 1 patients who complete the first cycle of therapy i.e. patients who started cycle 2 or discontinued at least 21 days after the first dose of either study medications in cycle

1, unless the patient discontinues due to a DLT, and is able to take more than 80% of the intended dose of both agents. The DLT analysis set will be used for the evaluation of the MTD in Phase 1.

11.6 Efficacy Evaluable (EE) Analysis Set

The EE analysis set will consist of all dosed (with either pembrolizumab or niraparib) FAS patients with at least one evaluable post-baseline tumor assessment. Tumor response endpoints including ORR and DCR will be analyzed using the EE analysis set.

11.7 Pooled OC EE Analysis Set

Given the similarities of the Phase 1 and Phase 2 patient population for the ovarian cancer cohort, corresponding efficacy analyses will be provided using the pooled Phase 1 and Phase 2 data. This analysis set will include all OC patients that are treated with any amount of study treatment and least one evaluable post-baseline tumor assessment.

11.8 Pharmacokinetic (PK) Analysis Set

The pharmacokinetic analysis set will consist of all patients with sufficient data to enable estimation of at least one PK parameter. Patients who are enrolled without meeting inclusion/exclusion criteria may be excluded upon Sponsor's review.

12.0 Interim Analyses

To minimize the risk of exposing patients to an ineffective treatment, a series of response assessments will be performed when 6, 12, 18, 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 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 $\geq$ 1 responder are 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 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 48 patients.

13.0 Data Review

Final data for analysis will be cleaned prior to receipt by statistical programming. Ongoing data handling will take place by the study programmer, until the time at which the study team has full access to the data.

13.1 Data Handling and Transfer

All the data will come from the TESARO data management group and be extracted in SAS® dataset format (SAS v9.4 or later) and converted to SDTM v3.2. Please refer to the Data Management Plan for details.

13.2 Data Cleaning

Beyond the data cleaning built into the DMP, PRA will be programming analysis datasets and TFLs and will provide additional data cleaning. Data issues identified during the process of programming analysis datasets and TFLs programming, will be sent to Data Management.

All derived datasets will include patient-level variables, such as analysis set inclusion, sex, tumor cohort, and dose dates.

Any methodologies used to address any issues identified in the data will be documented in the analysis data set specifications and finalized before database lock.

Variables generated at the patient level will be stored in a consolidated data set for the study. Variables at the patient level or below (e.g., at the visit level) will be generated in analysis data set programs, not in the programs generating the TFLs. Exceptions may include simple concatenation or formatting that will only be used once.

The content of the analysis data sets will be detailed in a separate document. For each derived data set, the label, sort order, and structure (expected number of records per patient/visit) will be specified. For each variable, the name, label, type, length, format, and source or derivation description will be specified. Detailed rules devised to handle specific data patterns found in data reviews will be included. The analysis dataset specifications will be finalized before database lock.

Review of a pre-lock TFL run on the ready-to-lock database allows for further data screening prior to lock. The pre-lock TFLs may be discussed with TESARO in a data review meeting to identify any final data issues and seek corrections prior to database lock. The PRA and TESARO statistician must approve database lock ahead of locking the database. The TESARO statistician will sign off per TESARO process.

13.3 Handling of Dropouts or Missing Data

Missing observations will generally be treated as missing at random and will not be imputed, unless otherwise noted.

Incomplete dates for disease history (e.g. initial diagnosis date, date of documented, locally advanced, metastatic disease diagnosis, date of response or progression in prior treatment) will be imputed as follows:

1. If the day is missing, it will be imputed to the 1st day of the month.
2. If both day and month are missing, the month and day will be imputed as January 1st.
3. If the date is completely missing, no imputation will be performed.

Incomplete days for the calculation of platinum-free interval (PFI) will be imputed as follows:

- Platinum start/end dates:
    - If the day is missing, it will be imputed to the 1st day of the month.
    - If both day and month are missing, the month and day will be imputed as January 1st.
    - If the date is completely missing, no imputation will be performed.

- Date of progression:
    - If the day is missing, it will be imputed to the 1st day of the month.
    - If day and month are missing or the date is completely missing, the start of the next chemotherapy regimen will be used.

Incomplete dates for adverse event and concomitant medication dates will be imputed as follows:

Start Date:

- If only 'day' is missing, and the month and year are not the same as the month and year of first dose, then impute day with '01'. Otherwise, if the month and year are the same as first dose date, use first dose date.
- If 'day' and 'month' are missing, and 'year' is not missing, then impute month and day with month and day of first dose date (assuming same 'year').
- If the year is not the same as the year of first dose, impute 01 for day and 01 for month.
- If the start date is completely missing, it will be set to the first dose date.

Stop Date:

- If only 'day' is missing, impute day with last day of the month.
- If 'day' and 'month' are missing, and 'year' is not missing, then impute month with '12' and day with '31' (or date of study discontinuation/completion if earlier than 12-31).
- If the stop date is completely missing, it will be set to the date of study discontinuation/completion. A stop date will not be applied to ongoing AEs.
- If the imputed stop date is greater than last contact date, then set to last contact date.

Note, for all listings the actual value for date (not imputed) will be presented in all data listings and imputed dates will only be used for programming flags, etc.

14.0 Statistical Methods

In general, categorical data will be summarized using number of patients (n), frequency and percentages, with the denominator for percentages being the number of patients in the analysis set for each cohort. Percentages will be rounded to 1 decimal place except for 100%, which will have no decimal place.

Continuous data will be summarized using the number of patients, mean, standard deviation, median, quartiles (Q1, Q3), minimum, and maximum. The mean, median and quartiles (Q1, Q3) will be presented to 1 decimal place greater than the original data; the standard deviation will be presented to 2 decimal places greater than the original data; and the minimum and maximum will have the same number of decimal places as the original data.

Results will be displayed for each of the TNBC and OC cohorts as well as the overall population. All statistical analyses and data listings will be performed using SAS.

Two-sided exact 90% confidence intervals (CIs) based on the Clopper-Pearson method (3) will be provided to summarize the binomial proportion of the derived best overall response for RECISTv1.1 assessments where applicable:

The Clopper-Pearson CI (3) can be carried out using the FREQ procedure in SAS v9.4 or higher.

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. Subgroup analyses will be performed using descriptive statistics and are considered exploratory.

In addition:

- Weeks will be calculated as number of days divided by 7
- Months will be calculated as number of days divided by 30.4375
- Study Day 1 will be considered the first day of study treatment

14.1 Patient Disposition

Disposition of patients includes the number and percentage of patients for the following categories:

- patients in each of the analysis sets,
- patients discontinued from treatment,
- primary reason for discontinuation from treatment,
- patients discontinued from the study, and
- primary reason for discontinuation from the study.

