NIRAPARIB, DOSTARLIMAB (TSR-042)

3000-02-006/213353

A PHASE 2 OPEN-LABEL, SINGLE-ARM STUDY TO EVALUATE THE EFFICACY AND SAFETY OF THE COMBINATION OF NIRAPARIB AND DOSTARLIMAB (TSR-042) IN PATIENTS WITH PLATINUM-RESISTANT OVARIAN CANCER (MOONSTONE)

Sponsor:	TESARO, Inc., a GlaxoSmithKline Company 1000 Winter Street Suite 3300 Waltham, MA 02451 PPD
Medical Monitor:	PPD, MD PPD PPD
Sponsor Protocol No.:	3000-02-006/213353
GOG Protocol No.	606-3032
IND No.:	100,996
Study Drug Names:	Niraparib (GSK3985771), Dostarlimab (GSK4057190)
Development Phase:	2
Date of Protocol:	15 December 2021
Version of Protocol:	4.0 (Amendment 03)

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

Confidentiality Statement

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

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Table 1: Document History

Document	Date	Document Number	Sponsor
Amendment 3 (Version 4)	15 December 2021	TMF-14140373	Tesaro, Inc., a GSK Company
Amendment 2 (Version 3)	17 November 2020	2020N458945_00	Tesaro*
Amendment 1 (Version 2)	18 October 2019	NA	Tesaro*
Original Protocol (Version 1.0)	04 October 2018	NA	Tesaro*

Abbreviations: GSK=GlaxoSmithKline.
*Tesaro is a wholly owned

Amendment 3 (15 December 2021)

Overall Rationale for the Amendment

Amendment 03 revises the protocol to reflect the post analysis continuation of treatment (PACT) for participants that will continue to receive study treatment following final data cut-off (DCO).

Summary of Changes for the Amendment

Table 2: Summary of Changes for Amendment 03 (15 December 2021)

Section(s) Affected	Description of Change	Brief Rationale
Headers, cover page, and Protocol Amendment Summary of Changes	Headers and cover page were updated with new version number; headers were updated with new document number; Protocol Amendment Summary of Changes section was updated to include rationale for new version	Editorial changes to align with the Sponsor's standard protocol template and ways of working
Synopsis 7.1.3 Continued Treatment After Final DCO	New section added to provide clarification on the continuation of treatment after the final DCO date.	To provide continued treatment options to patients still deriving clinical benefit from treatment when the final DCO date is reached
7.4.1 Niraparib Dose Adjustment	Added new requirement that if a patient is diagnosed with myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML), the patient	Program level update

7.4.2 Dostarlimab Dose Adjustment 9.2.3 Supportive Care for Adverse Events	must permanently discontinue niraparib. Updated dose modifications for adrenal insufficiency to include endocrine consultation as follow up. Expanded dose modifications for diarrhea / colitis to include recurrent Grade 3. Expanded dose modifications for pneumonitis to include recurrent Grade 2. "Permanently discontinue" for Grade 4 severity was removed from adrenal insufficiency, hypophysitis, hypothyroidism and hyperthyroidism. Added dose modifications for myocarditis, severe neurological events, severe skin reactions, hemophagocytic lymphohistiocytosis, and other immune-related adverse events of interest (irAEIs)	Clarifications, corrections, and program updates, including mitigation of potentially serious complications of immune-related events. Clinical management of these endocrinopathies are amenable to hormone replacement therapies or thyroid suppressive therapy and the adequacy of supplementation monitorable symptomatically and with laboratory assessments.
7.6.3 Continued Treatment After Final DCO	New section added to provide information on the study assessments required for patients continuing treatment after the final DCO date.	To provide continued treatment options to patients still deriving clinical benefit from treatment when the final DCO date is reached
10.6.1 Continued Access to Study Treatment After Final DCO	New section added to provide drug accountability and dispensing information for patients continuing treatment after the final DCO date.	To provide continued treatment options to patients still deriving clinical benefit from treatment when the final DCO date is reached
7.1.4 Schedule of Safety Assessments 12.3 Safety Monitoring For Continuation of Treatment After Final DCO	New section added to provide information on the safety monitoring requirements for patients continuing treatment after the final DCO date.	To provide continued treatment options to patients still deriving clinical benefit from treatment when the final DCO date is reached

SPONSOR SIGNATURE PAGE

Declaration of Sponsor or Responsible Medical Officer

Title (3000-02-006): A Phase 2 Open-label, Single-arm Study to Evaluate the Efficacy and Safety of the Combination of Niraparib and Dostarlimab (TSR-042) in Patients with Platinum-Resistant Ovarian Cancer (MOONSTONE)

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

Vivek Samnotra, MD Senior Medical Director	Date

INVESTIGATOR'S AGREEMENT

I have read this study protocol, including all appendices. By signing this protocol, I agree to conduct the clinical study, following approval by an Institutional Review Board (IRB)/Independent Ethics Committee (IEC), in accordance with the study protocol, the current International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP), the Declaration of Helsinki (2013), and applicable regulatory requirements. I will ensure that all personnel involved in the study under my direction will be informed about the contents of this study protocol and will receive all necessary instructions for performing the study according to the study protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

2. SYNOPSIS

Name of Sponsor/Company: TESARO, Inc., a GlaxoSmithKline Company

Name of Investigational Product(s): Niraparib and dostarlimab (TSR-042)

Name of Active Ingredient: Niraparib (niraparib tosylate monohydrate) and dostarlimab (TSR-042) (anti-programmed cell death-1 [anti-PD-1] monoclonal antibody, immunoglobulin G4)

Study Number: 3000-02-006/213353

Title of Study: A Phase 2 Open-label, Single-arm Study to Evaluate the Efficacy and Safety of the Combination of Niraparib and Dostarlimab (TSR-042) in Patients with Platinum-Resistant Ovarian Cancer (MOONSTONE)

Study center(s): Multi-center

Principal Investigator: N/A
Investigators: Multi-center

Studied period (years):	**Phase of development:**
Estimated date first patient enrolled: Q1 2019 Estimated date last patient last visit: Q2 2022	Phase 2

Hypothesis:

Treatment with the combination of niraparib and dostarlimab (TSR-042) in patients with platinum-resistant ovarian cancer (PROC) without breast cancer susceptibility gene (BRCA) mutation who were previously treated with bevacizumab may result in an objective response rate (ORR) that is higher than the ORR expected with other available approved therapies for this population. This study will evaluate the efficacy of combination therapy by estimating the ORR along with the duration of response (DOR) in these patients.

Objectives:

Primary:

The primary objective of this study is to evaluate the efficacy, as measured by confirmed ORR per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 based on Investigator assessment, of the combination of niraparib and dostarlimab (TSR-042) in:

- patients with PROC without a known BRCA mutation who have been previously treated with bevacizumab.
- subset of patients with PROC who have programmed cell death-ligand 1 (PD-L1) positive tumors (using a prespecified cut point) without a known BRCA mutation who have been previously treated with bevacizumab.

Secondary:

Secondary objectives of this study are as follows and will be evaluated in the overall population and in the subset of patients with PD-L1 positive tumors:

- To evaluate the overall clinical benefit of the niraparib and dostarlimab (TSR-042) combination as measured by the following secondary endpoints:
  - DOR per RECIST v1.1 based on Investigator assessment
  - progression-free survival (PFS) per RECIST v1.1 based on Investigator

assessment

- overall survival (OS)
- disease control rate (DCR), defined as the percentage of patients who have achieved best overall response (BOR) of confirmed partial response (PR), complete response (CR), or stable disease (SD) per RECIST v1.1 based on Investigator assessment

- To evaluate the ORR, DOR, PFS, and DCR per RECIST v1.1 based on independent review committee assessment
- To evaluate the safety and tolerability of the niraparib and dostarlimab (TSR-042) combination in patients with PROC as measured by standard safety assessments

Exploratory:

Exploratory objectives of this study are as follows and will be evaluated in the overall population and in the subset of patients with PD-L1 positive tumors:

- To evaluate efficacy of the niraparib and dostarlimab (TSR-042) combination among patients with BRCA wild type (BRCAwt) tumors, as measured by confirmed ORR, DOR, PFS, OS, and DCR based on Investigator assessment using RECIST v1.1
- To evaluate the duration of disease control among patients with BOR of CR, PR, or SD based on Investigator assessment and independent review committee assessment
- To evaluate health-related quality of life (HRQoL) in patients with PROC treated with the combination of niraparib and dostarlimab (TSR-042), as measured by the Functional Assessment of Cancer Therapy – Ovarian Symptom Index (FOSI)
- To identify additional potential disease-related or treatment-related biomarkers that correlate with responses to the niraparib and dostarlimab (TSR-042) combination, including, but not limited to, the measures of homologous recombination repair pathway defects and the optimal PD-L1 level for efficacy to be used in other dostarlimab ovarian cancer studies.

Methodology:

This is an open-label, single-arm Phase 2 study to evaluate the efficacy and safety of the combination of niraparib and dostarlimab (TSR-042) in patients with advanced, relapsed, high-grade ovarian, fallopian tube, or primary peritoneal cancer without known BRCA mutation who have platinum-resistant disease and who have also been previously treated with bevacizumab.

This study will consist of a screening period (Day -28 to Day -1), a treatment period, an end-of-treatment period when study treatment is discontinued for any reason, a Safety Follow-up Visit occurring 30 ± 7 days after the last dose of study treatment, and recurring survival assessments occurring every 90 ± 14 days after the last dose of study treatment. All patients will undergo an End of Treatment Visit within 7 days of the decision to discontinue treatment for any reason.

Patients must provide a sufficient tumor tissue sample (formalin fixed paraffin embedded

[FFPE] blocks) for BRCA testing and PD-L1 testing at screening. Slides cut from FFPE blocks must be approved by the Sponsor Blood samples will be collected at screening for central germline BRCA testing. Blood samples will also be collected for exploratory biomarker analysis at screening, at Cycle 3 Day 1, at the time of Investigator-assessed PR (+ 21 days), at the time of Investigator-assessed CR (+ 21 days), and at the End of Treatment Visit.

All patients will receive treatment with niraparib and dostarlimab (TSR-042) (collectively referred to as "study treatment") beginning on Cycle 1 Day 1 using the regimen detailed below. Treatment Cycles 1 to 4 are 3 weeks long and Cycles 5 and later are 6 weeks long.

Study Regimen

Niraparib	**Dostarlimab (TSR-042)**
Starting doses are as follows: • 300 mg PO QD continuously in patients with screening actual body weight ≥ 77 kg AND screening platelet count ≥ 150,000/μL until PD or toxicity • 200 mg PO QD continuously in patients with screening actual body weight < 77 kg OR screening platelet count < 150,000/μL until PD or toxicity	• 500 mg IV on Day 1 of each 3-week cycle (Q3W Cycles 1 to 4), followed by 1,000 mg IV on Day 1 of each 6-week cycle (Q6W Cycle 5 and later) until PD or toxicity

Abbreviations: IV = intravenous; PD = progressive disease; PO = orally; Q3W = every 3 weeks; Q6W = every 6 weeks; QD = once daily

Safety assessments performed will include collection of adverse events (AEs), vital sign measurements, symptom-directed physical examinations, and clinical laboratory assessments.

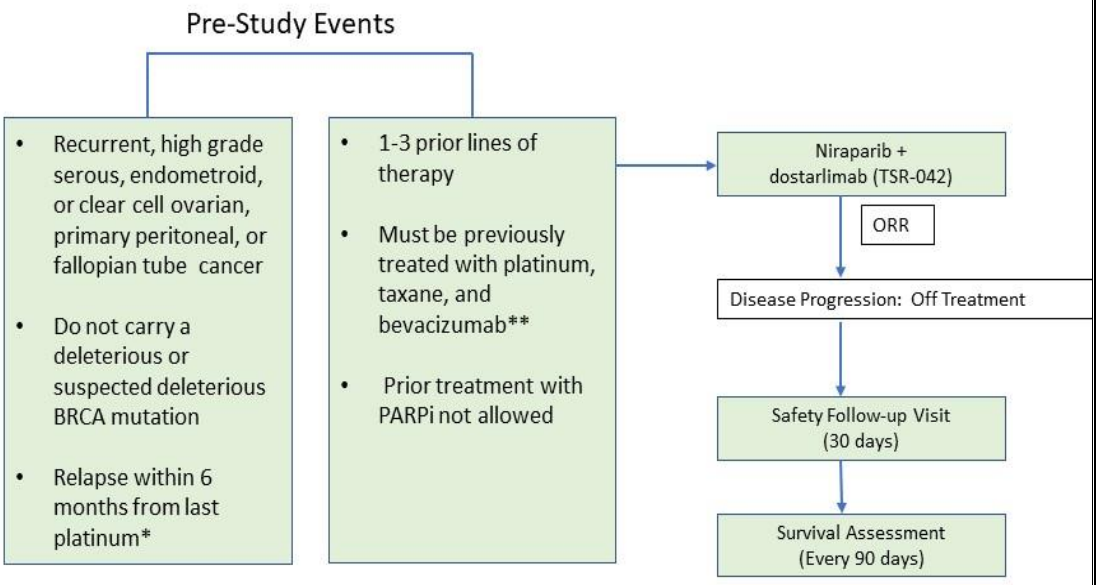
Radiographic evaluations (ie, computed tomography/magnetic resonance imaging of chest, abdomen, and pelvis) to assess the extent of disease will be conducted every 9 weeks (63 ± 7 days) for the first year of study treatment, independent of cycle delays or dose interruptions, or at any time when progression of disease is suspected. After 1 year of radiographic assessments (week 54), imaging will be performed every 12 weeks (84 ± 14 days). Per RECIST v.1.1, CR or PR should be confirmed; tumor imaging for confirmation of response must be performed at the earliest 28 days after the first indication of PR or CR but no later than 35 days after the response. The subsequent tumor imaging after the confirmatory scan should be obtained per the original scheduled interval (eg, 9 weeks [63 ± 7 days] from a confirmatory scan during the first year of study treatment and every 12 weeks thereafter). Radiographic evaluations will continue until progressive disease (PD), start of alternate anticancer therapy, withdrawal of consent to study participation, becoming lost to follow-up, death, or end of the study. If a patient discontinues treatment for a reason other than radiographic progression, death, withdrawal of consent, loss to follow-up, or the end of the study, radiographic evaluation and cancer antigen 125 (CA-125) testing should continue at the specified intervals (ie, every 9 weeks for the first year of study treatment and every 12 weeks thereafter until PD). Also, clinically stable patients should not be discontinued until progression is confirmed. If a patient discontinues treatment for clinical progression and does not meet RECIST criteria for progression, scans and CA-125 testing should continue at the specified intervals until progression is confirmed or until the start of subsequent anticancer treatment.

All AEs (serious and nonserious) will be collected and recorded for each patient from the day of signing the informed consent form until 90 days after last study drug administration or until alternate anticancer treatment has been initiated, whichever occurs earlier; any pregnancies that occur within 180 days post-treatment are to be reported.

All AESIs must be reported as outlined in Section 12.2.7. All AEs including SAEs experienced by a patient, regardless of the suspected causality, will be monitored until the AE or SAE has resolved, until any abnormal laboratory values have returned to baseline or normalized, until there is a satisfactory explanation for the change(s) observed, until the patient is lost to follow-up or withdraws consent, or until the patient has died.

After the final DCO date, for patients continuing study treatment, all SAEs, AESIs (as defined in Section 12.2.7), AEs leading to discontinuation, overdoses, and pregnancies must be reported as detailed in Section 12.2.5 to the Sponsor within 24 hours of becoming aware of a new event or of new (follow up) information on a previously reported event and signed by the Investigator or Sub-Investigator.

Overall Study Schema



*Excludes patients who experienced disease progression within 3 months of first-line platinum therapy
**Neoadjuvant, adjuvant, and the combination of both will be considered as one line of therapy. Treatment with single-agent bevacizumab given as maintenance is not counted as a separate line of therapy. If a therapeutic regimen is modified or changed for a reason other than lack of response or PD (such as allergic reaction, toxicity, or drug availability), this is not counted as a separate line of therapy. The use of single-agent hormonal therapy given for reasons other than progressive disease per RECIST v1.1 (ie, hormonal therapy given for increasing CA-125 levels) is not counted as a separate line of therapy.
Abbreviations: CA-125 = cancer antigen 125; BRCA = breast cancer susceptibility gene; ORR = objective response rate; PARPi = poly(adenosine diphosphate-ribose) polymerase inhibitor; PD = progressive disease; PD(L)-1 = programmed cell death-1 or programmed cell death-ligand 1.