Numbers and percentages of patients will be presented by dose level in the Phase 1 portion and for all patients by tumor cohort in the Phase 2 portion.

A listing will present data for patient disposition.

14.2 Protocol Deviations

A protocol deviation (PD) is any failure to comply with the study protocol as approved by the relevant regulatory authority, ethics committee and/or institutional review board, whether planned or unplanned.

PD will be assessed and classified as important or significant. A protocol deviation is classified as an important PD if there is the potential to:

- Impact the completeness, accuracy, and/or reliability of the study data, or
- Affect a subject's rights, safety, or well-being.

A protocol deviation is classified as a significant PD if it has been confirmed to:

- Adversely impact the completeness, accuracy, and/or reliability of the study data
- Affect a subject's rights, safety, or well-being.

All PDs will be identified and finalized prior to database lock.

The number of patients with each type of important protocol deviations and the number of deviations will be tabulated by deviation category and by deviation type for all patients in the safety analysis set per dose level in in Phase 1 and per tumor cohort in Phase 2. A listing of all deviations (including deviation date, deviation type, important or significant categorization, and deviation description) will be generated.

14.3 Treatments

14.3.1 **Extent of Study Treatment Exposure**

The following study drug exposure parameters will be summarized:

Any study drug

- Duration of study drug exposure in months defined as:

$$\frac{\max(\text{Date of last dose of niraparib}, \text{Date of last dose of pembrolizumab}, \text{ End of treatment date per CFR}) - \min(\text{Date of first dose of niraparib}, \text{Date of first dose of pembrolizumab}) + 1}{30.4375}$$

The number of study treatment cycles initiated as a categorical and continuous variable

A listing of patients who discontinued one treatment but continued with the other will be provided along with number of cycles and last dosing date for each treatment.

Niraparib

- Duration of niraparib treatment in months

$$\frac{\text{Date of last dose of niraparib} - \text{Date of first dose of niraparib} + 1}{30.4375}$$

- The number of niraparib treatment cycles initiated as a categorical and continuous variable
- Cumulative niraparib dose (mg) defined as the sum of all niraparib doses received. This will be derived using pill count data (dispensed - returned), when available. If the returned pill count data is not available for a particular cycle, the dosing data along with dosing modifications will be used to compute cumulative dose for that cycle.

- Actual dose intensity (mg/day) for niraparib defined as:

$$\frac{\text{Cumulative niraparib dosage (mg) received}}{(\#\text{ of } \textit{study treatment} \text{ cycles initiated}) * \#\text{ planned dosing days per cycle}}$$

The intended dose intensities (IDI) for the different dose levels are provided below:

  - Dose level 1: IDI =200mg/day
  - Dose level 2: IDI =300mg/day
  - Recommended phase 2 dose: IDI=200mg/day

- Relative dose intensity (%) for niraparib defined as:

$$\frac{\text{Actual dose intensity}}{\text{Intended dose intensity}} \times 100\%$$

- The number and percentage of patients with niraparib dose reductions, dose-escalations above starting dose, dose interruptions, and number of patients with at least one reported missed dose will also be presented.

In addition, the starting dose of niraparib by cycle will be summarized.

Pembrolizumab

- Duration of pembrolizumab treatment in months

$$\frac{\text{Date of last dose of pembrolizumab} - \text{Date of first dose of pembrolizumab} + 21}{30.4375}$$

- The number of pembrolizumab cycles initiated as a categorical and continuous variable.
- Cumulative pembrolizumab dose (mg) defined as the sum of all pembrolizumab doses received.

- Actual dose intensity (mg/cycle) for pembrolizumab defined as

$$\frac{\text{Cumulative pembrolizumab dosage (mg) received}}{(\#\text{ of } study\ treatment \text{ cycles initiated})}$$

- Intended dose intensity (mg/cycle) for pembrolizumab defined as

$$\frac{200\ (\text{mg})}{1\ (\text{cycle})} = 200\ (\text{mg/cycle})$$

- Relative dose intensity (%) for pembrolizumab defined as

$$\frac{\text{Actual dose intensity}}{\text{Intended dose intensity}} \times 100\%$$

- Number of patients with pembrolizumab infusion interruptions.

A by-patient listing based on the safety population will also be produced per each study treatment, disease type and phase of the study.

14.3.2 Prior and Concomitant Medications

Medications collected at Screening and during the study will be coded using the current version of the World Health Organization (WHO) Drug dictionary. The medications will be categorized as prior or concomitant using the following definitions:

- Prior medications: any medications, other than study treatments and pre-medications for study treatment, which started prior to the first dose date of study treatment.
- Concomitant medications: any medications, other than study treatments, being taken on or after the initial study treatment dosing date through 30 days after the last dose or until the start of subsequent antitumor therapy

Using the definition above, medications can be classified as both prior and concomitant. Both prior medications and concomitant medications will be summarized by Anatomical Therapeutic Chemical (ATC) classification drug class level 3 and WHO preferred name using the number and percentage of patients for each cohort (WHO Drug Dictionary, September 2017). A patient reporting the same medication more than once will be counted only once when calculating the number and percentage of patients who received that medication in a given time category (prior or concomitant). The summary of concomitant medications will be ordered by descending frequency with respect to drug class and by descending frequency of preferred name in total within the drug class. For drugs with the same frequency, sorting will be done alphabetically. Summaries will be based on the safety population.

All prior and concomitant medications (other than per-protocol study treatments) will be provided in a by-patient listing sorted by patient ID number and administration date in chronological order.

14.4 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized per dose level in Phase 1, per tumor cohort in Phase 2, and for all OC patients combined in Phase 1 and Phase 2. Descriptive statistics will be provided for age (<65, ≥65 to - <75, and ≥75), sex (male versus female), race (American Indian or Alaska Native, Asian, Black, Native Hawaiian or other Pacific Islander, White, or other), Ethnicity (Hispanic or Latino Not Hispanic or Latino), baselines for weight (kg), height (m), and BMI (kg/m^2). Additionally, PD-L1, BRCA, HRD, and HRR status will be summarized as below:

- PD-L1Status (Positive, Negative, Unknown)
- BRCA Status (BRCA-mut [gBRCA-mut, s-BRCA (gBRCAwt/tBRCA-mut), gBRCAunk/tBRCA-mut], BRCA-wt, Unknown)
- HRD Status (HRD-positive [BRCA-mut, BRCA-wt/HRD-positive], HRD-negative, Unknown)
- HRR Status (HRR-mut [BRCA-mut, BRCAwt/oHRR-mut, BRCAunk/oHRR-mut], HRR-wt, Unknown)

The concordance between gBRCA status and tBRCA status will also be evaluated.

14.4.1 Primary Cancer History

A summary of primary cancer history will be presented including: the tumor site, histology and grade of disease at diagnosis, the most recent cancer stage, and the most recent grade and histology.
A by-patient listing for primary cancer history characteristics will also be provided.

14.4.2 Medical History, Surgical History

General medical history information (including past and ongoing) and prior medications and will be summarized for category and conditions ongoing or resolved at study entry based on the FAS (Phase 2) or safety set (Phase 1). Medical history conditions will be collected by CRF at time of screening. General medical history information will be coded by System Organ Class (SOC) and Preferred Term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA), using version 20.0. The count and percentage of patients with each medical history event will be summarized by MedDRA SOC and PT for all patients and by dose cohort. SOCs will be presented by descending frequency with PTs in descending order of frequency for adverse events within the SOC (and further sorted alphabetically, for PTs with the same number of AEs reported within a SOC).

A by-patient listing of general medical history will be provided by patient ID number in ascending order.
A special table and listing will be added to summarize any prior blood disorders of thrombocytopenia, leukopenia, anemia or neutropenia.

Prior anticancer treatment will be summarized per agent preferred name and grouping for all patients in the FAS. Groupings are defined as platinum therapies (cisplatin and carboplatin); anthracycline therapies (doxorubicin, pegylated liposomal doxorubicin, doxorubicin hydrochloride, pegylated liposomal doxorubicin hydrochloride), taxanes (docetaxel, paclitaxel or nab-paclitaxel) and other. The following two summaries will be produced:

- All therapies (regardless of what setting therapy was given in)

- Therapies in metastatic/recurrent setting (excluding the treatments given in adjuvant or neoadjuvant setting)

Prior surgery, and prior anti-cancer regimens, along with prior response information will be listed. The number and percentage of patients in each of the following prior anti-cancer therapy categories will be tabulated:

- Patients with at least one type of any prior anti-cancer treatment (drug, radiotherapy or surgery)
- Patients with at least one prior anti-cancer drug therapy
- Patients with at least one prior anti-cancer radiotherapy
- Patients with at least one prior anti-cancer surgery

Prior anti-cancer drug therapy will be summarized as follows based on the number and percentage of patients with the following:

- Patients with at least one prior anti-cancer drug therapy
    - Number of any prior anti-cancer therapy regimens: 0, 1, 2, 3, 4, ≥5. Hormonal agents, monoclonal antibodies that inhibit angiogenesis, tyrosine kinase inhibitors and all investigational drugs are not considered for either cohort. Agents will be categorized as noted in Appendix 6.
    - Phase 1: Adjuvant and neo-adjuvant are not considered when counting lines.
    - Phase 2:
        - OC cohort, neo-adjuvant, adjuvant, and the combination of both will be considered as one line of therapy.
        - TNBC cohort, adjuvant and neo-adjuvant are not considered when counting lines.
    - Pooled OC: Phase 2 rules will be followed for the pooled analysis.
- Intent of Therapy: Neo-Adjuvant / Adjuvant / Chemotherapy/ Other.
- Prior Bevacizumab Therapy (Yes [first-line, recurrent setting, both], No)

In addition, the platinum-free interval (PFI) will be used to classify the response to last platinum therapy. Platinum-based therapeutics will consist of cisplatin and carboplatin regimens. PFI will be defined as the time between the end date of last platinum therapy to progression. If PD date is not available, the onset of the next therapy will be used. Using the PFI, the response to last platinum therapy will be determined using the following definitions for ovarian patients:

- Platinum-refractory: PFI <=28 days
- Platinum-resistant: 28 days < PFI < 180 days
- Platinum-sensitive: PFI >=180 days

For TNBC patients, the following categories will be used:

- PFI < = 56 days (8 weeks)
- PFI > 56 days (8 weeks)

14.5 Efficacy Analyses

All efficacy endpoints will be summarized on the Phase 2 FAS analysis set by disease type (OC, TNBC). In addition, response endpoints will be evaluated using the EE analysis set. In addition, given the similarities of the Phase 1 and Phase 2 patient population for the ovarian cancer cohort, corresponding efficacy analyses will be provided using the pooled Phase 1 and Phase 2 data.

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% CIs based on the Clopper-Pearson method will be presented for the primary efficacy endpoint ORR per RECIST v1.1 as well as the following secondary endpoints: DCR per RECIST v1.1. Time-to-event data will be summarized by 25th, 50th (median), and 75th percentiles with associated 2-sided 90% CIs as well as percent of censored observations.

Tumor size (sum of longest (non-nodal) dimension and shortest (nodal) axes of all target lesions) will be presented graphically using waterfall plots, to present each subject's best percentage change in tumor size as a separate bar, with the bars ordered from the largest increase to the largest decrease. A reference line at the –30% change in tumor size levels will be added to the plots, which corresponds with the definition of 'partial' response.

Swimmer plots will be produced. This depicts each patient's nature and duration of response as a separate bar (horizontally) over time.

14.5.1 Primary Endpoints

Objective Response Rate (ORR): Evaluated separately for TNBC and OC cohorts in Phase 2 of the study. The ORR is defined as the proportion of patients achieving a confirmed best overall response of CR or PR as assessed by the Investigator per RECIST (v1.1). Tumor assessments after the initiation of further anticancer therapy are excluded. Point estimates and two-sided 90% exact confidence intervals will be provided for ORR.

14.5.2 Methods for Handling Dropouts and Missing Data

Missing observations will generally be treated as missing at random and will not be imputed, unless otherwise noted. Adverse event and concomitant medication dates will be imputed as mentioned in Section 13.3. Note, for all listings the actual value for date (not imputed) will be presented in all data listings and imputed dates will only be used for programming flags, etc.

14.5.3 Multiplicity

Adjustments for multiplicity will not be made since this is an estimation study and separate inferences will be drawn for each tumor cohort.

14.5.4 Pooling of Sites

All data from all sites will be pooled. Study center or treatment-by-center interaction will not be included in any statistical analysis.

14.5.5 Secondary Endpoints

The following are the secondary endpoints to be evaluated in Phase 2 of the study per disease type:

- Duration of response: DOR by RECIST v1.1;
- Disease control rate: DCR by RECIST v1.1;
- Progression-free survival: PFS by RECIST v1.1;
- Overall survival (OS).

DOR, 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% CI's using the method of Brookmeyer and Crowley (5), number of events and number of censored observations.

Additionally, PFS will be summarized at months 3, 6, 9, 12 and 15 and OS rates will be summarized at months 3, 6, 9, 12, 15 and 18. The standard error of the KM estimates of event-free probability will be estimated using the Greenwood's formula (6).