Number of patients (planned): It is anticipated that approximately 150 patients will be enrolled and dosed.

Diagnosis and main criteria for inclusion:

Patients will be eligible for study entry if all of the following criteria are met:

1. Patient must be female ≥ 18 years of age, able to understand the study procedures,

and agree to participate in the study by providing written informed consent.

2. Patients must have recurrent high-grade serous, endometrioid, or clear cell ovarian, fallopian tube, or primary peritoneal cancer.
3. Patients must be considered resistant to the last administered platinum therapy, ie, the time from last administered platinum dose until the initial documented progression (as evidenced by radiographic progression per RECIST v.1.1) must be less than 6 months (183+7 days).
4. Patients must have completed at least 1 but no more than 3 prior lines of therapy for advanced or metastatic ovarian cancer. Neoadjuvant, adjuvant, and the combination of both will be considered as one line of therapy. Treatment with single-agent bevacizumab given as maintenance is not counted as a separate line of therapy. If a therapeutic regimen is modified or changed for a reason other than lack of response or PD (such as allergic reaction, toxicity, or drug availability), this is not counted as a separate line of therapy. The use of single-agent hormonal therapy given for reasons other than progressive disease per RECIST v1.1 (ie, hormonal therapy given for increasing CA-125 levels) is not counted as a separate line of therapy.
5. Patients must have been previously treated with platinum-based regimen, taxane agent(s), and bevacizumab (bevacizumab could be used as a single agent or in combination with another agent, in frontline therapy, as maintenance, or for treatment of recurrent disease).

   Note: Bevacizumab refers to bevacizumab and approved biosimilars, for example, bevacizumab –awwb (MVASI™), bevacizumab-bvzr (ZIRABEV™), etc.
6. Patient has measurable disease according to RECIST v.1.1.
7. Patient has an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (see Appendix 3).
8. Patient has adequate organ function, defined as follows:
   a. Absolute neutrophil count ≥ 1,500/μL, without growth factor support (granulocyte colony-stimulating factor or granulocyte-macrophage colony-stimulating factor administration is not permitted within 2 weeks of screening)
   b. Platelets ≥ 100,000/μL, without platelet transfusion support within 2 weeks of screening
   c. Hemoglobin ≥ 9 g/dL, without transfusion or growth factor support (recombinant erythropoietin) within 2 weeks of screening
   d. Serum creatinine ≤ 1.5 × upper limit of normal (ULN) or calculated creatinine clearance ≥ 50 mL/min using Cockcroft-Gault equation
   e. Total bilirubin ≤ 1.5 × ULN, except in patients with Gilbert's syndrome. Patients with Gilbert's syndrome may enroll if direct bilirubin is ≤ 1.5 × ULN.
   f. Aspartate aminotransferase and alanine aminotransferase ≤ 2.5 × ULN, unless liver metastases are present, in which case they must be ≤ 5 × ULN
9. Patient meets the following criteria:
   a. Female patient (of childbearing potential) is not breastfeeding, has a negative serum pregnancy test within 72 hours prior to taking study treatment, agrees to abstain from activities that could result in pregnancy, as outlined in Section 9.2.2, from enrollment through 180 days after the last dose of study treatment ; or

Note: (a) A urine pregnancy test may be performed if the serum pregnancy result is not available before dosing. (b) Women should not breastfeed or store breastmilk for use, during treatment, and for 30 days after receiving the final dose of study treatment.

b. Female patient is of nonchildbearing potential, for other than medical reasons, defined as any of the following:

- ≥ 45 years of age and has not had menses for > 1 year
- Amenorrheic for < 2 years without a hysterectomy and oophorectomy and a follicle-stimulating hormone value in the postmenopausal range upon screening evaluation
- Has undergone hysterectomy, bilateral oophorectomy, or tubal ligation. Documented hysterectomy or oophorectomy must be confirmed with medical records of the actual procedure or confirmed by an ultrasound. Tubal ligation must be confirmed with medical records of the actual procedure; otherwise, the patient must meet the pregnancy test criteria for women of childbearing potential in inclusion criterion 9a and must be willing to use highly effective contraception throughout the study, starting with the screening visit through 180 days after the last dose of study therapy.

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

10. Patient must provide FFPE tumor tissue block(s) with sufficient tumor content (as confirmed by the Sponsor's designated central laboratory) during screening to enable BRCA testing and PD-L1 testing. The use of slides created from paraffin-embedded tissue as opposed to FFPE blocks must be approved by the Sponsor.
11. Patient must agree to complete the HRQoL questionnaire throughout the study.

Main Criteria for Exclusion:

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

1. Patients who experienced disease progression within 3 months (12 weeks or 84 days) (as evidenced by radiographic progression per RECIST v1.1) of first-line platinum therapy.
2. Patients with known deleterious or suspected deleterious mutation in breast cancer susceptibility gene (BRCA) 1 or BRCA2 genes (local testing permitted).

   Note: This will apply to known germline BRCA mutations and known BRCA mutations in the tumor.
3. Patient has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-programmed death-ligand-2 (anti-PD-L2) agent.
4. Patient has received prior therapy with a poly(adenosine diphosphate-ribose) polymerase (PARP)-1/PARP-2 inhibitor.
5. Patient has known hypersensitivity to dostarlimab (TSR-042), niraparib, their components, or their excipients.
6. Patient has a known history of myelodysplastic syndrome or acute myeloid leukemia.

7. Patient has not recovered (ie, to Grade ≤ 1 or to baseline) from prior chemotherapy induced AEs. Note: Patient with Grade ≤ 2 neuropathy or alopecia is an exception to this criterion and may qualify for the study.
8. Patient has a known diagnosis of immunodeficiency or is receiving systemic steroid therapy exceeding an equivalent of prednisone 10 mg daily or any other form of immunosuppressive therapy within 7 days prior to the first dose of study treatment.
9. Patient is currently participating in a treatment study or has participated in a study of an investigational agent within 4 weeks of the first dose of treatment.
10. Patient has received prior systemic anticancer therapy including cytotoxic chemotherapy, hormonal therapy given with the intention to treat ovarian cancer, or biological therapy within 3 weeks of the first dose of study treatment.
11. Patient has received live vaccine within 14 days of planned start of study therapy.
12. Patient has symptomatic uncontrolled brain or leptomeningeal metastases. (To be considered "controlled," central nervous system [CNS] disease must have undergone treatment [eg, radiation or chemotherapy] at least 1 month prior to study entry. The patient must not have any new or progressive signs or symptoms related to the CNS disease and must be taking ≤ 10 mg of prednisone or equivalent per day or no steroids.) Patients who have untreated brain metastases and who are not symptomatic may enroll if the Investigator feels that treatment of these metastases is not indicated. A scan to confirm the absence of brain metastases is not required. Patients with spinal cord compression may be considered if they have received definitive treatment for this and evidence of clinically stable disease for 28 days prior to the first dose of study treatment.
13. Patient had major surgery within 4 weeks of starting the first dose of study treatment or patient has not recovered from any effects of any major surgery.
14. Patient has a known additional malignancy that progressed or required active treatment within the last 2 years. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin that has undergone potentially curative therapy, or in situ cancer that is considered to be low risk for progression by the Investigator.
15. Patient is considered a poor medical risk due to a serious, uncontrolled medical disorder, nonmalignant systemic disease, or active, uncontrolled infection. These include, but are not limited to, significant cardiovascular disease (eg, significant cardiac conduction abnormalities, myocardial infarction, cardiac arrhythmia or unstable angina within 6 months prior to enrollment, New York Heart Association Grade ≥ 2 congestive heart failure, uncontrolled hypertension, serious cardiac arrhythmia requiring medication, Grade ≥ 2 peripheral vascular disease, and history of cerebrovascular accident within 6 months prior to enrollment), uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, and any psychiatric disorder that prohibits obtaining informed consent.
16. Patient has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, might interfere with the patient's participation for the full duration of the study treatment, or is not in the best

interest of the patient to participate.

17. Patient has known active hepatitis B (eg, hepatitis B surface antigen reactive) or hepatitis C (eg, hepatitis C virus ribonucleic acid [qualitative] has been detected).
18. Patients with known human immunodeficiency virus (HIV) are allowed if they meet all of the following criteria:
    a. Cluster of differentiation 4 ≥350/μL and viral load <400 copies/mL
    b. No history of acquired immunodeficiency syndrome-defining opportunistic infections within 12 months prior to enrollment
    c. No history of HIV-associated malignancy for the past 5 years
    d. Concurrent antiretroviral therapy as per the most current National Institutes of Health (NIH) Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV started >4 weeks prior to study enrollment
19. Patient is immunocompromised. Patients with splenectomy are allowed.
20. Patient has an ongoing bowel obstruction, or has other conditions that would lead to impaired absorption of oral niraparib.
21. Patient has active autoimmune disease that has required systemic treatment in the past 2 years (ie, with use of disease-modifying agents, corticosteroids, or immunosuppressive drugs). Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment

Investigational product, dosage, and mode of administration:

Niraparib

The starting dose of niraparib will be 300 mg in patients with a screening actual body weight ≥ 77 kg AND screening platelet count ≥ 150,000/μL, and 200 mg in patients with a screening actual body weight < 77 kg OR screening platelet count < 150,000/μL. Niraparib will be administered QD continuously until PD or toxicity.

Dostarlimab (TSR-042)

Dostarlimab (TSR-042) will be administered via a 30-minute intravenous (IV) infusion on Day 1 every 3 weeks (Q3W) during Cycles 1 through 4 at 500 mg. Beginning at Cycle 5, dostarlimab (TSR-042) will be administered via a 30-minute IV infusion on Day 1 of each 6-week cycle at 1,000 mg until PD or toxicity, for a maximum of 3 years. Continued treatment with dostarlimab (TSR-042) beyond 3 years may be considered following discussion between the Sponsor and the Investigator.

Duration of treatment:

Treatment in this study will continue until disease progression or toxicity. Patients who discontinue one of the treatment agents due to an AE will be able to continue treatment with the second agent until disease progression or toxicity.

Dostarlimab (TSR-042) treatment may continue for up to 3 years or until PD, unacceptable toxicity, withdrawal of consent, Investigator's decision, or death. Continued treatment with dostarlimab (TSR-042) beyond 3 years may be considered following discussion between the Sponsor and the Investigator. Treatment with niraparib can continue, in the absence of disease progression or toxicity, at the discretion of the Principal Investigator. Postprogression treatment may be permitted after discussion with the Sponsor's Medical Monitor if the Investigator believes the patient may derive benefit from ongoing treatment.

Following the final data cut-off (DCO) date, patients may continue to receive study treatment per investigator discretion until disease progression or they develop intolerable side-effects, or are lost to follow-up, withdraw consent, or pass away. Patients will not be allowed to receive study treatment if they become pregnant or demonstrate severe non-compliance with the protocol.

Reference therapy, dosage, and mode of administration:

Not applicable.

Criteria for evaluation:

Efficacy:

The primary efficacy endpoint is Investigator-assessed confirmed ORR, which is defined as the proportion of patients who have achieved confirmed CR or PR. Tumor response will be evaluated using RECIST v.1.1. The primary analysis population will be the intent-to-treat (ITT) population, consisting of all patients who receive at least 1 complete dose of either study drug and who have measurable disease at baseline. Analyses will be performed overall (including all patients in the ITT population) and in the subset of patients with PD-L1 positive tumors.

Secondary efficacy endpoints include the following and will be analyzed overall (including all patients in the ITT population) and in the subset of patients with PD-L1 positive tumors:

- DOR based on Investigator/independent review committee assessment, defined as the time from first documentation of response (CR or PR) until the time of first documentation of disease progression by RECIST v.1.1 based on Investigator/independent review committee assessment or death by any cause in the absence of progression by RECIST v.1.1
- PFS based on Investigator/independent review committee assessment, defined as the time from the date of the first dose of study treatment to the earlier date of assessment of progression by RECIST v.1.1 based on Investigator/independent review committee assessment or death by any cause in the absence of progression by RECIST v.1.1
- OS, defined as the time from the date of the first dose of study treatment to the date of death by any cause
- DCR based on Investigator/independent review committee assessment, defined as the percentage of patients who have achieved BOR of CR, PR, or SD per RECIST v.1.1 based on the Investigator/independent review committee assessment

- ORR based on independent review committee assessment, defined as the percentage of patients who have achieved confirmed CR or PR per RECIST v1.1 based on the independent review committee assessment

Safety:

Safety parameters evaluated during this study will include AEs, vital signs, symptom-directed physical examination findings, and clinical laboratory values (including hematology, serum or plasma chemistry, coagulation, and thyroid function).

Exploratory:

Exploratory endpoints include the following:

- Duration of disease control, defined as the time from the date of the first dose of study treatment to the earlier date of assessment of progression by RECIST v.1.1 based on the Investigator/independent review committee assessment or death by any cause in the absence of progression by RECIST v1.1 among patients whose BOR is CR, PR or SD.
- The observed change from baseline and time to symptom worsening in the FOSI questionnaire.
- Efficacy endpoints will also be evaluated in patients with tumors that are BRCAwt.
- Disease-related or treatment-related biomarkers (eg, homologous recombination repair pathway deficiency and PD-L1 expression) may be assessed to explore the correlations with responses to the combination of niraparib and dostarlimab (TSR-042).

Statistical methods:

A sample size of approximately 150 patients overall will provide sufficient precision for assessment of the primary endpoint of ORR in the overall and PD-L1 positive populations. No inferential testing will be performed, and no adjustments will be made for multiplicity. Primary analysis will be based on the ORR point estimate and the corresponding 95% exact confidence interval (CI).

With 150 patients overall, if the true ORR is 25%, there is an 87% chance that the lower bound of the 95% CI will exceed 15%.

Assuming the prevalence of PD-L1 positive disease is 50% in this study population, it is expected that approximately 75 patients with PD-L1 positive tumors will be enrolled and dosed. With 75 patients, if the true ORR is 30%, there is an 84% chance that the lower bound of the 95% CI will exceed 15%.

Analysis Populations:

The analysis populations will be defined as follows:

- Safety (SAF) Population: All patients who receive any amount of study treatment.
- ITT Population: All patients who receive at least 1 complete dose of either study drug and who have measurable disease at baseline. Measurable disease at baseline is defined by the existence of at least 1 target lesion at baseline tumor assessment by RECIST v1.1 criteria.

- Efficacy-Evaluable (EE) Population: All patients who receive at least 1 complete dose of either study drug and who have measurable disease at baseline and do not have protocol deviations with the potential to significantly impact the interpretation of efficacy results. Patients who withdraw without obtaining a post-baseline tumor assessment due to withdrawal of consent, loss to follow-up, or non-compliance will also be excluded from the EE population.

Efficacy Analyses:

All efficacy analyses will be performed using the ITT population, overall (including all patients in the ITT population) and in the subset of patients with PD-L1 positive tumors. The primary analysis population is the ITT population. Additional supportive analyses may be performed using the EE population.

Primary efficacy analyses of ORR, based on Investigator assessment using RECIST v1.1, will be performed on the ITT population. BOR will be summarized by number and percentage. The ORR and 2-sided 95% CI, using the exact (Clopper-Pearson) method, will be provided.

The point estimate and corresponding 2-sided 95% exact CI will be provided for DCR. DCR will be evaluated in the ITT and EE populations. Changes from baseline in tumor burden will be summarized by time-point. ORR based on independent review will be analyzed using similar methodology as described for the primary endpoint.

DOR, PFS, OS, and the exploratory endpoint of duration of disease control will be summarized using Kaplan-Meier analysis, including number and percentage of events, number and percentage of censored patients, and 25th, 50th (median), and 75th percentiles of times to event.

Analyses of ORR, DOR, PFS, OS, and DCR based on Investigator assessment using RECIST v1.1 will be repeated in the BRCAwt population.

Descriptive, exploratory subgroup analysis will be performed by baseline characteristics and biomarker status.

Descriptive summary statistics will be used to assess changes from baseline in overall FOSI score. Kaplan-Meier methodology will be used to summarize time to symptom worsening as assessed by minimally important changes in the overall FOSI score.

Additional exploratory analyses to explore the correlation of clinical activity with biomarker subpopulations and other baseline disease characteristics may be performed.

An interim futility analysis will be performed on the overall population after the first 40 patients (regardless of PD-L1 status) have had the opportunity for at least 1 scan (approximately 9 weeks of treatment). Eligible patients with a non-evaluable scan will not be included.

Safety Analyses:

AEs will be coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA) for purposes of summarization. All AEs occurring during the study will be included in by-patient data listings and tabulated by MedDRA system organ class and preferred term. Safety endpoints for AEs include the following: incidence of treatment-emergent adverse events (TEAEs), SAEs, AESIs, immune-related AEs, AEs leading to discontinuation, and AEs leading to death. Tabulations of TEAEs will also be produced by severity and by relationship to study treatment.

Additional safety summaries will be provided for vital signs, symptom-directed physical examination findings, and clinical laboratory tests.

3. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Table 3: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
BOR	best overall response
BRCA	breast cancer susceptibility gene
BRCAmut	breast cancer susceptibility gene mutated
BRCAwt	breast cancer susceptibility gene wild type
CA-125	cancer antigen 125
CNS	central nervous system
CBC	complete blood count
CI	confidence interval
CPS	complete positive scores
CR	complete response
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCR	disease control rate
DCO	data cut-off
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EE	Efficacy-Evaluable
EOT	end of treatment

Abbreviation or Specialist Term	Explanation
EU	European Union
FDA	Food and Drug Administration
FFPE	formalin fixed paraffin embedded
FOSI	Functional Assessment of Cancer Therapy – Ovarian Symptom Index
gBRCA	germline breast cancer susceptibility gene
gBRCAmut	germline breast cancer susceptibility gene mutated
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HR	hazard ratio
HRD	homologous recombination deficiency
HRQoL	health-related quality of life
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	independent ethics committee
IgG4	immunoglobulin G4
IL-2	interleukin-2
IND	Investigational New Drug application
irAE	immune-related adverse event
irAEI	immune-related adverse event of interest
IRB	institutional review board
ITT	intent-to-treat (population)
IV	intravenous
mAb	monoclonal antibody
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MID	minimally important difference
MRI	magnetic resonance imaging
MSI H	microsatellite instability-high
mut	mutant

Abbreviation or Specialist Term	Explanation
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
neg	negative
NIH	National Institutes of Health
NOAEL	no observed adverse effect level
NSAID	non-steroidal anti-inflammatory drug
NSCLC	non-small cell lung cancer
OC	ovarian cancer
ORR	objective response rate
OS	overall survival
PACT	post-analysis continuation of treatment
PARP	poly (adenosine diphosphate-ribose) polymerase
PARPi	PARP inhibitor
PCA	primary completion achieved
PD	progression of disease
PD-1	programmed cell death-1
PD-L1	programmed cell death-ligand 1
PD-L2	programmed cell death-ligand 2
PFI	platinum-free interval
PFS	progression-free survival
PK	pharmacokinetic(s)
PLD	pegylated liposomal doxorubicin
PO	orally
pos	positive
PR	partial response
PRO	patient-reported outcome
PROC	platinum-resistant ovarian cancer
Q3W	every 3 weeks
Q6W	every 6 weeks
QD	once daily
RAVE RTSM IRT	Rave Randomisation and Trial Suppy Management Interactive Response Technology
RECIST	Response Evaluation Criteria in Solid Tumors

Abbreviation or Specialist Term	Explanation
RP2D	recommended phase 2 dose
SAE	serious adverse event
SAF	safety (population)
SAP	statistical analysis plan
SD	stable disease
STING	stimulator of interferon gene
T1DM	type 1 diabetes mellitus
TEAE	treatment-emergent adverse event
TGI	tumor growth inhibition
ULN	upper limit of normal
unk	unknown
US	United States
WHO	World Health Organization

5. INTRODUCTION

Niraparib is an orally available, potent, and highly selective poly (adenosine diphosphate-ribose) polymerase (PARP)-1 and PARP-2 inhibitor. Zejula® (niraparib) was approved for the maintenance treatment of women with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete response (CR) or partial response (PR) to platinum-based combination chemotherapy by the United States (US) Food and Drug Administration (FDA) on 27 March 2017 and received a Marketing Authorization in the European Union (EU) on 16 November 2017.

Niraparib treatment as monotherapy and in combinations is being studied by TESARO through a global development plan that involves several ongoing company-sponsored clinical studies in ovarian, lung, and breast cancer indications. In addition, TESARO and Janssen have a partnership investigating niraparib for use in prostate cancer.

Dostarlimab (TSR-042) is an anti-programmed cell death-1 (anti PD-1) humanized monoclonal antibody (mAb) of the immunoglobulin G4 (IgG4)-κ isotype. TESARO submitted the original Investigational New Drug application (IND) for dostarlimab (TSR-042) on 22 December 2015 and obtained the IND approval on 22 January 2016 with Study 4010-01-001 titled "A Phase 1 Dose Escalation and Cohort Expansion Study of TSR-042, an anti-PD-1 Monoclonal Antibody, in Patients with Advanced Solid Tumors." Dostarlimab (TSR-042) is being studied by TESARO in a global development plan as monotherapy in microsatellite instability-high (MSI H) tumors, including endometrial cancer, and in combination with other approved and investigational drugs under development by TESARO, such as niraparib in other solid tumors, including ovarian cancer and non-small cell lung cancer (NSCLC).

The objective of the proposed study is to evaluate the efficacy and safety of the combination of niraparib and dostarlimab (TSR-042) in patients with advanced, relapsed, high-grade ovarian, fallopian tube, or primary peritoneal cancer without known breast cancer susceptibility gene (BRCA) mutation who have platinum-resistant disease and who have also been previously treated with bevacizumab.

5.1. Overview of Ovarian Cancer

Ovarian cancer is the most common cause of gynecologic cancer death in the US, with 22,240 new cases of ovarian cancer estimated to be diagnosed in 2018.[1] Most patients with ovarian cancer present with advanced disease at diagnosis. The majority of these patients will relapse after initial treatment, which typically includes a combination of surgery and platinum-based chemotherapy. It has been long recognized that the most robust predictive factor for response to subsequent platinum-based therapy at first relapse is the length of response to the first platinum-based chemotherapy.[2] Based on the time from the administration of last platinum treatment until progression — platinum-free interval (PFI), ovarian cancer can be categorized as "platinum-sensitive" (PFI > 6 months) or "platinum-resistant" (PFI < 6 months), including "platinum refractory" (progression on platinum-based therapy or within 30 days of the last dose). In patients with multiple prior lines of treatment, the convention has been to define platinum-sensitivity status based on the length of response to the last administered platinum, regardless of outcomes to subsequent non-platinum treatments.

The therapies approved by the FDA for treatment of platinum-resistant disease include paclitaxel, pegylated liposomal doxorubicin (PLD), or topotecan as single agents, or bevacizumab in combination with the above chemotherapeutic agents.[3-6] There is no standard or well-defined treatment regimen for patients who progress after bevacizumab treatment. Single-agent chemotherapy typically has limited efficacy.[7-9] Lack of known effective therapies in patients with platinum-resistant disease following administration of bevacizumab-based therapy remains a high unmet medical need.

5.1.1. Biology of Ovarian Cancer

In an analysis of approximately 500 high-grade serous ovarian cancer tumors, approximately 50% contained homologous recombination defects, which could sensitize tumors to poly (adenosine diphosphate-ribose) polymerase inhibitors (PARPi).[10] In ovarian cancers, biomarkers used to identify homologous recombination deficiency (HRD) tumors include BRCA mutations and homologous recombination deficiency assays such as MyChoice® HRD by Myriad Genetics and fLOH by Foundation Medicine.

The tumor microenvironment can be targeted to improve patient outcomes from ovarian cancer. Angiogenesis is essential for both tumor growth and metastases, making it one of the hallmarks of cancer and an actionable aberration for drug development. Bevacizumab is used in the treatment of newly diagnosed ovarian cancer, platinum-sensitive recurrent ovarian cancer, and platinum-resistant ovarian cancer (PROC).[11-14]

Immune cells represent a critical component of the tumor microenvironment.[15] The presence of intratumoral T cells in patients with newly diagnosed ovarian cancer is associated with improved progression-free survival (PFS) and overall survival (OS).[16] Programmed cell death-ligand 1 (PD-L1) expression in tumors results in T cell inactivation/anergy. Survival outcomes are negatively impacted in tumors with high PD-L1 expression regardless of tumor stage, histologic type, residual tumor burden, and chemotherapy.[17] These data suggest a potential role of immune checkpoint inhibitors in treatment of ovarian cancers.

5.1.2. Treatment for Platinum Resistant or Refractory Advanced Ovarian Cancer

For patients with platinum-resistant or refractory ovarian cancer, the National Comprehensive Cancer Network (NCCN) guidelines recommend nonplatinum-based regimens such as docetaxel, oral etoposide, gemcitabine, paclitaxel with or without pazopanib, liposomal doxorubicin or topotecan (with or without bevacizumab), and paclitaxel/bevacizumab.[18] Use of a single chemotherapeutic agent will yield a reported objective response rate (ORR) in the range of approximately 5% to 20%, depending on the line of therapy, with a median duration of response (DOR) of 4 to 9 months; PFS ranges from 3 to 5 months.[5,8,9,19,20] The clinical benefit from these agents is even lower for patients with platinum-refractory disease. The anti-angiogenesis agent bevacizumab has a modest single-agent activity with an ORR of 15% and a median PFS of 4.4 months reported for patients with platinum-resistant disease treated with no more than 3 prior treatment regimens.[21] Chemotherapy with or without bevacizumab was evaluated in patients with platinum-resistant disease (excluding patients with platinum-refractory disease), who had received 1 to 2 prior lines of therapy in the Phase 3 AURELIA study;

the ORR and median PFS were 11.8% and 3.4 months, respectively, for patients receiving chemotherapy versus 27.3% and 6.7 months, respectively, for patients receiving chemotherapy plus bevacizumab.[14] Based on these results, bevacizumab in combination with paclitaxel, PLD, or topotecan was approved for the treatment of platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer.[3]

Currently approved PARPi in the treatment setting are only indicated for patients with a BRCA mutation who are ≥ 4th line (olaparib) and ≥ 3rd line (rucaparib).[22,23] Efficacy of single-agent PARPi in patients with PROC who have BRCA wild type (BRCAwt) tumors has a reported ORR of 5%.[24-26] Therefore, the unmet need in PROC is highlighted among patients without a known BRCA mutation.

5.2. Background of Niraparib

5.2.1. Clinical Experience

Niraparib is approved in multiple countries worldwide including the US, EU, Switzerland, Australia, Canada, and Saudi Arabia. Niraparib was approved by the Food and Drug Administration (FDA) on 27 March 2017 (NDA 208447) and received European Commission approval on 16 November 2017 as maintenance therapy for women with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in CR or PR to platinum-based chemotherapy. Niraparib was approved by the FDA on 23 October 2019 for patients with advanced ovarian, fallopian tube, or primary peritoneal cancer treated with three or more prior chemotherapy regimens and whose cancer is associated with HRD-positive status. Additionally, the FDA approved the Myriad myChoice® CDx test (PMA P190014) as a companion diagnostic for determination of tumor HRD status to select patients for treatment with niraparib in the late line setting. A supplemental NDA (NDA 208447- S017) based on results of the PRIMA study, which evaluated the efficacy of niraparib in participants with newly diagnosed advanced ovarian cancer after a response to first-line platinum-based chemotherapy, is currently under real-time oncology review (RTOR) with the FDA.

Niraparib has shown an acceptable clinical and pre-clinical safety profile.

Niraparib was initially approved in the US and EU with a starting dose of 300 mg for all patients; the European Summary of Product Characteristics allowed for a 200 mg starting dose for a subset of patients (ie, patients with low body weight). In the ENGOT-OV16/NOVA study, the selection of the 300 mg starting dose of niraparib was based on data from the Phase 1 multiple ascending dose study PN001 conducted by Merck & Company. No formal Phase 2 dose-ranging studies were conducted. The Phase 1 study included both a dose-escalation phase to determine the maximum tolerated dose and an expansion arm to further evaluate the selected dose. A total of 104 patients with advanced tumors were evaluated in this study, including 60 during dose escalation from 30 mg to 400 mg; during expansion, a total of 54 patients were treated at the 300-mg dose level. The dose-escalation stage determined that the 400-mg dose level exceeded the maximum tolerated dose (by traditional dose-limiting toxicity [DLT] evaluations and by using the pooled adjacent violators algorithm). No DLTs were observed in the dose-escalation stage at the 290- or 300-mg dose level.

In the ENGOT-OV16/NOVA study, the most commonly observed nonhematologic treatment-emergent adverse events (TEAEs) of any National Cancer Institute (NCI) - Common Terminology Criteria for Adverse Events (CTCAE) grade were nausea, fatigue, constipation, and vomiting; the majority of the nonhematologic TEAEs were mild to moderate in severity. The most commonly observed hematologic TEAEs (any grade) were anemia (48.5%), thrombocytopenia (66.2%), and neutropenia (31.4%). The incidence of myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML) in patients who received niraparib in the ENGOT-OV16/NOVA study was similar to that in patients who received placebo (1.4% and 1.1%, respectively). MDS/AML and secondary cancers (new malignancies other than MDS or AML) are potential risks of PARPi. Since the initial approval of niraparib based on the ENGOT-OV16/NOVA Study, the safety profile has been updated to provide cumulative safety; this information can be found in the current version of the Investigator's Brochure. Recommendations for dose modification strategies to be used during this study based on the safety profile of niraparib are provided in Section 7.4.

5.2.2. Baseline Body Weight and Platelet Count as Predictors of Thrombocytopenia

Additional exploratory analysis of the ENGOT-OV16/NOVA study data identified that patients with a baseline body weight < 77 kg or with a baseline platelet count < 150,000/μL before the initiation of niraparib treatment have a higher incidence of Grade 3 or 4 thrombocytopenia and other adverse events (AEs) during niraparib treatment. A dose-response relationship between AEs and dose was also observed for most of the commonly reported Grade 3 or 4 events, with the incidence highest at the 300-mg dose level. The incidence of these Grade 3 or 4 events was lower for patients whose doses were reduced to the 200-mg dose level.

The dose modification approach employed in ENGOT-OV16/NOVA study allowed patients to reach their optimal individual dose within the first 3 cycles. Overall, dose interruptions for any reason were instituted for 80% of patients on niraparib; 72% of patients underwent a dose reduction. Dose reductions tended to occur early and most patients reached their individual adjusted dose level by Month 4 of treatment.

A PFS analysis from the ENGOT-OV16/NOVA study by dose at Month 4 demonstrated that, once the patients reach their optimal individualized dose, the efficacy was not compromised. Therefore, a lower starting dose will assist in reducing the incidence of Grade 3 or 4 thrombocytopenia in these subgroups of patients without a decrement in efficacy. Further, despite the intent to deliver a starting dose of 300 mg, the median daily dose taken within the first 2 months (where most dose reductions and interruptions occurred) was only 207 mg for patients with baseline body weight < 77 kg or baseline platelet count < 150,000/μL compared with a median of 295 mg for patients with baseline body weight ≥ 77 kg and baseline platelet count ≥ 150,000/μL. Therefore, the efficacy in the ENGOT-OV16/NOVA study was achieved with these patients receiving a true starting dose consistent with a 200-mg starting dose.

The safety data from 2 ongoing niraparib studies, QUADRA and TOPACIO, were also evaluated for the incidence of thrombocytopenia. In the QUADRA study, the association of a decreased incidence of Grade 3 or 4 thrombocytopenia during the first cycle for

patients with a baseline body weight ≥ 77 kg and with baseline platelet count ≥ 150,000/μL was 13.6% compared to those patients with a baseline body weight < 77 kg or with a platelet count < 150,000/μL (30.2%).

As of 4 September 2018, the Phase 2 portion of the ongoing TOPACIO study in patients with PROC included 62 patients treated at a starting dose of niraparib of 200 mg QD in combination with pembrolizumab 200 mg IV Q3W.[28] This study represents the largest dataset available with this proactively defined 200-mg niraparib starting dose. The lower starting dose in this study led to a lower incidence of Grade 3 or 4 thrombocytopenia overall and in patients with the baseline characteristics of body weight < 77 kg or platelet counts < 150,000/μL than in studies such as NOVA and QUADRA that utilized the 300-mg starting dose.