DOR and PFS defined by RECIST v1.1 will be analyzed separately by both criteria. The time to event endpoints (PFS, DOR, and OS) will also be summarized graphically with KM estimates of the survivor function and the number of patients at risk for selected timepoints. Additionally, the figures will include the median of the survival distribution.

All time to event analysis (i.e. PFS, OS and DOR) may be performed if more than 10 events are observed in each cohort. Additionally, duration of follow-up, defined as the time from first dose until date of death or date patients were censored for overall survival, will be summarized. The KM estimate of the median potential follow-up, treating death as censors, and censored observations as events, will be presented.

Tumor response endpoints (ORR, DOR, DCR) will also be analyzed without the confirmation requirements for CR and PR and without duration requirement for SD using the same methodology as described above.

Protocol specified irRECIST secondary endpoints were not consistently collected across all patients and therefore cannot formally be evaluated using standard summaries. These endpoints will be listed. For patients who received treatment beyond radiological progression per RECIST v1.1 by ≥ 28 days and who have post-progression tumor assessments, the irRECIST evaluations will be listed along-side the RECIST v1.1 evaluations, as available. Date of study treatment discontinuation will also be included.

Exploratory analyses of clinical benefit rate (CBR) at 18 weeks, per definition in Section 8, will be performed for the EE population.

14.5.6 Examination of Subgroups

Descriptive exploratory subgroup analyses of ORR, DCR (with and without confirmation requirements), PFS and OS will be performed. The EE population will be used for ORR and DCR whereas the FAS will be used to analyze PFS and OS. For the TNBC cohort, the respective Phase 2 populations will be of focus, whereas for the OC cohort, the respective pooled Phase 1 and Phase 2 populations will be used.

- Prior Lines of Therapy: OC cohort (1-2; 3+); TNBC cohort (0-1; 2+)
- Response to Last Platinum-Based Therapy in OC cohort (refractory, resistant, sensitive and refractory/resistant pooled)
- Prior Bevacizumab Use in OC cohort (yes [first line setting, recurrent setting, both first line/recurrent], no prior bevacizumab)
- BRCA status (BRCA-mut, BRCA-wt, unknown) for OC and TNBC.

- HRD status (HRD-pos, HRD-neg, unknown); further breakdown of HRD-pos as BRCA-mut and BRCA-wt will be performed for OC and TNBC.
- HRR status for TNBC cohort only (HRR-mut, HRR-wt, unknown); further breakdown of HRR-mut as BRCA-mut and non-BRCA-mut/oHRR-mut will be performed. Non-BRCA-mut includes BRCAwt and BRCAunk.
- PD-L1 status (PDL1-pos, PDL1-neg, unknown) for OC and TNBC.

A detailed listing for responders and patients with SD will be produced including the above-mentioned variables. A summary of all analyses to be conducted by population and subgroups is included in Table 4.

Table 4: Efficacy analyses to be conducted by population and subgroup

Analysis	TNBC Phase 2		OC Phase 2		OC Pooled (Phase 1+Phase 2)	
	FAS	EE	FAS	EE	FAS	EE
ORR/DCR	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]
DOR	X[a]		X[a]		X[a]	
PFS	X		X		X	
OS	X		X		X	
ORR/DCR Subgroups		X[a]				X[a]
PFS Subgroups	X				X	
OS Subgroups	X				X	

a) Analyses will be performed using RECIST v1.1 and repeated for Best Observed Overall Response.

Note:
TNBC Subgroups:
1. Prior Lines of Therapy;
2. BRCA Status
3. HRR Status
4. HRD Status
5. PD-L1 Status

OC Subgroups:
1. Prior Lines of Therapy
2. Prior Bevacizumab Use
3. Response to Last Platinum Therapy
4. BRCA Status
5. HRD Status
6. PD-L1 Status

14.6 Safety Analyses

Safety Tables and Listings will be presented to summarize TEAE's, laboratory data and vital signs and in Phase 1 as well as Phase 2. Phase 1 patients with RP2D dose levels may be pooled with Phase 2 patients in the same tables/listings by tumor type if deemed necessary at the end of the study. In general, all summaries of by-cycle and day safety parameters will be summarized through all cycles where information is available, as well as at the treatment discontinuation visit. This includes laboratory values, vital signs and ECG parameters. Additional summaries will be derived as the minimum and maximum for all on-study assessments and presented similarly to the other time points at the end of the summary table. This will allow an assessment of either the best or worst value assessed throughout the conduct of the study. The maximum and minimum calculations will use all post-baseline data, including any unscheduled assessments.

14.6.1 **Adverse Events**

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 20.0. Only TEAE's (refer to Section 8 for definition) will be analyzed but all AEs occurring on-study will be listed in patient data listings. By-patient listings will also be provided for the following: patient deaths, SAEs, and AEs leading to withdrawal.

A high-level overview of AEs will be presented in a summary table. This table will include the numbers and percentages of patients who had:

- at least one TEAE,
- any TEAE's related to study treatment,
- any grade 3 or higher TEAE,
- any grade 3 or higher TEAE's related to study treatment,
- any SAE
- any SAE related to study treatment,
- any grade 3 or higher SAE related to study treatment,
- any TEAE's resulting in withdrawal of study medication,
- any TEAE's resulting in dose reduction of niraparib,
- any TEAE's resulting in dose interruption of either study treatment,
- any TEAE's of clinical interest,
- any drug-related TEAE leading to withdrawal of study medication,
- any TEAE with outcome of death.
- any drug-related TEAE with outcome of death
- DLT's for the Phase 1 portion only.

AEs will be tabulated by SOC and preferred term. Summary tabulations include the following subsets:

- DLT's during the period of Cycle 1/Day 1 through Cycle 1/Day 21 for Phase 1 will be summarized by dose level to which they were originally assigned, including those who receive subsequent treatment at a different dose. The AE's will also be classified by their CTCAE 4.03 grades.
- Incidence of TEAEs.