Overall, the data demonstrate that while AEs appear to be dose dependent, the relationship between dose and efficacy is not apparent. In addition, in the NOVA study, patients with a baseline body weight < 77 kg or a baseline platelet count < 150,000/μL in effect received an average daily dose approximating 200 mg (median = 207 mg) due to dose interruption and reduction; the use of a 200-mg niraparib starting dose leads to a lower incidence of Grade 3 or 4 thrombocytopenia events without compromising efficacy. Therefore, the starting dose of niraparib 200 mg QD is being prospectively evaluated in this and other clinical studies in patients with a baseline body weight < 77 kg or a baseline platelet count < 150,000/μL.

5.2.3. Clinical Experience of Niraparib Monotherapy in PROC Patients

TESARO conducted the QUADRA study to assess the activity of single-agent niraparib across a broad population of diverse patients in the late line treatment setting. This study aimed to enroll patients with the highest unmet need (4th line and later), regardless of biomarker status and platinum status, and represents the largest clinical study dataset of PARPi administered to patients in a treatment setting that included the BRCAwt population.

QUADRA enrolled 463 patients. The majority of the patients were platinum refractory (relapse within 28 days from the last administered platinum, 35%) or platinum resistant (relapse 1 to 6 months from the last administered platinum, 33%). The median time from last treatment prior to study entry until first niraparib dose was 2 months, suggesting a population largely refractory to their last treatment, and 62% of enrolled patients had received bevacizumab as part of their prior therapy. Biomarker distribution was consistent with previously described prevalence of BRCA mutation (19%) and HRD positivity (48%) among patients with high-grade serous ovarian cancer.

The study met its primary endpoint, demonstrating activity in the primary efficacy population of 4th and 5th line HRD-positive patients who were PARPi naïve, and considered platinum sensitive to the last platinum therapy (n = 47), with an ORR of 28% and median DOR of 9.2 months.

Among patients with PROC who had received at least 3 prior lines of treatment, including platinum-refractory disease, meaningful activity of niraparib and durable responses were demonstrated in the subgroup of BRCAmut patients, with ORR of 33% (n = 21) in patients who progressed 1 to 6 months after their last platinum and 19% (n = 16)

among patients who progressed within 28 days from the last platinum. Outside of the biomarker selected patient population, namely among patients with HRD-negative platinum-resistant disease, the clinical benefit to patients treated with single-agent niraparib was best evidenced by meaningful disease stabilization (as measured by 16-week clinical benefit rate of 19%) and importantly median OS of 17.1 and 10.3 months for patients progressing 1 to 6 months and within 28 days after their last platinum, respectively, while the formal Response Evaluation Criteria in Solid Tumors (RECIST) ORR remained modest at 3%. Of note, median OS with standard of care chemotherapy, regardless of platinum status, is expected to be < 10 months for patients receiving 4th-, 5th-, or 6th-line therapy.[29]

5.3. Background of Dostarlimab (TSR-042)

Dostarlimab (TSR-042) is a humanized mAb of the IgG4-κ isotype that binds with high affinity to PD-1, resulting in inhibition of binding to PD-L1 and programmed cell death-ligand 2 (PD-L2). This antibody was generated based on a proprietary platform that utilizes affinity maturation to select highly specific antibodies with desired functional characteristics. The functional antagonist activity of dostarlimab (TSR-042) was confirmed in a mixed lymphocyte reaction assay, demonstrating enhanced interleukin-2 (IL-2) production upon addition of dostarlimab (TSR-042).[30] Furthermore, dostarlimab (TSR-042) has an acceptable safety profile based on toxicology studies in cynomolgus monkeys. The nonclinical development with dostarlimab (TSR-042) is discussed in Section 5.3.1 and in the dostarlimab (TSR-042) Investigator's Brochure.

Dostarlimab (TSR-042) has shown an acceptable clinical and nonclinical safety profile. The clinical development with dostarlimab (TSR-042) is discussed in Section 5.3.2 and in the dostarlimab (TSR-042) Investigator's Brochure.

5.3.1. Nonclinical Development

Dostarlimab (TSR-042) binds with high affinity to human and monkey PD-1. Dostarlimab (TSR-042) blocks the binding of soluble ligands to human PD-1 that is artificially expressed with a half-maximal inhibitory concentration of approximately 1 nM. Dostarlimab (TSR-042) enhances T cell activation as measured by the production of IL-2 from activated human cluster of differentiation 4+ T cells, with a half-maximal effective concentration of approximately 1 nM. Full PD-1 receptor occupancy by dostarlimab (TSR-042) in vitro is achieved at concentrations of approximately 1 μg/mL.

Linear pharmacokinetics (PK) was observed for dostarlimab (TSR-042) over the range of 10 to 100 mg/kg in 18 cynomolgus monkeys. Sex had no effect on exposure. The volume of distribution at steady state was low and suggested minimal tissue penetration, which is consistent with other therapeutic monoclonal antibodies. Weekly administration resulted in approximately a 2- to 3-fold increase in dostarlimab (TSR-042) exposure.

In a 4-week repeat-dose toxicology study in cynomolgus monkeys, weekly intravenous (IV) dostarlimab (TSR-042) at doses of 0, 10, 30, or 100 mg/kg was well tolerated and did not result in any study drug-related adverse effects as measured by clinical signs, body weight, food consumption, electrocardiography, ophthalmology, safety pharmacology parameters, clinical pathology, gross pathology, organ weight, or

histopathology. The no observed adverse effect level (NOAEL) was ≥ 100 mg/kg in this study.

In a 13-week repeat-dose toxicology study in cynomolgus monkeys, weekly IV dostarlimab (TSR-042) at doses of 0, 10, 30, and 100 mg/kg was well tolerated at 30 and 100 mg/kg. One male (10 mg/kg/week) was euthanized because of chronic, unresolved generalized skin findings associated with swollen and firm inguinal lymph nodes on both sides. Microscopic findings noted in the skin of this animal were indicative of an immune reaction, which could have been a result of the mechanism of action of dostarlimab (TSR-042). Terminal necropsies of the remaining animals showed microscopic findings of an immune-mediated nature in the kidney, liver, and heart in animals dosed with dostarlimab (TSR-042) at ≥ 10 mg/kg/week. Although these findings are commonly observed in cynomolgus monkeys, the severity of these findings was slightly increased in dostarlimab (TSR-042)-dosed animals compared to control animals. Considering the mechanism of action of dostarlimab (TSR-042), these microscopic findings could be a result of the pharmacological effects of dostarlimab (TSR-042). Because of the euthanasia of 1 male dosed in the 10-mg/kg dose group, the NOAEL could not be determined in this study.

5.3.2. Clinical Development

In Study 4010-01-001 (GARNET), dostarlimab monotherapy demonstrated clinical benefit in participants with recurrent or advanced solid tumours that are DNA mismatch repair-deficient (dMMR) or have high microsatellite instability (MSI-H), a phenotype of mismatch repair deficiency. As of 08 July 2019, objective response rates (ORRs; blinded independent central review using Response Evaluation Criteria in Solid Tumors [RECIST] v1.1) of 43.1% and 44.0% were observed in participants with dMMR/MSI-H endometrial and nonendometrial cancer.

5.3.2.1. Dostarlimab (TSR-042) Monotherapy

Dostarlimab is not currently approved in any country. An Original BLA for dostarlimab was submitted to the FDA on 19 December 2019 for patients with recurrent or advanced dMMR EC who progressed on or following prior treatment with a platinum-containing regimen and a Conditional Marketing Authorization Application (CMAA) was submitted to the European Medicines Agency (EMA) on 06 March 2020, both of which are currently under review. The primary study used for this submission is Study 4010-01-001 (GARNET).

Additionally, the clinical benefit of dostarlimab as a single agent or in combination with other anticancer agents is being studied in 12 ongoing company-sponsored clinical studies in EC, ovarian cancer, nonsmall cell lung cancer (NSCLC), and other solid tumors. A summary of all ongoing studies with dostarlimab can be found in the current version of the dostarlimab Investigator's Brochure and a summary is provided in Section 5.3.2.2.

GARNET (Study 4010-01-001) is an ongoing, first-in-human Phase 1 study of dostarlimab (TSR-042) that aims to evaluate the safety and tolerability, PK, pharmacodynamics, and clinical activity of dostarlimab (TSR-042) in patients with recurrent or advanced solid tumors. As of 21 January 2019, a total of 21 patients were

dosed in the dose-escalation phase of the study (Part 1). Dose escalation continued to a maximally administered dose of 10 mg/kg every 2 weeks and a maximum tolerated dose was not identified. No DLTs were observed. In Part 2A of the study, the safety and tolerability of dostarlimab (TSR-042) was evaluated at 2 fixed dosing schedules: 500 mg every 3 weeks (Q3W) and 1,000 mg every 6 weeks (Q6W). No DLTs were observed in Part 2A. The recommended Phase 2 dose (RP2D) regimen was determined to be 500 mg Q3W for 4 cycles followed by 1,000 mg Q6W for all cycles thereafter, which is being evaluated in expansion cohorts for MSI H and microsatellite stable endometrial cancer, NSCLC, and non-endometrial MSI H or polymerase ε-mutated cancer in Part 2B of the study.

Dostarlimab demonstrated an acceptable safety profile, based on safety profile of GARNET. Of note, Grade ≥3 TEAEs regardless of causality were reported in 50.3% of patients, and events in 13.6% of patients were assessed to be treatment-related. Serious TEAEs regardless of causality were reported in 39.4% of patients, and events in 7.8% of patients were assessed to be treatment-related. Immune-related adverse events (irAEs) (Grade ≥2) regardless of causality were reported in 34.8% of patients; however, immune-related serious TEAEs were uncommon (5.0% of patients), with treatment-related immune-related serious TEAEs reported in 4.1% of patients. TEAEs leading to treatment discontinuation regardless of causality were not common and were reported in 9.5% of patients, with events in 4.9% of patients assessed to be treatment-related. TEAEs leading to death regardless of causality were rare and were reported in 3.1% of patients. None of the deaths were due to treatment-related TEAEs. Most of the observed adverse events (AEs) were in line with those expected in patients with recurrent or advanced solid tumors and were consistent with reported safety profiles of monoclonal antibodies blocking the PD-(L)1 interactions ("OPDIVO® (nivolumab) injection, for intravenous use prescribing information. Princeton, NJ: Bristol-Myers Squibb; 2016." ; "KEYTRUDA® (pembrolizumab) injection, for intravenous use prescribing information. Whitehouse Station, NJ: Merck & Co.; 2017.").

5.3.2.2. Investigational Therapeutic Combinations with Dostarlimab (TSR-042)

In addition to Study 4010-01-001 of dostarlimab (TSR-042) monotherapy, the following additional studies involving dostarlimab (TSR-042) and other therapeutic agents are being evaluated.

Study 4020-01-001 is an open-label, first-in-human Phase 1 study of another mAb, TSR-022 (anti-T cell immunoglobulin and mucin domain 3), that is being conducted in 2 parts in patients with advanced solid tumors. In Part 1C, dostarlimab (TSR-042) is administered in combination with TSR-022 to establish the RP2D regimen for this study drug combination. In Part 2 of the study, the efficacy of TSR-022 ± dostarlimab (TSR-042) is evaluated in patients with advanced solid tumors (expansion cohorts for melanoma, NSCLC, or colorectal cancer).

Study 3000-01-002 is a Phase 1b dose-finding study of niraparib, niraparib/bevacizumab, carboplatin/paclitaxel, carboplatin-paclitaxel/bevacizumab, carboplatin-paclitaxel/TSR-022, carboplatin/pemetrexed, carboplatin-pemetrexed/TSR-022, carboplatin/nab-paclitaxel, or carboplatin-nab-paclitaxel/TSR-022 in combination with dostarlimab (TSR-042) in patients with advanced or metastatic cancer. The study was initiated on

12 October 2017 and is the first to assess dostarlimab (TSR-042) and niraparib combination treatment, which have nonoverlapping safety profiles. In Part A of this study, the objectives are to evaluate the DLTs of dostarlimab (TSR-042) and niraparib combination treatment during the first cycle of treatment, to establish an RP2D of niraparib in combination with dostarlimab (TSR-042), and to evaluate the safety and tolerability of dostarlimab (TSR-042) and niraparib combination treatment.

As of 21 January 2019, only Part A of Study 3000-01-002 (dostarlimab [TSR-042] in combination with niraparib), Part B (dostarlimab [TSR-042] in combination with carboplatin and paclitaxel), Part C (dostarlimab [TSR-042] in combination with niraparib and bevacizumab), and Part D (dostarlimab [TSR-042] in combination with carboplatin and paclitaxel and bevacizumab) had subjects enrolled. An initial cohort of 16 patients was enrolled at niraparib dose level 1 (200 mg), which has been determined to be safe. A cohort of 6 patients with baseline weight ≥ 77 kg and baseline platelet count ≥ 150,000/μL was enrolled at niraparib dose level 2 (300 mg), which has also been determined to be safe. Of the 12 evaluable patients treated with niraparib 200 mg orally once daily (QD) and dostarlimab (TSR-042) 500 mg, 2 patients experienced a DLT (Grade 3 mucosal inflammation, related to niraparib, and Grade 3 exacerbated hypertension, related to niraparib). No patients experienced a DLT with niraparib 300 mg and dostarlimab (TSR-042) 500 mg. There were no new safety findings at either dose level. Thus, the RP2D of the 2-drug combination of dostarlimab (TSR-042) and niraparib is dostarlimab (TSR-042) 500 mg IV every 3 weeks and niraparib 200 mg in patients with baseline weight < 77 kg or baseline platelet count < 150,000/μL, and niraparib 300 mg in patients with baseline weight ≥ 77 kg and baseline platelet count ≥ 150,000/μL.

Study 4040-01-001 is an open-label, first-in-human Phase 1 study of another mAb, TSR-033 (anti-lymphocyte activation gene-3), that is being conducted in 2 parts in patients with advanced solid tumors. In Part 1C of the study, dostarlimab (TSR-042) will be administered in combination with TSR-033 to establish the RP2D regimen for this study drug combination. In Part 2 of the study, the efficacy of TSR-033 with or without dostarlimab (TSR-042) will be evaluated in patients with advanced solid tumors (expansion cohorts for epithelial ovarian cancer, triple-negative breast cancer, and urothelial carcinoma).

Study 3000-02-001 is an open-label Phase 2 study to evaluate the efficacy and safety of single-agent niraparib in patients with locally advanced and metastatic squamous NSCLC and of the combination of niraparib and a PD-1 inhibitor (including dostarlimab) in patients with locally advanced and metastatic NSCLC (all histologies).

Study 3000-02-005 is an open-label, Phase 2 study to evaluate the efficacy and safety of niraparib novel treatment combinations in patients with advanced, relapsed, high-grade ovarian, fallopian tube, or primary peritoneal cancer. All patients receive niraparib in combination with dostarlimab (TSR-042) and bevacizumab.

Please refer to the most current version of the dostarlimab (TSR-042) Investigator's Brochure for updated safety information on these combinations.

Given the encouraging clinical activity in heavily pretreated patients with diverse tumor types and the manageable safety profile of dostarlimab (TSR-042), the benefit-risk profile

for dostarlimab (TSR-042) as a treatment for patients with advanced cancers appears positive.

5.4. Rationale for Synergy Between Immune Checkpoint Inhibitors and PARP Inhibitors

5.4.1. Nonclinical Activity

It has been demonstrated that PARPi treatment is able to increase lymphocyte infiltration and activation in mouse tumor models,[31] turning "cold" tumors into "hot" tumors, which are more likely to respond to anti-PD-1 therapies. The rationale behind this finding is that PARP inhibition leads to accumulation of deoxyribonucleic acid (DNA) damage and cytoplasmic DNA, which induces the stimulator of interferon gene (STING)-dependent immune response[32,33] and results in activation of type I interferon pathway. Multiple molecular mechanisms have been reported indicating that intrinsic DNA repair deficiency is also able to trigger an innate immune response through the accumulation of cytosolic DNA and activation of the STING pathway.[34] Type I interferon has been reported to activate antitumor immunity through multiple mechanisms, including stimulation of innate and adaptive cytotoxic lymphocytes, downregulation of suppressive immune cells such as regulatory T-cells and myeloid-derived suppressor cells, and direct inhibition of tumor cell proliferation. The type I interferon-mediated activation of immune cells is mediated by upregulation of tumor antigen expression; activation of antigen-presenting dendritic cells; and stimulation of the release of secondary mediators such as chemokines, cytokines, and interleukins.[35] Recently, PARPi have been shown to elevate PD-L1 expression.[36] This finding suggests that the immunomodulatory effects of PARPi could be muted by the expression of PD-L1. Thus, blocking PD-1 or PD-L1 may enhance the ability of niraparib to induce durable responses.