- Incidence of related TEAEs defined as treatment-emergent AEs assessed by the Investigator as related to either study treatment ('Related', 'Possibly Related', or missing),
- Incidence of treatment-emergent SAEs. In addition, a by-patient listing of SAEs will be presented (the patient listing will contain all SAEs regardless of treatment-emergent AE status).
- Incidence of related treatment-emergent SAEs.
- Incidence of TEAEs with outcome of death. A by-patient listing of deaths (including days since last dose) will be presented. All AEs with outcome of deaths occurring on-study and during follow-up will be displayed in the listing (regardless of treatment-emergent AE status).
- Incidence of related TEAEs with outcome of death.
- Incidence of TEAEs resulting in withdrawal of study treatment, and a by-patient listing of TEAEs resulting in withdrawal of study treatment will be presented.
- Incidence of related TEAEs resulting in withdrawal of study treatment
- Incidence of TEAEs resulting in dose reduction of niraparib.
- Incidence of TEAEs resulting in dose interruption of either study drugs.
- Incidence of TEAEs by maximum CTCAE grade
- Incidence of related TEAEs by maximum CTCAE grade
- Incidence of CTCAE Grade 3 or greater TEAEs.
- Incidence of CTCAE Grade 3 or greater treatment related TEAE's.
- Most commonly reported (at least 5% of all patients) TEAEs.
- Most commonly reported (at least 5% of all patients) treatment related TEAEs.
- Incidence of AE's of clinical interest as specified in the protocol:
    - Overdose of pembrolizumab (defined as a dose ≥ 1000 mg [5 times the dose]).
    - An elevated aspartate aminotransferase (AST) or alanine aminotransferase (ALT) value that is ≥ 3× upper limit of normal (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.
    - New malignancy
    - Overdose of niraparib
    - MDS/AML
        - Myelodysplastic syndrome
        - Myelodysplastic syndrome transformation
        - Myelodysplastic syndrome unclassifiable
        - Acute myeloid leukaemia
        - Acute myeloid leukaemia recurrent
        - Blast crisis in myelogenous leukaemia
        - Myeloid leukaemia
- A summary of hematologic events including thrombocytopenic (preferred terms='thrombocytopenia' or 'platelet count decreased'), anemic (preferred terms='anaemia' and 'haemoglobin decreased') and neutropenic events (preferred terms = 'neutropenia', 'febrile neutropenia', 'neutrophil count decreased' and 'neutropenic sepsis').
- A summary of immune related adverse events as defined in Appendix 7.

Overall, patients with the same AE more than once will have that event counted only once within each SOC, and once within each PT. When summarized by severity, patients with the same AE more than once will have the maximum severity of that event counted within each SOC, and once within each PT.

Adverse event summaries will be ordered by decreasing frequency for SOC and decreasing frequency for PT within SOC (and further sorted alphabetically, for PTs with the same number of AEs reported within a SOC).

Additionally, by-patient listings of AE's of clinical interest will be presented if appropriate.

14.6.2 Laboratory Data

All laboratory values, for which a normal range is available, will be classified into NCI CTCAE v 4.03 grades. The categories are defined according to the criteria available on the following website: http://evs.nci.nih.gov/ftp1/CTCAE/About.html.

For the purposes of summarization in both the tables and listings, all laboratory values will be converted to standardized units and differentials of white blood cell (WBC) count should always be converted to absolute counts in SI units for summarization (e.g. % is not an SI unit). If a laboratory value is reported using a non-numeric qualifier it will not be taken into consideration in the derivation of CTCAE criteria (e.g., hypokalemia grade 1 and grade 2 are only distinguished by a non-numerical qualifier (symptomatic; intervention indicated) and therefore grade 2 will not be derived). In general, clinical assessments listed will not be considered, only numeric results will be assessed. Additional laboratory results that are not part of NCI-CTCAE will be presented according to the categories: below normal limit, within normal limits and above normal limit (according to the laboratory normal ranges). Furthermore, only the numeric part in laboratory values that contain non-numeric qualifiers, such as less than (<) a certain value, or greater than (>) a certain value, will be used in the summary statistics.

Multiple measurements taken during the visit for a patient will be represented by the most severe value for each hematology test. The most severe value will be determined first by the value closest to the upper or lower limit of the normal limits (dependent on which direction is considered severe) if the value is within the normal limits. If the value is outside the normal limits, the value furthest from the upper or lower limit will be selected (dependent on which direction is considered severe). If this algorithm does not allow for determining the most severe (i.e., a tie) the measurement closest to dosing date (either niraparib or pembrolizumab) will be selected. Patients who develop ≥ Grade 3 toxicity will be listed.

The following hematology tests will be summarized:

- WBC count, lymphocytes, monocytes, absolute neutrophil count, eosinophils, basophils, hemoglobin, platelets, erythrocyte mean corpuscular volume.

The following chemistry tests will be summarized:

- Sodium, amylase, potassium, total bilirubin, calcium, alkaline phosphatase (ALP), magnesium, AST, chloride, ALT, glucose, total protein, creatinine, albumin, urea or blood urea nitrogen, lactate dehydrogenase. Only non-fasting glucose will be included in summary tables as fasting glucose was only collected per-protocol at screening.

The following coagulation factors will be listed: International normalized ratio (INR) and activated partial thromboplastin time (aPTT).

The following urinalysis parameters will be summarized:

- Specific gravity, protein, leukocyte esterase, glucose, nitrite, ketones, blood, urobilinogen, bilirubin.

Additionally, a by-patient listing will be presented for thyroid functions (thyroid-stimulating hormone, triiodothyronine (T3), or free T3 and free thyroxin), serum CA-125 (OC patients only) and serum pregnancy testing /urine pregnancy testing

NCI CTCAE grades (given in Appendix 1) will be applied for the following lab parameters:

- Hematology: hemoglobin (anemia), WBC (leukopenia), lymphocytes (lymphopenia), neutrophils (neutropenia), and platelets (thrombocytopenia).
- Chemistry: albumin (hypoalbuminemia), alkaline phosphatase (alkaline phosphatase increased), ALT, AST, total bilirubin (blood bilirubin increased), corrected calcium (hypocalcemia, hypercalcemia), creatinine (creatinine increased), glucose (hyperglycemia, hypoglycemia), magnesium (hypermagnesemia, hypomagnesemia), potassium (hyperkalemia, hypokalemia), and sodium (hyponatremia, hypernatremia).
- Coagulation: aPTT, INR.

Where corrected calcium is derived with the following formula:
Corrected calcium (mmol/L) = (0.02 * (40 (g/L) – normal albumin (g/L))) + serum calcium (mmol/L).

For Hyperglycemia, CTCAE grades 1 and 2 will not be derived as they require fasting glucose. Fasting glucose was required by the protocol only at screening, and therefore, will not be utilized in any summaries. These will be displayed in Table as NA (not applicable).

A summary of maximum severity observed on-study treatment for all parameters noted above will be generated for the coded hematology and chemistry parameters. Patients will only be included once, in the maximum severity, for each laboratory parameter. Additionally, a shift summary of baseline to maximum severity on-study treatment will also be produced. All patients in safety population will be included, patients without an assessment present at baseline or on-study treatment will be included as a missing category.