The efficacy and tolerability of niraparib in combination with anti-PD-1 therapy was evaluated in immune-competent nonclinical models, and the combination was well tolerated in these studies. The combination was first tested in an HRD ovarian cancer mouse model derived from BRCA null genetic background, as PARP inhibition was previously shown to increase immune cell infiltration in BRCA-deficient models.[31] The combination of low-dose niraparib (30 mg/kg QD) and mouse anti-PD-1 antibody (10 mg/kg twice every 3 days followed by 3 days of rest) achieved complete tumor regression, while niraparib monotherapy induced 64% tumor growth inhibition (TGI) and anti-PD-1 antibody monotherapy resulted in 65% TGI. Full dose of niraparib (50 mg/kg, QD) also drove the tumor to full regression, but adding anti-PD-1 to full-dose niraparib enhanced the anti-tumor activity by accelerating the time to complete regression. When the treatments stopped after 29 days of dosing, tumors in the niraparib and anti-PD-1 combination groups demonstrated no signs of tumor regrowth during the 5-week drug-free observation period. Interestingly, no sign of tumor growth was observed when the tumor-free mice in the combination groups were re-inoculated with the same tumor cells, suggesting the establishment of durable response and immune memory.[32,33,37] These results suggest that the therapeutic approach of combining niraparib with a PD-1 inhibitor such as dostarlimab (TSR-042) may provide additional benefit for patients with HRD tumors.

The enhanced anti-tumor activity was also observed when combining niraparib with anti PD-1 agent in BRCA-proficient tumor models, for example, the breast cancer syngeneic transplant MMTV-LPA1-T22 model. Mice treated with either niraparib or anti-PD-1 monotherapies showed moderate responses of 45% and 30% TGI, respectively. In comparison, the combination of the 2 drugs led to a significantly improved anti-tumor response of 91% TGI.[38] In the lung squamous syngeneic model KLN205, stronger tumor growth inhibition was observed for the combination (52.3%) than for niraparib alone (36.7%) or anti-PD-1 alone (30.5%).[39] In the anti-PD-1 refractory mouse syngeneic skin tumor model SA9003, combination of niraparib and anti-PD-1 antibody treatment resulted in 51% TGI, while niraparib or anti-PD-1 monotherapies were not effective with TGI at 17% and 1%, respectively. These results clearly demonstrated the benefit of combination approaches with niraparib and anti-PD-1 antibody in BRCA-proficient mouse models. In 5 of 11 immunocompetent BRCA-proficient models, greater than additive antitumor responses were observed in 5/11 BRCA-proficient models.[32,33] These results suggest that the therapeutic approach of combining niraparib with PD-1 inhibitors, such as dostarlimab (TSR-042), may provide additional benefit for patients with HR proficient tumors.[32]

5.4.2. Clinical Activity in Ovarian Cancer

Checkpoint inhibitors, such as PD-1 or PD-L1 inhibitors, have demonstrated modest activity in ovarian cancer. Preliminary efficacy rates for single-agent PD-1 or PD-L1 inhibitors range from 5.9% to 15% in unselected recurrent ovarian cancer patients, in clinical studies that include patients with platinum-sensitive disease.[40-43] In a small study of the safety and antitumor activity of nivolumab in patients with PROC (n = 20), the response rate was 15%.[40] Two Phase 1b studies of pembrolizumab, a humanized monoclonal IgG4-κ PD-1 blocking antibody, and avelumab, a human IgG1 lambda monoclonal PD-L1 blocking antibody, demonstrated similar modest response rates of 11.5% and 10.7%, respectively.[44,45]

In the Phase 1b study KEYNOTE-028, 26 patients with ovarian cancer who had PD-L1 positive tumors had an ORR of 11.5% when treated with pembrolizumab alone, with 1 CR and 2 PR. Seven other patients achieved SD.[46] Pembrolizumab in patients with PD-L1 positive tumors was further evaluated in KEYNOTE-100, in which 376 patients with reoccurring ovarian cancer who had received multiple lines of prior therapy were administered pembrolizumab alone. In a confirmation set of patients who received 1 to 3 prior lines of treatment with a platinum-free interval or treatment-free interval between 3 and 12 months (n = 188), patients who had complete positive scores (CPS) ≥ 10 for PD-L1 (indicating a high number of PD-L1 detected) had the highest ORR (10.0%) compared with patients who had lower CPS (4.1% for CPS < 1; 5.7% for CPS ≥ 1). In the overall population, this trend of highest ORR in patients with the highest PD-L1-expressing tumors held true despite differences in the number of prior lines of therapies (1 to 3 versus 4 to 6) and other various baseline characteristics (eg, age and platinum sensitivity).[47]

In a Phase 3 study of patients with platinum-resistant or refractory epithelial ovarian cancer treated with avelumab, PLD, or avelumab plus PLD,[48] median PFS was 1.9 months (95% CI: 1.8 to 1.9) for avelumab (n = 188), 3.5 months (95% CI: 2.1 to 4.0) for PLD (n = 190), and 3.7 months (95% CI: 3.3 to 5.1) for avelumab plus PLD

(n = 188). ORR was 3.7% (95% CI: 1.5% to 7.5%) for avelumab, 4.2% (95% CI: 1.8% to 8.1%) for PLD, and 13.3% (95% CI: 8.8% to 19.0%) for avelumab plus PLD.

PD-L1 positive tumors were defined as tumors for which the percentage of tumor cells expressing membranous PD-L1 was ≥ 1% and/or the percentage of tumor area populated by PD-L1 positive immune cells was ≥ 5%. Median PFS in patients with PD-L1 positive tumors was 1.9 months (95% CI: 1.8 to 2.3) for avelumab (n = 100), 3.0 months (95% CI: 1.9 to 3.7) for PLD (n = 88), and 3.7 months (95% CI: 2.7 to 6.1) for avelumab plus PLD (n = 100), and median PFS in PD-L1 negative patients was 1.9 months (95% CI: 1.8 to 1.9) for avelumab (n = 70), 3.7 months (95% CI: 2.1 to 5.5) for PLD (n = 77), and 3.6 months (95% CI: 1.9 to 4.6) for avelumab plus PLD (n = 73).[49]

The TOPACIO study was conducted to evaluate the safety and efficacy of combination treatment with niraparib and pembrolizumab in patients with advanced triple-negative breast cancer or PROC, including patients considered “platinum ineligible” (a previous PFI ≥ 6 months but patients were deemed ineligible for subsequent platinum by the Investigator). The Phase 1 portion of the study is a dose-escalation evaluation to determine the RP2D and schedule of niraparib to be administered in combination with the recommended dose of pembrolizumab (n = 14). The Phase 2 portion includes patients treated at the RP2D of niraparib 200 mg orally QD on Days 1 to 21, and pembrolizumab 200 mg IV on Day 1 of each 21-day cycle (n = 108). The primary endpoint of this study was Investigator-assessed ORR per RECIST v.1.1.

In the PROC cohort, a total of 62 patients were enrolled in Phase 1 and Phase 2. The median age was 60 years of age. All patients were either Eastern Cooperative Oncology Group (ECOG) 0 or 1 at baseline (44 [71%] and 18 [29%], respectively) and 49 patients (79%) were BRCAwt. The median number of prior lines of therapy was 3 (range: 1 to 5). In this population, all had received prior platinum (100%); 98% had received prior paclitaxel, and 63% had received prior bevacizumab. Overall, 48% (30/62) of patients were platinum resistant and 27% (17/62) of patients were platinum refractory.[28]

No new safety signals were identified for the combination of niraparib and pembrolizumab. In the Phase 2 PROC cohort of TOPACIO, incorporating a starting dose of 200 mg, the most common Grade ≥ 3 related TEAEs were anemia (21%) and thrombocytopenia (9%).

In the evaluable population (at least 1 on-treatment scan; n = 60), there were 11 patients with confirmed responses (3 CRs and 8 PRs) for a confirmed ORR of 18% (90% CI: 11% to 29%), with a disease control rate (DCR) of 65% (90% CI: 54% to 75%). Median DOR was not reached at the time of the data cutoff (range: 4.2 to ≥ 14.5 months). In patients with platinum resistant disease, ORR was 21% (6/29), and in patients with platinum refractory disease, ORR was 13% (2/16). Patients positive for PD-L1 had an ORR of 21% (7/33), and patients negative for PD-L1 had an ORR of 10% (2/21).

The results of clinical activity in patients by platinum response and biomarker status are displayed in Table 4.

Table 4: Tumor Response by Platinum Response and Biomarker Status – Efficacy-Evaluable Population (Phase 1 + Phase 2)

Response	All (%)	Platinum Resistant (%)	Platinum Refractory (%)	tBRCAmut (%)[a]	HRDpos (%)[a]	tBRCAwt (%)[a]	HRDneg (%)[a]
ORR[b]	11/60 (18%)	6/29 (21%)	2/16 (13%)	2/11 (18%)	3/21 (14%)	9/47 (19%)	6/32 (19%)

Source: Konstantinopoulos et al 2019.[28]

Abbreviations: HRD=homologous recombination deficiency; mut=mutant; neg=negative; ORR=objective response rate; pos=positive; tBRCA=tumor breast cancer susceptibility gene; wt=wild type

[a] Only patients with known biomarker status were included.

[b] Includes only confirmed responses using Response Evaluation Criteria in Solid Tumors, version 1.1.

Response rates and stable disease rates were similar across the biomarker-defined populations as defined by tBRCA mutation and HRD status. Responses observed among BRCAwt populations were significantly higher than expected with single-agent PARPi or checkpoint inhibitor, suggesting potential combination benefit in this population with significant unmet medical need.

5.5. Rationale for Current Study

Development of more efficacious treatment options for patients with PROC, in particular among patients with BRCAwt tumors, remains a high unmet need.

Nonclinical rationale suggests synergic activity between PARPi and immune checkpoint inhibitors. In the Phase 1/2 proof of principle study TOPACIO, results observed in the PROC cohort support the synergistic activity of the combination. Activity was not limited to biomarker selected populations, and in fact response rates were similar between BRCAmut and BRCAwt patient populations. Additionally, the activity of the combination in patients previously treated with bevacizumab was not diminished compared to patients that were bevacizumab naïve. Based on the nonclinical rationale and early clinical data supporting the proof of principle, we propose this study to evaluate the efficacy of the combination of niraparib with PD-1 inhibitor dostarlimab (TSR-042) in patients without known BRCA mutation who have PROC and who also have been previously treated with bevacizumab.

6. STUDY OBJECTIVES

6.1. Hypothesis

Treatment with the combination of niraparib and dostarlimab (TSR-042) in patients with non-BRCAmut PROC who were previously treated with bevacizumab may result in an ORR that is higher than the ORR expected with other available approved therapies for this population. This study will evaluate the efficacy of combination therapy by estimating the ORR along with the DOR in these patients.

6.2. Primary Objective

The primary objective of this study is to evaluate the efficacy, as measured by confirmed ORR per RECIST v1.1 based on Investigator assessment, of the combination of niraparib and dostarlimab (TSR-042) in:

- patients with PROC without a known BRCA mutation who have been previously treated with bevacizumab.
- subset of patients with PROC who have PD-L1 positive tumors (using a prespecified cut point) without a known BRCA mutation who have been previously treated with bevacizumab.

6.3. Secondary Objectives

Secondary objectives of this study are as follows and will be evaluated in the overall population and in the subset of patients with PD-L1 positive tumors:

- To evaluate the overall clinical benefit of the niraparib and dostarlimab (TSR-042) combination as measured by the following secondary endpoints:
  - DOR per RECIST v1.1 based on Investigator assessment
  - PFS per RECIST v1.1 based on Investigator assessment
  - OS
  - DCR, defined as the percentage of patients who have achieved best overall response (BOR) of confirmed PR, CR, or SD per RECIST v1.1 based on Investigator assessment
- To evaluate the ORR, DOR, PFS, and DCR per RECIST v1.1 based on independent review committee assessment
- To evaluate the safety and tolerability of the niraparib and dostarlimab (TSR-042) combination in patients with PROC as measured by standard safety assessments

6.4. Exploratory Objectives

Exploratory objectives of this study are as follows and will be evaluated in the overall population and in the subset of patients with PD-L1 positive tumors:

- To evaluate efficacy of the niraparib and dostarlimab (TSR-042) combination among patients with BRCAwt tumors, as measured by confirmed ORR, DOR, PFS, OS, and DCR based on Investigator assessment using RECIST v1.1
- To evaluate the duration of disease control among patients with BOR of CR, PR, or SD based on Investigator assessment and independent review committee assessment
- To evaluate health-related quality of life (HRQoL) in patients with PROC treated with the combination of niraparib and dostarlimab (TSR-042), as measured by the Functional Assessment of Cancer Therapy – Ovarian Symptom Index (FOSI)
- To identify additional potential disease-related or treatment-related biomarkers that correlate with responses to the niraparib and dostarlimab (TSR-042) combination, including, but not limited to, the measures of homologous recombination repair pathway defects and the optimal PD-L1 level for efficacy to be used in other dostarlimab (TSR-042) ovarian cancer studies.

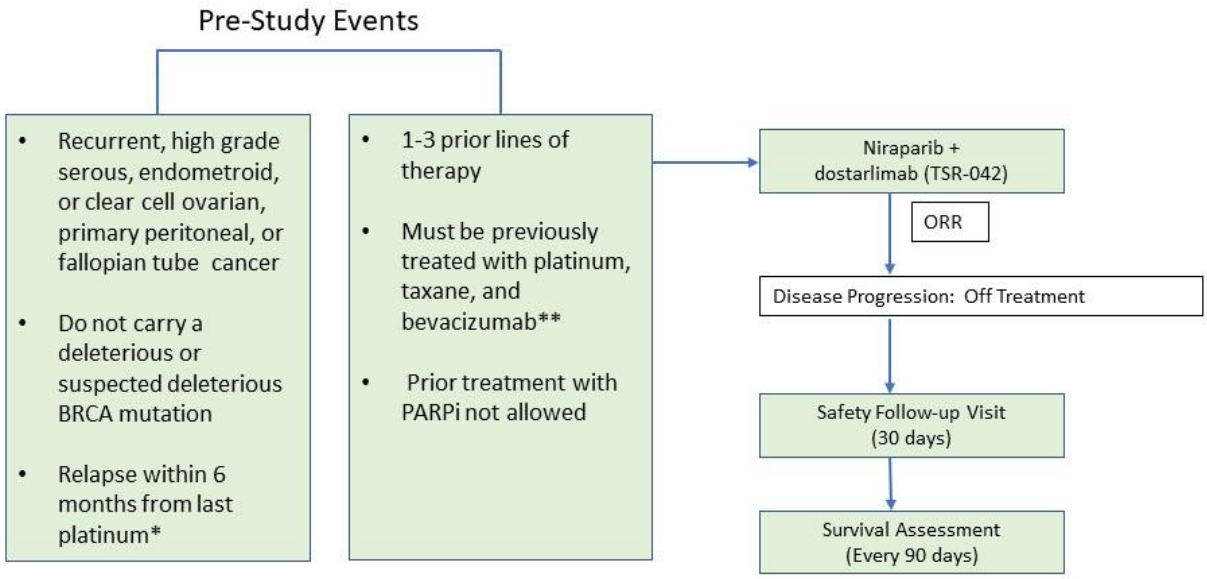
7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This is an open-label, single-arm, Phase 2 study which will evaluate the efficacy and safety of the niraparib and dostarlimab (TSR-042) combination in patients with advanced, relapsed, high-grade, ovarian, fallopian tube, or primary peritoneal cancer without known BRCA mutation who have platinum-resistant disease and who have also been previously treated with bevacizumab.

A study schema is shown in Figure 1.

Figure 1: Overall Study Schema



*Excludes patients who experienced disease progression within 3 months of first-line platinum therapy.
**Neoadjuvant, adjuvant, and the combination of both will be considered as one line of therapy. Treatment with single-agent bevacizumab given as maintenance is not counted as a separate line of therapy. If a therapeutic regimen is modified or changed for a reason other than lack of response or PD (such as allergic reaction, toxicity, or drug availability), this will not be counted as a separate line of therapy. The use of single-agent hormonal therapy given for reasons other than progressive disease per RECIST v1.1 (ie, hormonal therapy given for increasing CA-125 levels) is not counted as a separate line of therapy.
Abbreviations: CA-125 = cancer antigen 125; BRCA = breast cancer susceptibility gene; ORR = objective response rate; PARPi = poly(adenosine diphosphate-ribose) polymerase inhibitor; PD = progression of disease; PD(L)-1 = programmed cell death-1 or programmed cell death-ligand 1; RECIST = Response Evaluation Criteria in Solid Tumors.