Laboratory measurements that are within their institutional limits of normal and are not graded as 1-4, per the CTCAE, will be summarized as “Grade 0,” which is defined as normal. Additionally, if a lab parameter is graded in both directions (e.g. glucose: hyperglycemia and hypoglycemia), then low direction toxicity grades at baseline and post baseline will be set to 0 when the variables are derived for summarizing high direction toxicity, and vice versa. Hyperglycemia will only be coded to grades ≥ 3 using non-fasting glucose and therefore will not be included in shift tables.

Liver function tests: ALT, AST, and total bilirubin are used to assess possible drug induced liver toxicity. The ratios of test result over ULN will be calculated and classified for these three parameters during the on-treatment period.

Summary of liver function tests will include the following categories. The number and percentage of patients with each of the following during the on-treatment period will be summarized by treatment group:

- ALT ≥ 3×ULN, ALT ≥ 5×ULN, ALT ≥ 10×ULN, ALT ≥ 20×ULN
- AST ≥ 3×ULN, AST ≥ 5xULN, AST ≥ 10×ULN, AST ≥ 20×ULN
- (ALT or AST) ≥ 3×ULN, (ALT or AST) ≥ 5×ULN, (ALT or AST) ≥ 10×ULN, (ALT or AST) ≥ 20×ULN
- Total bilirubin ≥ 2×ULN
- Concurrent ALT ≥ 3×ULN and total bilirubin ≥ 2×ULN

- Concurrent AST ≥ 3×ULN and total bilirubin ≥ 2×ULN
- Concurrent (ALT or AST) ≥ 3×ULN and total bilirubin ≥ 2×ULN
- Concurrent (ALT or AST) ≥ 3×ULN and total bilirubin ≥ 2×ULN and ALP > 2×ULN
- Potential Hy's law: Concurrent (ALT or AST) ≥ 3×ULN and total bilirubin ≥ 2×ULN and ALP < 2×ULN or missing

Concurrent measurements are those occurring on the same date.
Categories will be cumulative, i.e., a patient with an elevation of AST ≥ 10×ULN will also appear in the categories ≥ 5×ULN and ≥ 3×ULN. Liver function elevation and possible Hy's Law cases will be summarized using frequency and percentage.

By-patient listings will be presented for hematology, coagulation factors, urinalysis and serum chemistry. Any laboratory values assessed as clinically significant should be recorded as an AE.

14.6.3 Vital Signs

Vital signs: diastolic and systolic blood pressure (mm Hg), body temperature, pulse rate (beats/min) at each visit, change from baseline to each post-baseline visit, post-baseline maximum/minimum, and change from baseline to post-baseline maximum/minimum will be summarized for the safety analysis set using descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) by dose level or tumor cohort.
A by-patient listing of vital signs will be provided by patient ID number and visit in chronological order.

14.6.4 Physical Examinations and Other Observations Related to Safety

ECOG parameters will be presented by tumor cohort for each dose level and within each tumor cohort at baseline, at each post-treatment time point and at the end of treatment. The ECOG shift from baseline to highest score during the on-treatment period will be summarized by dose level or tumor cohort.
Height, Weight, Pregnancy test results will be presented in a by-patient listing. Physical examination at screening will also be listed.

14.6.5 ECG

The following analyses will be performed for each applicable ECG parameters (RR, PR, QRS, QT, ventricular rate -denoted as HR in what follows, QTcB and QTcF) by treatment group, during the on-treatment period.

- For each of the ECG parameters (HR, and QT, QTcF, QTcB, QRS, PR intervals), descriptive statistics at baseline, at each post-baseline time point and changes from baseline at each post-baseline time point
- Frequency (number and percentage) of patients with notable ECG values according to the following categories presented in
-
- Table 5.

Table 5: Notable ECG Values for QTc Interval Prolongation

TEST	Notable ECG Values
Heart Rate	≤ 50 bpm and decrease from baseline ≥ 20 bpm

	≥ 120 bpm and increase from baseline ≥ 20 bpm
PR Interval	≥ 220 ms and increase from baseline ≥ 20 ms
QRS	≥ 120 ms
QTcF and QTcB Absolute	interval >450 msec and interval ≤480 msec interval >480 msec and interval ≤ 500 msec interval >500 msec
QTcF and QTcB change from baseline	Increase from baseline > 30 ms and ≤ 60 ms Increase from baseline > 60 ms

Frequency (number and percentage) of patients with post-baseline qualitative ECG abnormalities (morphology) will be summarized.
Patients with notable ECG interval values and qualitative ECG abnormalities will be listed for each patient and time point and the corresponding notable values and abnormality findings will be included in the listings.
Unscheduled ECG measurements will not be used in computing the descriptive statistics for change from baseline at each post-baseline time point. However, they will be used in the analysis of notable ECG changes.

15.0 Validation

PRA's goal is to ensure that each table, listing and figure (TFL) delivery is submitted to the highest level of quality. Our quality control procedures will be documented separately in the study-specific quality control plan.

- Derived datasets are independently reprogrammed by a second programmer. The separate datasets produced by the 2 programmers must match 100%. Detailed specifications for the derived datasets are documented in the study Data Mapping Tool provided to the client at study conclusion.
- Tables are independently quality controlled by a second programmer for numeric results.
- Figures are checked for consistency against corresponding tables and listings, or independently reprogrammed if there are no corresponding tables or listings.
- Listings are double programmed and checked for consistency against corresponding tables, figures, and derived datasets.

The complete set of TFLs are checked for completeness and consistency prior to its delivery to the client by the lead clinical programmer, the lead statistician, and a senior level or above statistician, who is not a member of the project team.

The PRA Health Sciences validation process is repeated any time TFL are redelivered using different data. Execution of this validation process is documented through the study Table of Programs that is provided to the client at study conclusion.

PRA's goal is to ensure that each TFL delivery is submitted to the highest level of quality. Our quality control procedures will be documented separately in the study specific quality control plan.