This study will consist of a screening period (Day -28 to Day -1), a treatment period (Day 1 to disease progression or toxicity), an end-of-treatment period (occurs when study treatment is discontinued for any reason), a Safety Follow-up Visit (30 ± 7 days after the last dose of study treatment), and recurring survival assessments (every 90 ± 14 days after the last dose of study treatment). All patients will undergo an End of Treatment Visit within 7 days of the decision to discontinue treatment for any reason.

Patients must provide a sufficient tumor tissue sample (formalin fixed paraffin embedded [FFPE] blocks) for BRCA testing and PD-L1 testing at screening. Slides cut from FFPE

blocks must be approved by the Sponsor. Blood samples will be collected at screening for central gBRCA testing. Blood samples will also be collected for exploratory biomarker analysis at screening, at Cycle 3 Day 1, at the time of Investigator-assessed PR (+ 21 days), at the time of Investigator-assessed CR (+ 21 days), and at the End of Treatment Visit. All patients will receive treatment with niraparib and dostarlimab (TSR-042) (collectively referred to as "study treatment") beginning on Cycle 1 Day 1, using one of the regimens detailed in Table 5, depending on body weight and platelet count at screening. Cycles 1 to 4 are 3 weeks long and Cycles 5 and later are 6 weeks long. A window of ± 3 days is allowed to start the following cycle to accommodate holidays, clinic closing due to inclement weather, or other administrative reasons.

Niraparib and dostarlimab (TSR-042) will be administered according to the treatment regimens displayed in Table 5 below.

Table 5: Treatment Regimens for Patients by Actual Body Weight and Platelet Count at Screening

Baseline Criteria	Starting Dose
Body weight ≥ 77 kg AND platelet count ≥ 150,000/µL	Niraparib: 300 mg QD continuously until PD or toxicity Dostarlimab (TSR-042): Cycles 1 through 4: 500 mg Q3W Cycles ≥ 5: 1000 mg Q6W until PD or toxicity
Body weight < 77 kg OR platelet count < 150,000/µL	Niraparib: 200 mg QD continuously until PD or toxicity Dostarlimab (TSR-042): Cycles 1 through 4: 500 mg Q3W Cycles ≥ 5: 1000 mg Q6W until PD or toxicity

Abbreviations: PD = progression of disease; Q3W = every 3 weeks; Q6W = every 6 weeks; QD = once daily.
Note: Each cycle is either 3 weeks (21 days) or 6 weeks (42 days), and nominally begins on Day 1.

Radiographic evaluations (ie, computed tomography [CT]/magnetic resonance imaging [MRI] of chest, abdomen, and pelvis) will be used to assess the extent of disease and will be conducted every 9 weeks (63 ± 7 days) for the first year of study treatment, independent of cycle delays or dose interruptions, or at any time when PD is suspected (Appendix 2). After 1 year of radiographic assessments (week 54), patients will undergo imaging every 12 weeks (84 ± 14 days).

7.1.1. Schedule of Radiographic Tumor Assessment

In accordance with the RECIST v.1.1, CR and PR should be confirmed. Tumor imaging for confirmation of response must be performed at the earliest 28 days after the first indication of PR or CR but no later than 35 days after the first indication of response. The subsequent tumor imaging after the confirmatory scan should be obtained per the original scheduled interval (eg, 9 weeks [63 ± 7 days] from confirmatory scan during the first year of study treatment and every 12 weeks thereafter). Radiographic evaluations will continue until any of the following occurs: PD, start of alternate anticancer therapy, withdrawal of consent to study participation, becoming lost to follow-up, death, or study termination. If a patient discontinues treatment for a reason other than radiographic PD,

death, withdrawal of consent, loss to follow-up, or the end of the study, radiographic evaluation and CA-125 testing should continue at the specified intervals (ie, every 9 weeks for the first year of study treatment and every 12 weeks thereafter until PD). Also, clinically stable patients should not be discontinued until progression is confirmed. If a patient discontinues treatment for clinical progression and does not meet RECIST criteria for progression, scans and CA-125 testing should continue at the specified intervals until progression is confirmed or until the start of subsequent anticancer treatment.

7.1.2. Postprogression Therapy

Patients with radiographic evidence of PD who are clinically stable may continue treatment at the Investigator's discretion and after discussion with the Sponsor, while awaiting confirmatory tumor imaging. Repeat imaging should be performed at ≥ 4 weeks. If repeat imaging shows SD, PR, or CR, patients can continue study treatment at the Investigator's discretion. In the event that PD is confirmed, patients still may continue to receive study treatment even after confirmed radiographic progression if the patient is clinically stable and the Investigator deems that the patient is deriving clinical benefit. This allowance to continue treatment despite radiographic progression takes into account the observation that some patients may have a transient tumor flare in the first few months after the start of immunotherapy, but with subsequent treatment response.

7.1.3. Continued Treatment after Final DCO

A protocol clarification letter was issued by the sponsor on July 08 2021 regarding a decision to not resume study enrollment. Final analysis will be perfomed with data collected until August 18 2021 (the date of primary completion achieved [PCA] and final data cut-off [DCO]). Following the final DCO date, the data collection for all recruited participants who no longer received study treatment was stopped entirely and the clinical trial database was closed. Patients may continue to receive study treatment per investigator discretion until disease progression or they develop intolerable side-effects, or are lost to follow-up, withdraw consent, or pass away. Patients will not be allowed to receive study treatment if they become pregnant or demonstrate severe non-compliance with the protocol. Section 7.6.3 describes the study conduct for participants continuing treatment following the final DCO date, and Section 12.3 outlines the safety data that will be collected for these patients.

7.1.4. Schedule of Safety Assessments

Safety assessments will include the collection of AEs, vital sign measurements, symptom-directed physical examinations, and clinical laboratory assessments (Section 12.1). All AEs (serious and nonserious) will be collected and recorded for each patient from the day of signing the informed consent form until 90 ± 14 days after the last study drug administration or until alternate anticancer treatment has been initiated, whichever occurs earlier; any pregnancies that occur within 180 days post-treatment are to be reported. All AESIs must be reported as outlined in Section 12.2.7. All AEs including SAEs experienced by a patient, regardless of causality, will be monitored until one of the following occurs: the AE or SAE has resolved, any abnormal laboratory values have returned to baseline or have normalized, there is a satisfactory explanation for the

change(s) observed, the patient is lost to follow-up or withdraws consent, or the patient has died. The safety assessments required for patients continuing study treatment following the final DCO date are described in Section 12.3.

7.2. Number of Patients

It was planned that approximately 150 patients would be enrolled and dosed.

7.3. Treatment Assignment

All patients in this single-arm study will receive treatment with niraparib combined with dostarlimab (TSR-042).

7.4. Dose Adjustment

7.4.1. Niraparib

Adverse reactions should be managed with either interruption of treatment, dose reduction, or dose discontinuation; the recommended dose modifications for adverse reactions should be followed as listed in Table 6, Table 7, and Table 8.[50] Niraparib should be discontinued for selected AEs that persist beyond 28 days, as noted in the tables.

For patients whose initial dose is 3 capsules QD, dose reductions to 2 capsules QD (200 mg/day) and subsequently to 1 capsule QD (100 mg/day) will be allowed. No further dose reduction will be allowed without discussion with the Sponsor's Medical Monitor.

For patients whose initial dose is 2 capsules QD, dose reduction to 1 capsule QD (100 mg/day) will be allowed. No further dose reduction will be allowed without discussion with the Sponsor's Medical Monitor.

If an AE leading to niraparib dose interruption is clearly attributed to niraparib alone, the next treatment cycle can start on time with dostarlimab (TSR-042) administration. Niraparib can restart once the AE resolves with an appropriate dose reduction.

If the attribution of an AE is not clear between dostarlimab (TSR-042) and niraparib (examples might include diarrhea and alkaline phosphatase [ALP], AST, or ALT elevation), both agents should be withheld, and a discussion with the Sponsor's Medical Monitor is recommended. If the AE has not resolved prior to the scheduled start of a new cycle, the new cycle will be delayed until AE resolution. A delay of more than 28 days needs to be discussed with the Sponsor's Medical Monitor.

If a diagnosis of MDS or AML is confirmed by a hematologist, the patient must permanently discontinue niraparib.

If niraparib is permanently discontinued due to AEs that are clearly attributed to niraparib alone, patients may continue treatment with dostarlimab (TSR-042) alone.

Table 6: Recommended Niraparib Dose Modifications for Adverse Reactions

Dose level	Initial Dose: 3 capsules/day	Initial Dose: 2 capsules/day
Starting dose	300 mg QD (three 100-mg capsules)	200 mg QD (two 100-mg capsules)
First dose reduction	200 mg QD (two 100-mg capsules)	100 mg QD[a] (one 100-mg capsules)
Second dose reduction	100 mg QD[a] (one 100-mg capsules)	N/A

Abbreviations: N/A = not applicable, QD = once daily.
[a] If further dose reduction is required for adverse-event management, discussion with the Sponsor's Medical Monitor is required.

Table 7: Niraparib Dose Modifications for Non-hematologic Adverse Reactions

Non-hematologic NCI-CTCAE ≥ Grade 3 adverse reaction where prophylaxis is not considered feasible or adverse reaction event persists despite treatment	• Withhold niraparib for a maximum of 28 days or until resolution of adverse reaction. • For those adverse reactions that do not resolve within 28 days, niraparib should be discontinued. Otherwise, discussion with the Sponsor's Medical Monitor is required to resume niraparib. • Resume niraparib at a reduced dose per Table 6.
NCI-CTCAE ≥ Grade 3 treatment-related adverse reaction event lasting more than 28 days while the patient is administered niraparib 100 mg/day	Discontinue medication.
NCI CTCAE Grade ≥2 adverse reaction of PRES	Discontinue medication.

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

Table 8: Niraparib Dose Modifications for Hematologic Adverse Reactions

Monitor CBC weekly for the first cycle, on Day 1 of Cycles 2 through 4, on Day 1 and Day 22 of Cycles 5 and 6, on Day 1 and Day 29 of Cycles 7 through 11, and on Day 1 of each cycle thereafter. CBC needs to be performed and results evaluated prior to dosing. If dose interruption or modification is required at any point on study because of hematologic toxicity, weekly blood draws for CBC will be done until the AE resolves. To ensure safety of the new dose, weekly blood draws for CBC will also be required for an additional 4 weeks after the AE has been resolved.	
Platelet count < 100,000/µL	First occurrence: • Withhold niraparib for a maximum of 28 days and monitor blood counts weekly until platelet counts return to ≥ 100,000/µL. • For those adverse reactions that do not resolve within 28 days, niraparib should be discontinued. Otherwise, discussion with the Sponsor's Medical Monitor is required to resume niraparib. • Resume niraparib at same or reduced dose per Table 6. • If nadir platelet count was < 75,000/µL, resume at a reduced dose after recovery.
	Second occurrence: • Withhold niraparib for a maximum of 28 days and monitor blood counts weekly until platelet counts return to ≥ 100,000/µL. • For those adverse reactions that do not resolve within 28 days, niraparib should be discontinued. Otherwise, discussion with the Sponsor's Medical Monitor is required to resume niraparib. • Resume niraparib at a reduced dose per Table 6. • Discontinue niraparib if the platelet count has not returned to acceptable levels within 28 days of the dose interruption period, or if the patient has already undergone dose reduction to 100 mg QD.[a]
Neutrophil < 1,000/µL or Hemoglobin < 8 g/dL	• Withhold niraparib for a maximum of 28 days and monitor blood counts weekly until neutrophil counts return to ≥ 1,500/µL or hemoglobin returns to ≥ 9 g/dL. • For those adverse reactions that do not resolve within 28 days, niraparib should be discontinued. Otherwise, discussion with the Sponsor's Medical Monitor is required to resume niraparib. • Resume niraparib at a reduced dose per Table 6. • Discontinue niraparib if neutrophil or hemoglobin level has not returned to acceptable levels within 28 days of the dose interruption period or if the patient has already undergone dose reduction to 100 mg QD.[a]
Hematologic adverse reaction requiring transfusion	• For patients with platelet count ≤ 10,000/µL, platelet transfusion should be considered. If there are other risk factors, such as co administration of anticoagulation or antiplatelet drugs, consider interrupting these drugs and/or transfusion at a higher platelet count. Red blood cell transfusion(s) may be given at the discretion of the Investigator. • Resume niraparib at a reduced dose.

Abbreviations: AE = adverse event; AML = acute myeloid leukemia; CBC = complete blood count; MDS = myelodysplastic syndrome; QD = once daily.

[a] If MDS/AML is confirmed, discontinue niraparib.

For clinical situations not covered by this dose modification guidance the Investigator must contact the Sponsor's Medical Monitor.

The reason for interruption or discontinuation of niraparib should be recorded in the electronic Case Report Form (eCRF).

7.4.2. Dostarlimab (TSR-042)

AEs (both nonserious and serious) associated with dostarlimab (TSR-042) exposure may represent an immunologic etiology. These AEs may occur shortly after the first dose or several months after the last dose of treatment.

In general, dostarlimab (TSR-042) must be withheld for drug-related Grade 3 toxicities, as well as for certain immune-related adverse events of interest (irAEIs), but may be resumed upon recovery to Grade ≤ 1; dostarlimab (TSR-042) will be permanently discontinued for any drug-related Grade 4 AE. Dostarlimab (TSR-042) must be permanently discontinued for certain irAEIs as described in Table 9.

The specific immune-related AEs (irAEs) typically observed with anti-PD-1 antibodies will be managed according to the guidelines summarized below, and clinical management may be supplemented by the recent joint American Society of Clinical Oncology (ASCO) and NCCN guidelines for diagnosis and management of irAEs (see Section 9.2.3).[51]

If an AE leading to dostarlimab (TSR-042) dose interruption is clearly attributed to dostarlimab (TSR-042) alone, the next treatment cycle can start on time with niraparib administration. If dostarlimab (TSR-042)-related AE resolves by day 7 of this cycle, dostarlimab (TSR-042) can be administered with up to 7 day delay. If AE does not resolve by day 7 (or is considered by the Investigator unlikely to resolve within 7 days), dostarlimab (TSR-042) should be omitted until the subsequent cycle. If dostarlimab (TSR-042)-related AE does not resolve within 28 days, Sponsor's Medical Monitor should be contacted.

If dostarlimab (TSR-042) interruption is necessary after Cycle 4 (when cycle length changes to 6 weeks), Sponsor's Medical Monitor should be contacted.

Of note, if the attribution of an AE is not clear between dostarlimab (TSR-042) and niraparib (examples might include diarrhea and ALP, AST, or ALT elevation), both agents should be withheld and a discussion with the Sponsor's Medical Monitor is recommended. If the AE has not resolved prior to the scheduled start of a new cycle, the new cycle will be delayed until AE resolution. A delay of more than 28 days needs to be discussed with the Sponsor's Medical Monitor.

If dostarlimab (TSR-042) is permanently discontinued due to AEs that are clearly attributed to dostarlimab (TSR-042) alone, patients may continue treatment with niraparib alone.

For clinical situations not covered by this dose modification guidance the Investigator must contact the Sponsor's Medical Monitor.

The reason for interruption or discontinuation of dostarlimab (TSR-042) should be recorded in the eCRF.