16.0 References

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17.0 List of Abbreviations

Abbreviation	Definition
AE	adverse event
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the concentration × time curve
AUC_{ss}	area under the concentration × time curve at steady state
BP	blood pressure
CBC	complete blood count
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
CR	complete response
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DCR	disease control rate
DKA	diabetic ketoacidosis
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

EE	efficacy-evaluable
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
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	homologous recombination
HRD	homologous recombination deficiency
ICF	informed consent form
ICH	International Conference on Harmonisation
Ig	immunoglobulin
IgG	immunoglobulin G
INR	international normalized ratio
IRB	Institutional Review Board
irRECIST	immune-related Response Evaluation Criteria in Solid Tumors
IV	intravenous(ly)
KM	Kaplan-Meier
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
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
PET	positron emission tomography
PFI	Platinum-free interval
PFS	progression-free survival
PK	pharmacokinetics
PO	oral(ly)
PR	partial response
PR-	progesterone receptor
PT	prothrombin time
PTT	partial thromboplastin time
QD	once daily
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended Phase 2 dose
SAE	serious adverse event
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal

18.0 Appendix 1: Common Terminology Criteria for Adverse Events V4.03 (CTCAE)

Lab Test Name	Lab Test Code	Standard Unit	CTCAE v4.03 SOC	CTCAE v4.03 Term	Grade 1	Grade 2	Grade 3	Grade 4
Activated partial thromboplastin time	APTT	sec	Investigations	Activated partial thromboplastin time prolonged	>ULN - 1.5 x ULN	>1.5 - 2.5 x ULN	>2.5 x ULN	
Albumin	ALB	g/L	Metabolism and nutrition disorders	Hypoalbuminemia	<LLN - 3 g/dL; <LLN - 30 g/L	<3 - 2 g/dL; <30 - 20 g/L	<2 g/dL; <20 g/L	
Hemoglobin	HGB	g/L	Blood and lymphatic system disorders	Anemia	<LLN - 100 g/L	<100 - 80g/L	<80 g/L	
Leukocytes	WBC	10^9/L	Investigations	White blood cell decreased	<LLN - 3.0 × 10^9/L	<3.0 - 2.0 × 10^9/L	<2.0 - 1.0 × 10^9 /L	<1.0 × 10^9/L
Platelets	PLAT	10^9/L	Investigations	Platelet count decreased	<LLN - 75.0 × 10^9/L	<75.0 - 50.0 × 10^9/L	<50.0 - 25.0 × 10^9/L	<25.0 × 10^9/L
Neutrophils	NEUT	10^9/L	Investigations	Neutrophil count decreased	<LLN - 1.5 × 10^9/L	<1.5 - 1.0 × 10^9/L	<1.0 - 0.5 × 10^9/L	<0.5 × 10^9/L
Lymphocytes	LYM	10^9/L	Investigations	Lymphocyte count decreased	<LLN - 0.8 x10^9 /L	<0.8 - 0.5 × 10^9 /L	<0.5 - 0.2 × 10^9 /L	<0.2 × 10^9 /L
Lymphocytes	LYM	10^9/L	Investigations	Lymphocyte count increased		>4x10^9/L – 20*10^9/L	>20*10^9/L	
Sodium	SODIUM	mmol/L	Metabolism and nutrition disorders	Hyponatremia	<LLN - 130 mmol/L		<130 - 120 mmol/L	<120 mmol/L
Sodium	SODIUM	mmol/L	Metabolism and nutrition disorders	Hypernatremia	>ULN - 150 mmol/L	>150 - 155 mmol/L	>155 - 160 mmol/L	>160 mmol/L
Potassium	K	mmol/L	Metabolism and nutrition disorders	Hypokalemia	<LLN - 3.0 mmol/L		<3.0 - 2.5 mmol/L	<2.5 mmol/L
Potassium	K	mmol/L	Metabolism and nutrition disorders	Hyperkalemia	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L	>6.0 - 7.0 mmol/L	>7.0 mmol/L
Creatinine	CREAT	umol/L	Investigations	Creatinine increased	>ULN - 1.5 × ULN	>1.5 - 3.0 × ULN	>3.0 - 6.0 × ULN	>6.0 × ULN
Glucose	GLUC	mmol/L	Metabolism and nutrition disorders	Hypoglycemia	<LLN - 3.0 mmol/L	<3.0 - 2.2 mmol/L	<2.2 - 1.7 mmol/L	<1.7 mmol/L
Glucose	GLUC	mmol/L	Metabolism and nutrition disorders	Hyperglycemia	NA	NA	>13.9 - 27.8 mmol/L	>27.8 mmol/L
Bilirubin	BILI	umol/L	Investigations	Blood bilirubin increased	>ULN - 1.5 × ULN	>1.5 - 3.0 × ULN	>3.0 - 10.0 × ULN	>10.0 × ULN
Alanine Aminotransferase	ALT	U/L	Investigations	Alanine aminotransferase increased	>ULN - 3.0 × ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 × ULN
Aspartate Aminotransferase	AST	U/L	Investigations	Aspartate aminotransferase increased	>ULN - 3.0 × ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 × ULN

Alkaline phosphatase	ALP	U/L	Investigations	Alkaline phosphatase increased	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
Magnesium	MG	mmol/L	Metabolism and nutrition disorders	Hypomagnesemia	<LLN - 1.2 mg/dL; <LLN - 0.5 mmol/	<1.2 - 0.9 mg/dL; <0.5 - 0.4 mmol/L	<0.9 - 0.7 mg/dL; <0.4 - 0.3 mmol/L	<0.7 mg/dL; <0.3 mmol/ L
Magnesium	MG	mmol/L	Metabolism and nutrition disorders	Hypermagnesemia	>ULN - 3.0 mg/dL; >ULN - 1.23 mmol/L		>3.0 - 8.0 mg/dL; >1.23 - 3.30 mmol/L	>8.0 mg/dL; >3.30 mmol/ L
Calcium (corrected)	CA	mmol/L	Metabolism and nutrition disorders	Hypocalcemia	<LLN - 2.0 mmol/L	<2.0 - 1.75 mmol/L	<1.75 - 1.5 mmol/L	<1.5 mmol/ L
Calcium (corrected)	CA	mmol/L	Metabolism and nutrition disorders	Hypercalcemia	>ULN - 2.9 mmol/L	>2.9 - 3.1 mmol/L	>3.1 - 3.4 mmol/L	>3.4 mmol/ L
Prothrombin Intl. Normalized Ratio	INR		Investigations	INR increased	>1 - 1.5 x ULN	>1.5 - 2.5 x ULN	>2.5 x ULN	

19.0 Appendix 2: 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		
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.

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: Procedure:	-21 to -1	1	8[3]	15	Cycle n, Day 1		30 + 7 days	
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	
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.

20.0 Appendix 3 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).

Table 8: 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 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 9: 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.

21.0 Appendix 4: Immune-Related response evaluation criteria in solid tumors

Table 10: Imaging and Treatment after First Radiologic Evidence of Progressive

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

22.0 Appendix 5: Laboratory Standard Units

Laboratory Test	SI Unit
Albumin	g/L
Alkaline Phosphatase	U/L
Absolute neutrophil count	10^9/L
Basophils	10^9/L
Bicarbonate	mmol/L
Total Bilirubin	µmol/L
Blood Urea Nitrogen	mmol/L
Calcium	mmol/L
Chloride	mmol/L
Creatinine	µmol/L
Eosinophils	10^9/L
Glucose	mmol/L
Granulocytes	10^9/L
Hematocrit	frac of 1
Hemoglobin	g/L
INR	1
Lymphocytes	10^9/L
Magnesium	mmol/L
Mean Corpuscular Hemoglobin	pg
Mean Corpuscular Volume	fL
Monocytes	10^9/L
Platelets	10^9/L
Potassium	mmol/L
Total Protein	g/L
Prothrombin Time	s
Partial Thromboplastin Time	s
Red Blood Cells	10^{12}/L
Aspartate Transaminase	U/L
Alanine Transaminase	U/L
Sodium	mmol/L
White Blood Cells	10^9/L

23.0 Appendix 6: Drugs Excluded from Prior Lines of Therapy

The following table lists the drugs that are not included when counting the number of prior lines of therapy.