Table 9: Guidelines for Treatment of Immune-related Adverse Events of Interest

Toxicity	Hold Treatment For CTCAE Grade	Restarting Treatment/ discontinuation
Uveitis	Symptomatic any grade	Restart the treatment when toxicity resolves to Grade 0. For any recurrent uveitis or uveitis resistant to topical steroids, permanently discontinue study treatment.
Diarrhoea/colitis	2-3	Restart dosing when toxicity resolves to Grade 0-1.
	4 or recurrent Grade 3	Permanently discontinue study treatment.
AST, ALT, or increased bilirubin	2 (AST or ALT >3 and ≤5×ULN or total bilirubin >1.5 and ≤3×ULN)	Restart dosing when toxicity resolves to Grade 0-1.
	3-4 (AST or ALT >5×ULN or total bilirubin >3×ULN)	Permanently discontinue study treatment (see exception below)[a].
T1DM or hyperglycaemia	3-4 hyperglycaemia or T1DM (associated with metabolic acidosis or ketonuria)	Restart dosing in appropriately managed, clinically and metabolically stable participants. Insulin replacement therapy is required.
Immune-related encephalitis	Any grade	Permanently discontinue study treatment.
Hypophysitis	2-4	For Grade 2-3, hold until hormonal therapy results return to adequate levels by laboratory values and restart dosing when toxicity resolves to Grade 0-1. For recurrence or worsening of Grade ≥2 hypophysitis after steroid taper has been completed and is on adequate hormone replacement therapy, permanently discontinue study treatment.
Adrenal insufficiency	2-4	Hold until hormonal therapy results in return to adequate levels by laboratory values and restart dosing when toxicity resolves to Grade 0-1. For recurrent or worsening Grade ≥2 adrenal insufficiency while adequate hormonal replacement is continuing, permanently discontinue study treatment.
Hypo- and hyperthyroidism	3-4	Hold until hormonal therapy results in return to adequate levels by laboratory values and restart dosing when toxicity resolves to Grade 0-1.
Infusion-related reaction	2[b]	Restart dosing when toxicity resolves to Grade 0-1.
	3-4	Permanently discontinue study treatment.

Toxicity	Hold Treatment For CTCAE Grade	Restarting Treatment/ discontinuation
Pneumonitis	2	Restart dosing when toxicity resolves to Grade 0-1. If Grade 2 recurs, permanently discontinue study treatment.
	3-4 or recurrent Grade 2	Permanently discontinue study treatment.
Severe exfoliative dermatologic events	3 or Suspected DRESS, SJS or TEN	Withhold
	4 or Confirmed DRESS, SJS or TEN	Permanently discontinue study treatment.
Renal failure or nephritis	2	Restart dosing when toxicity resolves to Grade 0-1.
	3-4	Permanently discontinue study treatment.
Myositis	2-3	Restart dosing when toxicity resolves to Grade 0-1.
	4	Permanently discontinue study treatment.
Myocarditis	Grade 2, 3 or 4	Permanently discontinue
Severe neurologic events (myasthenic syndrome/myasthenia gravis, Guillain Barré Syndrome, transverse myelitis)	Grade 2, 3 or 4	Permanently discontinue
Hemophagocytic lymphohistiocytosis	Any grade	Permanently discontinue
Recurrence of irAEI in this table after resolution to Grade ≤1	3-4	Permanently discontinue study treatment.
Other irAEIs	Based on severity and type of reaction (Grade 2 or 3)	Restart dosing when toxicity resolves to Grade 1
	Grade 4 or recurrent Grade 3	Permanently discontinue

Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; DRESS=drug reaction with eosinophilia and systemic symptom; irAEI=immune-related adverse event of interest; T1DM=type 1 diabetes mellitus; ULN=upper limit of normal. SJS=Stevens Johnson Syndrome; TEN=toxic epidermal necrolysis

[a] For participants with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by ≥50% relative to baseline and lasts for at least 1 week, then participant should be discontinued.

[b] Upon resolution within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (eg, from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose; refer to Section 9.2.3.2, Infusion-related Reaction Treatment Guidelines, for further management details.

In addition to the immune-related adverse events listed in Table 9, treatment with dostarlimab may be associated with other irAEs, including events which may be less commonly associated with PD-(L)1 inhibitors but can similarly result from activation of

cellular immune response, e.g. pancreatitis. For these events, the general guidance from ASCO/NCCN should be considered. Patients should receive appropriate supportive care measures as deemed necessary by the treating Investigator, including but not limited to the items outlined below:

- In general, treatment can continue with close monitoring for Grade 1 toxicities.
- Hold treatment for most Grade 2 toxicities and consider resuming when symptoms and/or laboratory values revert to Grade 1 or less. Corticosteroids (initial dose 0.5 to 1mg/kg/day of prednisone or equivalent) must be administered.
- Hold for Grade 3 toxicities and initiate high-dose corticosteroids (prednisone 1 to 2 mg/kg/day or methylprednisolone IV 1 to 2 mg/kg/day). Corticosteroids should be tapered over the course of at least 4 to 6 weeks. If symptoms do not improve within 48 to 72 hours of high-dose corticosteroids, infliximab may be offered for some toxicities.
  It is highly recommended that investigators discuss any adverse events with the Sponsor prior to using infliximab.
- When symptoms and/or laboratory values revert to Grade 1 or less, rechallenging with immunotherapy may be offered, however caution is advised, especially in patients with early-onset immune-mediated events. Dose adjustments are not recommended.

7.5. Criteria for Study Termination

The Sponsor may terminate this study at any time. The Sponsor will notify the Investigators when the study is to be placed on hold, completed, or terminated.

7.6. Study Conduct

Cycles 1 to 4 are 3 weeks long and Cycles 5 and later are 6 weeks long. A window of ± 3 days is allowed to start the following cycle to accommodate holidays, clinic closing due to inclement weather, or other administrative reasons.

7.6.1. Schedule of Events

Refer to Table 10 for a detailed summary of the events performed during the study.

Table 10: Schedule of Events

Cycle/Day[a]	Screening -28 to -1	C1 D1	C2 D1	C3 D1	C4 D1	C5 D1	C5 D22	C6 D1	C6 D22	C7 D1	C8D1 and Subsequent Cycles D1	EOT[b]	Safety Follow-up Visit 30 ± 7 days post-treatment	Survival Assessments every 90 ± 14 days)
Cycle Length[a]		**3 weeks / 21 days ± 3 days**				**6 weeks / 42 days ± 3 days**								
Approximate Week		**1**	**4**	**7**	**10**	**13**	**16**	**19**	**22**	**25**	**31**			
Procedure														
Informed consent	X													
Demographics	X													
Medical, surgical, cancer (including genotyping), and medication history	X													
Physical examination	X											X	X	
Symptom-directed physical examination		X	X	X	X	X	X	X	X	X	X			
Vital signs (temperature) , height, and weight[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital signs: Blood pressure and heart rate (pulse)[c]	X	X[c]	X[c]	X[c]	X	X	X	X	X	X[c]	X[c]	X	X	
12-lead ECG	X													
ECOG performance status	X	X	X	X	X	X	X	X	X	X	X	X		
Required tumor tissue sample (FFPE block)[d]	X													
CBC with differential[e,f]	X	X[e]	X	X	X	X	X	X	X	X[e]	X[e]	X	X	
Coagulation	X	As clinically indicated												

Cycle/Day[a]	**Screening -28 to -1**	**C1 D1**	**C2 D1**	**C3 D1**	**C4 D1**	**C5 D1**	**C5 D22**	**C6 D1**	**C6 D22**	**C7 D1**	**C8D1 and Subsequent Cycles D1**	**EOT**[b]	**Safety Follow-up Visit 30 ± 7 days post-treatment**	**Survival Assessments every 90 ± 14 days)**
Cycle Length[a]		**3 weeks / 21 days ± 3 days**				**6 weeks / 42 days ± 3 days**								
Approximate Week		**1**	**4**	**7**	**10**	**13**	**16**	**19**	**22**	**25**	**31**			
Procedure														
Serum/plasma chemistry[f,g]	X	X	X	X	X	X	X	X	X	X	X	X	X	
Urinalysis	X													
Thyroid panel[h]	X	Every 12 weeks (84 ± 7 days) from C1D1 and at EOT												
Amylase	X	Every 12 weeks (84 ± 7 days) and at EOT												
Serum or urine pregnancy test[i]	X	X	X	X	X	X	X	X	X	X	X		X	
HBV/HCV test[j]	X													
CA-125	X	X	X	X	X	X	X	X	X	X	X	X	X	X[k]
CT or MRI for RECIST v.1.1 assessment[l]	X	X (every 9 weeks)[l]										X[l]		
Blood sample for central gBRCA testing[m]	X													
Blood sample for exploratory biomarkers	X[m]			X	At the time of Investigator assessment of PR (+ 21 days) and at the time of Investigator assessment of CR (+ 21 days)							X		
HRQoL[n]		X	X	X	X	X		X		X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	
Oral niraparib dispensed/collected		X[o]	X[o]	X[o]	X[o]	X[o]	X	X[o]	X	X[o]	X[o]	X		

Cycle/Day[a]	Screening -28 to -1	C1 D1	C2 D1	C3 D1	C4 D1	C5 D1	C5 D22	C6 D1	C6 D22	C7 D1	C8D1 and Subsequent Cycles D1	EOT[b]	Safety Follow-up Visit 30 ± 7 days post-treatment	Survival Assessments every 90 ± 14 days)
Cycle Length[a]		**3 weeks / 21 days ± 3 days**				**6 weeks / 42 days ± 3 days**								
Approximate Week		**1**	**4**	**7**	**10**	**13**	**16**	**19**	**22**	**25**	**31**			
Procedure														
IV dostarlimab (TSR-042) administered[p]		500mg	500 mg	500 mg	500mg	1000mg		1000mg		1000mg	1000mg			
Adverse event monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X[q]
Anticancer therapies assessment														X
Survival assessment														X

Abbreviations: AE = adverse event; AESI = adverse event of special interest; ALT = alanine aminotransferase; ALP = alkaline phosphatase; AML = acute myeloid leukemia; AST = aspartate aminotransferase; BRCA = breast cancer susceptibility gene; CA-125 = cancer antigen 125; CBC = complete blood count; CR = complete response; CT = computed tomography; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ECI = event of clinical interest; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; FFPE = formalin fixed paraffin embedded; FOSI = Functional Assessment of Cancer Therapy – Ovarian Symptom Index; gBRCA = germline breast cancer susceptibility gene; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HRQoL = health-related quality of life; IV = intravenous; MDS = myelodysplastic syndrome; MRI = magnetic resonance imaging; OC = ovarian cancer; PD = progression of disease; PD-L1 = programmed cell death-ligand 1; PR = partial response; Q3W = every 3 weeks; Q6W = every 6 weeks; RECIST = Response Evaluation Criteria in Solid Tumors; RNA = ribonucleic acid; SAE = serious adverse event.

[a] Treatment cycles are 21 days (± 3 days) for the first 4 cycles (12 weeks); subsequently, treatment cycles are 42 days (± 3 days).

[b] All patients will undergo an End of Treatment Visit within 7 days of the decision to discontinue treatment for any reason. If a patient discontinues treatment for clinical progression and does not meet RECIST criteria for progression, scans and CA-125 testing should continue at the specified intervals until progression is confirmed or until the start of subsequent anticancer treatment. Also, clinically stable patients should not be discontinued until progression is confirmed.

[c] Height will be measured only at screening. Weight, temperature, blood pressure, and heart rate (pulse) will be measured at screening, on Day 1 of each treatment cycle, and on Day 22 of Cycles 5 and 6. Blood pressure and heart rate (pulse) should also be measured weekly (Day 8 and Day 15) during the first 8 weeks (Cycles 1 through 3) and on Day 29 ±7 days in Cycles 7 through 11, and entered as an unscheduled visit if abnormal.

[d] Patient must provide FFPE tumor tissue block(s) with sufficient tumor content (as confirmed by the Sponsor's designated central laboratory) during screening to enable BRCA testing and PD-L1 testing. Slides cut from FFPE blocks must be approved by the Sponsor.

[e] Monitor CBC weekly for the first cycle, on Day 1 of Cycles 2 through 4, on Day 1 and Day 22 of Cycles 5 and 6, on Day 1 and Day 29 of Cycles 7 through 11, and on Day 1 of each cycle thereafter. CBC needs to be performed and results evaluated prior to dosing. If dose interruption or modification is required at any point on study because of hematologic toxicity, weekly blood draws for CBC will be done until the AE resolves. To ensure safety of the new dose, weekly blood draws for CBC will also be required for an additional 4 weeks after the AE has been resolved.

[f] Clinical laboratory tests may be performed within 36 hours prior to each visit. Serum/plasma chemistry and CBC need to be performed and results evaluated prior to dosing.

[g] The following serum/plasma chemistry parameters will be measured: sodium, potassium, chloride, calcium, magnesium, glucose, total bilirubin, ALP, AST, ALT, total protein, albumin, creatinine, and urea or blood urea nitrogen.

[h] Thyroid-stimulating hormone, triiodothyronine or free triiodothyronine, and free thyroxine.

[i] For patients of childbearing potential only, a negative serum or urine pregnancy test is required within 72 hours prior to Day 1 of each cycle. If the clinic standard is to do a serum or urine pregnancy test more frequently, that is acceptable with the protocol as written.

[j] Only if clinically indicated. Testing should be done for HBsAg (or equivalent) and HCV RNA.

[k] If a patient discontinues treatment for a reason other than radiographic progression, death, withdrawal of consent, loss to follow-up, or the end of the study, CA-125 testing should continue every 9 weeks for the first year of study treatment and every 12 weeks thereafter until PD. If a patient discontinues treatment for clinical progression and does not meet RECIST criteria for progression, CA-125 testing should continue at the specified intervals until progression is confirmed or until the start of subsequent anticancer treatment. Also, clinically stable patients should not be discontinued until progression is confirmed.

[l] RECIST v.1.1 tumor assessment via CT or MRI scan of abdomen/pelvis and clinically indicated areas required at screening, every 9 weeks (63 ± 7 days) from Cycle 1 Day 1 for the first year (week 54), then every 12 weeks (84 ± 14 days) until disease progression, at which point a final follow up set of imaging is required. Per RECIST v.1.1, tumor imaging for confirmation of response must be performed at the earliest 28 days after the first indication of PR or CR but no later than 35 days after the response. The subsequent tumor imaging after the confirmatory scan should be obtained 9 weeks (63 ± 7 days) from confirmatory scan during the first year of study treatment and every 12 weeks thereafter. If a patient discontinues treatment for clinical progression and does not meet RECIST criteria for progression, scans should continue at the specified intervals until progression is confirmed or until the start of subsequent anticancer treatment. Also, clinically stable patients should not be discontinued until progression is confirmed.

[m] The exploratory biomarker samples are to be collected at the same time with blood samples for central gBRCA testing.

[n] For HRQoL evaluation, the FOSI assessment will be collected during the treatment period at Cycle 1 Day 1 (prior to dosing and clinical procedures), Cycle 2 Day 1, and on Day 1 of every cycle thereafter. For patients who discontinue treatment, FOSI assessments should be collected at the EOT Visit, at the Safety Follow-up Visit, and at Survival Assessments.

[o] On Day 1 of each cycle, niraparib will be administered after completion of the dostarlimab (TSR-042) infusion.

[p] IV dostarlimab (TSR-042) will be administered 500 mg Q3W from Cycles 1 through 4. Starting at Cycle 5, administration will change to 1000 mg Q6W. Dostarlimab (TSR-042) treatment may continue for up to 3 years or until PD, unacceptable toxicity, withdrawal of consent, Investigator's decision, or death. Continued treatment with dostarlimab (TSR-042) beyond 3 years may be considered following discussion between the Sponsor and the Investigator. Dostarlimab (TSR-042) may be administered up to 3 days before or after the scheduled Day 1 of each cycle after Cycle 1 due to administrative reasons. If dostarlimab (TSR-042) is administered on Day 1 of the cycle, it will be administered after all procedures and assessments have been completed, unless otherwise indicated. If dostarlimab (TSR-042) is administered earlier or later than Day 1 of the cycle, patients will continue to take niraparib as scheduled.

[q] All AEs (serious and nonserious) are required to be collected and recorded until 90 ± 14 days after last study drug administration or until alternate anticancer treatment has been initiated, whichever occurs earlier. All AESIsmust be reported as outlined in Section 12.2.7. Any pregnancies that occur within 180 days post-treatment discontinuation are to be reported.

7.6.2. Procedures and Assessments

Standard of care tests/procedures, including laboratory assessments, electrocardiogram (ECG), physical examination, vital signs, height, and weight, performed before the patient signs the Informed Consent Form (ICF) can be used as part of the screening assessments as long as the tests/procedures meet the protocol-required timelines. Scans performed prior to informed consent as part of routine clinical management are also acceptable for use as initial tumor imaging if they are of diagnostic quality and are performed within 28 days prior to first dose date. Note that source documents must clearly identify the standard of care tests/procedures that are used for screening and the results of these tests/procedures must be entered in the eCRF.