Agent Name	Agent If Other, specify	Agent If Other, specify PT	Group
Bevacizumab			monoclonal antibody
Other	ABEMACICLIB	ABEMACICLIB	CDK inhibitor
Other	ABT 888	VELIPARIB	investigational drug
Other	ADENOSINE A2A RECEPTOR ANTAGONIST CPI-444	ANTINEOPLASTIC AGENTS	investigational drug
Other	ANASTRAZOLE	ANASTROZOLE	Hormonal therapy
Other	ANASTROZOLE	ANASTROZOLE	Hormonal therapy
Other	ANTI-PTK7 ANTIBODY-DRUG CONJUGATE	PROTEIN KINASE INHIBITORS	investigational drug
Other	ARIMIDEX	ANASTROZOLE	Hormonal therapy
Other	ARQ 092	PROTEIN KINASE INHIBITORS	investigational drug
Other	AVASTATIN (BEVACIZUMAB)	BEVACIZUMAB	monoclonal antibody
Other	AVASTATIN (BEVACIZUMAB)	BEVACIZUMAB	monoclonal antibody
Other	AVASTIN (BEVACIZUMAB)	BEVACIZUMAB	monoclonal antibody
Other	AVASTIN(BEVACIZUMAB)	BEVACIZUMAB	monoclonal antibody
Other	AVASTIN(NFI)	BEVACIZUMAB	monoclonal antibody
Other	AZD1775	PROTEIN KINASE INHIBITORS	investigational drug
Other	BEVACIZUMAB	BEVACIZUMAB	monoclonal antibody
Other	CRLX101	OTHER ANTINEOPLASTIC AGENTS	investigational drug
Other	ENZALUTAMIDE	ENZALUTAMIDE	nonsteroidal antiandrogen
Other	EVEROLIMUS	EVEROLIMUS	motor inhibitor investigational drug
Other	FEMARA	LETROZOLE	Hormonal therapy
Other	FULVESTRANT	FULVESTRANT	Hormonal therapy

Other	GLUTAMINASE INHIBITOR CB-839	ANTINEOPLASTIC AGENTS	investigational drug
Other	GOG 212 (PACLITAXEL)	PACLITAXEL	Chemo maintenance therapy
Other	GSK 2141795	UPROSERTIB	investigational drug
Other	HERCEPTIN	TRASTUZUMAB	monoclonal antibody
Other	INTRAPERITONEAL THERAPY-DRUG UNKNOWN	ALL OTHER THERAPEUTIC PRODUCTS	investigational drug
Other	INVESTIGATIONAL PRODUCT	INVESTIGATIONAL DRUG	investigational drug
Other	IPAFRICEPT	IPAFRICEPT	investigational drug
Other	KADYCLA	TRASTUZUMAB EMTANSINE	monoclonal antibody
Other	LDE225 600 MG DAILY	SONIDEGIB	investigational drug
Other	LETROZOLE	LETROZOLE	Hormonal therapy
Other	LUPRON	LEUPRORELIN ACETATE	Hormonal therapy
Other	MIFAPRISTONE	MIFEPRISTONE	RU 486, for the abortion
Other	PALBOCICLIB	PALBOCICLIB	CDK inhibitor
Other	PERJECTA	PERTUZUMAB	monoclonal antibody
Other	PERJETA	PERTUZUMAB	monoclonal antibody
Other	PERTUZUMAB	PERTUZUMAB	monoclonal antibody
Other	PEXIDARTINIB (PLX3397)	PEXIDARTINIB	investigational drug
Other	PFIZER B - B7661001- PF-6657020 - CLINICAL TIRAL	INVESTIGATIONAL DRUG	investigational drug
Other	PLACEBO	PLACEBO	
Other	TAMOXIFEN	TAMOXIFEN	Hormonal therapy
Other	TARGETED T-CELL THERAPY ON A CLINICAL TRIAL	INVESTIGATIONAL ANTINEOPLASTIC DRUGS	investigational drug
Other	TRAMETINIB	TRAMETINIB	inhibitor tyrosine kinase

			investigational drug
Other	TRASTUZUMAB	TRASTUZUMAB	monoclonal antibody
Other	VANTICTUMAB	VANTICTUMAB	monoclonal antibody
Other	VX-970	PROTEIN KINASE INHIBITORS	investigational drug

24.0 Appendix 7: Immune-Related Adverse Events

Below is a list of MedDRA preferred terms that will be used to identify immune-related adverse events.

Pneumonitis
Autoimmune colitis
Autoimmune hepatitis
Hypophysitis
Hyperthyroidism
Hypothyroidism
Thyroiditis
Diabetic ketoacidosis
Hyperglycaemia
Adrenal insufficiency
Autoimmune dermatitis
Autoimmune nephritis
Dermatitis exfoliative
Pemphigoid
Toxic epidermal necrolysis
Steven Johnson syndrome
Encephalitis autoimmune
Arthritis
Uveitis
Myositis
Guillain-Barre syndrome
Myasthenia gravis
Vasculitis
Pancreatitis
Haemolytic anaemia
Seizure
Myelitis
Myocarditis
Infusion related reaction
Rhabdomyolysis
Iritis
Facial paresis
Demyelination
Polymyalgia rheumatica
Autoimmune neuropathy
Hypopituitarism

Systemic inflammatory response syndrome
Gastritis
Duodenitis
Sarcoidosis
Histiocytic necrotising lymphadenitis
Motor dysfunction
Aplastic anaemia
Pericarditis
Myasthenic syndrome
Vogt-Koyanagi-Harada syndrome

25.0 Document History

Version Date	Version Number	Modified/Reviewed By	Brief Summary of Changes
5-Feb-2016	1.0	PPD	Initial version
22-Jun-2018	1.1	PPD	Incorporated addition of the OC Pooled analyses as well as other changes based on Amendment 2 of the protocol and the updated clinical study database at the time of approval.
21-Mar-2019	2.0	PPD PP D	Incorporated changes as a result of dry run review August 2018.