7.6.3. Continued Treatment after Final DCO

Following the final DCO date, patients may continue to receive study treatment as they were doing previously, for as long as they and their physician feel that they are gaining clinical benefit from and tolerating the study treatment and have not met any study discontinuation criterion. The patients will come into the clinic to receive the study treatment and follow the same cycle they were on before, and they will continue to be monitored according to routine clinical practice as defined by the investigators, but no other study assessments will be conducted. The investigators and site staff may conduct any safety assessments that they feel the patient requires and follow the local standard of care procedures for the patients. The investigators can contact the Medical Monitor at any stage to discuss any concerns.

When the patients withdraw from the study/study treatment or progress, every effort should be made to conduct an EOT visit. The only procedure to be performed at the EOT visit is the collection of a blood sample for exploratory biomarkers, as described in Table 10. No other assessments listed in Table 10 need to be conducted at the EOT visit, unless required as part of standard of care.

8. SELECTION AND WITHDRAWAL OF PATIENTS

Prior to undergoing any study-specific procedures, all patients will undergo the informed consent process, which will be documented by site staff. Results of any BRCA testing will not be shared with the patient.

8.1. Patient Inclusion Criteria

Patients will be eligible for study entry if all of the following criteria are met:

1. Patient must be female ≥ 18 years of age, able to understand the study procedures, and subsequently agreed to participate in the study by providing written informed consent.
2. Patients must have recurrent high-grade serous, endometrioid, or clear cell ovarian, fallopian tube, or primary peritoneal cancer.
3. Patients must be considered resistant to the last administered platinum therapy, ie, the time from last administered platinum dose until initial documented progression (as evidenced by radiographic progression per RECIST v.1.1) must be less than 6 months (183+7 days).
4. Patients must have completed at least 1 but no more than 3 prior lines of therapy for advanced or metastatic ovarian cancer. Neoadjuvant, adjuvant, and the combination of both will be considered as one line of therapy. Treatment with single-agent bevacizumab given as maintenance is not counted as a separate line of therapy. If a therapeutic regimen is modified or changed for a reason other than lack of response or PD (such as allergic reaction, toxicity, or drug availability), this is not counted as a separate line of therapy. The use of single-agent hormonal therapy given for reasons other than progressive disease per RECIST v1.1 (ie, hormonal therapy given for increasing cancer antigen 125 [CA-125] levels) is not counted as a separate line of therapy.
5. Patients must have been previously treated with platinum-based regimen, taxane agent(s) and bevacizumab (bevacizumab could be used as a single agent or in combination with another agent, in frontline therapy, as maintenance, or for treatment of recurrent disease).

   Note: Bevacizumab refers to bevacizumab and approved biosimilars, for example, bevacizumab-awwb (MVASI™), bevacizumab-bvzr (ZIRABEV™), etc.
6. Patient has measurable disease according to RECIST v.1.1.
7. Patient has an ECOG performance status of 0 or 1 (see Appendix 3).
8. Patient has adequate organ function, defined as follows:
   a. absolute neutrophil count ≥ 1,500/μL, without growth factor support (granulocyte colony-stimulating factor [G-CSF] or granulocyte-macrophage colony-stimulating factor administration is not permitted within 2 weeks of screening)
   b. platelets ≥ 100,000/μL without platelet transfusion support within 2 weeks of screening

c. hemoglobin ≥ 9 g/dL without transfusion or growth factor support (recombinant erythropoietin) within 2 weeks of screening
d. serum creatinine ≤ 1.5× upper limit of normal (ULN) or calculated creatinine clearance ≥ 50 mL/min using Cockcroft-Gault equation
e. total bilirubin ≤ 1.5× ULN, except in patients with Gilbert's syndrome. Patients with Gilbert's syndrome may enroll if direct bilirubin is ≤ 1.5× ULN.
f. AST and ALT ≤ 2.5× ULN, unless liver metastases are present, in which case they must be ≤ 5× ULN

9. Patient meets the following criteria:

   a. Female patient (of childbearing potential) is not breastfeeding, has a negative serum pregnancy test within 72 hours prior to taking study treatment, and agrees to abstain from activities that could result in pregnancy, as outlined in Section 9.2.2, from enrollment through 180 days after the last dose of study treatment; or

      Note: (a) A urine pregnancy test may be performed if the serum pregnancy result is not available before dosing. (b) Women should not breastfeed or store breastmilk for use, during treatment, and for 30 days after receiving the final dose of study treatment.

   b. Female patient is of nonchildbearing potential, for other than medical reasons, defined as any of the following:

      – ≥ 45 years of age and has not had menses for > 1 year

      – amenorrheic for < 2 years without a hysterectomy and oophorectomy and a follicle-stimulating hormone value in the postmenopausal range upon screening evaluation

      – has undergone hysterectomy, bilateral oophorectomy, or tubal ligation. Documented hysterectomy or oophorectomy must be confirmed with medical records of the actual procedure or confirmed by an ultrasound. Tubal ligation must be confirmed with medical records of the actual procedure; otherwise, the patient must meet the pregnancy test criteria for women of childbearing potential in inclusion criterion 9a and must be willing to use highly effective contraception (see Appendix 1) throughout the study, starting with the screening visit through 180 days after the last dose of study therapy.

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

10. Patient must provide FFPE tumor tissue block(s) with sufficient tumor content (as confirmed by the Sponsor's designated central laboratory) during screening to enable BRCA testing and PD-L1 testing. The use of slides created from paraffin-embedded tissue as opposed to FFPE blocks must be approved by the Sponsor.
11. Patient must agree to complete the HRQoL questionnaire throughout the study.

8.2. Patient Exclusion Criteria

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

1. Patients who experienced disease progression within 3 months (12 weeks or 84 days) (as evidenced by radiographic progression per RECIST v1.1) of first-line platinum therapy.
2. Patients with known deleterious or suspected deleterious mutations in BRCA1 or BRCA2 genes (local testing permitted).

   Note: This will apply to known germline BRCA mutations and known BRCA mutations in the tumor.
3. Patient has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent.
4. Patient has received prior therapy with a PARP-1/PARP-2 inhibitor.
5. Patient has known hypersensitivity to dostarlimab (TSR-042), niraparib, their components, or their excipients.
6. Patient has a known history of myelodysplastic syndrome or acute myeloid leukemia.
7. Patient has not recovered (ie, to Grade ≤ 1 or to baseline) from prior chemotherapy induced AEs. Note: Patient with Grade ≤ 2 neuropathy or alopecia is an exception to this criterion and may qualify for the study.
8. Patient has a known diagnosis of immunodeficiency or is receiving systemic steroid therapy exceeding an equivalent of prednisone 10 mg daily or any other form of immunosuppressive therapy within 7 days prior to the first dose of study treatment.
9. Patient is currently participating in a treatment study or has participated in a study of an investigational agent within 4 weeks of the first dose of treatment.
10. Patient has received prior systemic anticancer therapy including cytotoxic chemotherapy, hormonal therapy given with the intention to treat ovarian cancer, or biological therapy within 3 weeks of the first dose of study treatment.
11. Patient has received live vaccine within 14 days of planned start of study therapy.
12. Patient has symptomatic uncontrolled brain or leptomeningeal metastases. (To be considered "controlled," central nervous system [CNS] disease must have undergone treatment [eg, radiation or chemotherapy] at least 1 month prior to study entry. The patient must not have any new or progressive signs or symptoms related to the CNS disease and must be taking ≤ 10 mg of prednisone or equivalent per day or no steroids.) Patients who have untreated brain metastases and who are not symptomatic may enroll if the Investigator feels that treatment of these metastases is not indicated. A scan to confirm the absence of brain metastases is not required. Patients with spinal cord compression may be considered if they have received definitive treatment for this and evidence of clinically stable disease for 28 days prior to the first dose of study treatment.
13. Patient had major surgery within 4 weeks of starting the first dose of study treatment or patient has not recovered from any effects of any major surgery.

14. Patient has a known additional malignancy that progressed or required active treatment within the last 2 years. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin that has undergone potentially curative therapy, or in situ cancer that is considered to be low risk for progression by the Investigator.
15. Patient is considered a poor medical risk due to a serious, uncontrolled medical disorder, nonmalignant systemic disease, or active, uncontrolled infection. These include, but are not limited to, significant cardiovascular disease (eg, significant cardiac conduction abnormalities, myocardial infarction, cardiac arrhythmia or unstable angina within 6 months prior to enrollment, New York Heart Association Grade ≥ 2 congestive heart failure, uncontrolled hypertension, serious cardiac arrhythmia requiring medication, Grade ≥ 2 peripheral vascular disease, and history of cerebrovascular accident within 6 months prior to enrollment), uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, and any psychiatric disorder that prohibits obtaining informed consent.
16. Patient has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, might interfere with the patient's participation for the full duration of the study treatment, or is not in the best interest of the patient to participate.
17. Patient has known active hepatitis B (eg, hepatitis B surface antigen reactive) or hepatitis C (eg, hepatitis C virus ribonucleic acid [qualitative] has been detected).
18. Patients with known human immunodeficiency virus (HIV) are allowed if they meet all of the following criteria:
    a. Cluster of differentiation 4 ≥350/μL and viral load <400 copies/mL
    b. No history of acquired immunodeficiency syndrome-defining opportunistic infections within 12 months prior to enrollment
    c. No history of HIV-associated malignancy for the past 5 years
    d. Concurrent antiretroviral therapy as per the most current National Institutes of Health (NIH) Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV started >4 weeks prior to study enrollment
19. Patient is immunocompromised. Patients with splenectomy are allowed.
20. Patient has an ongoing bowel obstruction or has other conditions that would lead to impaired absorption of oral niraparib.
21. Patient has active autoimmune disease that has required systemic treatment in the past 2 years (ie, with use of disease-modifying agents, corticosteroids, or immunosuppressive drugs). Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment.

8.3. Patient Withdrawal Criteria

8.3.1. Discontinuation from Treatment

Patients may be discontinued from study treatment at any time. Patients who discontinue from study treatment or from the study will not be replaced.

Specific reasons for discontinuing either treatment include the following, in addition to those indicated in Section 7.4:

- AE
- Disease progression according to RECIST v.1.1 criteria per Investigator assessment
- Risk to patient, as judged by the Investigator, Sponsor, or both
- Severe noncompliance with the protocol, as judged by the Investigator, Sponsor, or both
- Patient becomes pregnant
- Withdrawal of consent
- Loss to follow-up
- Death

For patients who have attained a confirmed CR and have received study treatment for at least 2 years, discontinuation of treatment may be considered by the Investigator after discussion with the Sponsor's Medical Monitor. In this instance, patients may be permitted to resume treatment only after discussion with the Sponsor's Medical Monitor if the Investigator believes the patient may derive benefit from ongoing treatment.

Patients with radiographic evidence of PD who are clinically stable may continue treatment at the Investigator's discretion and after discussion with the Sponsor, while awaiting confirmatory tumor imaging. Repeat imaging should be performed at ≥ 4 weeks. If repeat imaging shows SD, PR, or CR, patients can continue study treatment at the Investigator's discretion. In the event that PD is confirmed, patients still may continue to receive study treatment even after confirmed radiographic progression if the patient is clinically stable and the Investigator deems that the patient is deriving clinical benefit. This allowance to continue treatment despite radiographic progression takes into account the observation that some patients may have a transient tumor flare in the first few months after the start of immunotherapy, but with subsequent disease response.

If a patient discontinues treatment for a reason other than radiographic progression, death, withdrawal of consent, loss to follow-up, or the end of the study, radiographic evaluation and CA-125 testing should continue every 9 weeks for the first year of study treatment and every 12 weeks thereafter until PD. Also, clinically stable patients should not be discontinued until progression is confirmed.

If a patient discontinues treatment for clinical progression and does not meet RECIST criteria for progression, scans and CA-125 testing should continue at the specified

intervals until progression is confirmed or until the start of subsequent anticancer treatment.

Patients who discontinue from all study treatments will continue to receive follow-up assessments as part of the study unless they are discontinued from the study.

8.3.2. Discontinuation from the Study

Specific reasons for discontinuing from the study include the following:

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

If a patient is thought to be lost to follow-up, discontinues study treatment, or discontinues the study, attempts should be made to contact the patient to determine the reason for discontinuation. For patients who are thought to be lost to follow-up, at least 3 documented attempts, including 1 attempt via certified mail, should be made to contact the patient before the patient is deemed lost to follow-up.

9. TREATMENT OF PATIENTS

9.1. Description of Study Drug

The Pharmacy Manual contains descriptions of the packaging of niraparib and dostarlimab (TSR-042) and instructions for the preparation and administration of these drugs. Table 11 describes the investigational products.

Table 11: Investigational Product

	Investigational Product	
Product Name:	Niraparib	Dostarlimab (TSR-042)
Dosage Form:	Capsule	Solution for IV infusion
Unit Dose	100 mg per capsule	160 mg, 20 mg/mL, or 500 mg, 50 mg/mL
Route of Administration	Oral	Intravenous
Physical Description	Capsules in high-density polyethylene bottles	Solution for IV infusion in single-use vial

Abbreviations: IV = intravenous.

9.2. Concomitant Medications

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

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

9.2.1. Prohibited Medications

Known prior medications that exclude a patient from participating in the study are described in the exclusion criteria (Section 8.2).

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

- Systemic anticancer or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol

- Investigational agents other than niraparib and dostarlimab (TSR-042)
- Prophylactic cytokines (eg, G-CSF) should not be administered in the first cycle of the study but may be administered in subsequent cycles according to local guidelines.
- Systemic glucocorticoids for any purpose other than to manage symptoms of suspected irAEs. (Note: Use of inhaled steroids, local injection of steroids, topical steroids, and steroid eye drops are allowed.) If medically deemed necessary (eg, acute asthma or chronic obstructive pulmonary disease exacerbation, prophylaxis for IV contrast if indicated), Investigators are allowed to use their judgment to treat patients with systemic steroids. In such cases, systemic steroids should be stopped at least 24 hours prior to the next dose of dostarlimab (TSR-042).

An increased risk of infection by the administration of live virus and bacterial vaccines has been observed with conventional chemotherapy drugs. Effects with niraparib are unknown; therefore, live virus and bacterial vaccines should not be administered to patients in the study. Seasonal flu vaccines that do not contain live viruses are allowed. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, Bacillus Calmette-Guérin, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed. Intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.

No other anticancer therapy is permitted during the course of the study treatment for any patient. Palliative radiotherapy (excluding the pelvic region and/or palliative radiotherapy encompassing > 20% of the bone marrow within 1 week of the first dose of study treatment) is allowed for pre-existing small areas of painful metastases that cannot be managed with local or systemic analgesics, as long as no evidence of disease progression is present.

The niraparib safety profile includes risk for thrombocytopenia; therefore, patients should be advised to use caution when taking anticoagulants (eg, warfarin) and antiplatelet drugs (eg, aspirin).

Physicians should follow the current versions of the niraparib Investigator's Brochure and the dostarlimab (TSR-042) Investigator's Brochure for information on the general management of the patients receiving these therapies.

9.2.2. Contraception

Niraparib and dostarlimab (TSR-042) are known to have properties that require patients to use contraception. For details on niraparib and dostarlimab (TSR-042), please refer to the respective Investigator's Brochures.

Based on its mechanism of action, niraparib may cause teratogenicity and/or embryo-fetal death when administered to a pregnant woman.

Patients of childbearing potential may only be enrolled if they have a negative serum pregnancy test within 72 hours prior to taking study treatment. Note: A urine pregnancy test may be performed if the serum pregnancy result is not available before dosing.

Patients must agree to abstain from activities that could result in pregnancy from screening through 180 days after the last dose of study treatment, be willing to use a highly effective contraception (see Appendix 1), or be of non-childbearing potential, as defined in Section 8.1.

See Appendix 1 for a list of highly effective contraception methods. Patients should be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study. To participate in the study, they must adhere to the contraception requirements described above. If there is any question that a patient will not reliably comply with the requirements for contraception, that patient should not be enrolled in the study.

9.2.3. Rescue Medications and Supportive Care Guidelines During Treatment with Dostarlimab (TSR-042)

9.2.3.1. Supportive Care for Adverse Events

During treatment with dostarlimab (TSR-042), patients should receive appropriate supportive care measures for AEs as deemed necessary by the treating Investigator, including but not limited to the items outlined below. Additional guidance for clinical management can be found in the joint ASCO and NCCN guidelines for diagnosis and management of irAEs.[51] Prophylactic cytokines (eg, G-CSF) should not be administered in the first cycle of the study but may be administered in subsequent cycles according to current ASCO guidelines.[52] Note: It may be necessary to perform additional procedures such as bronchoscopy, endoscopy, or skin photography as part of the evaluation of the AE. The following sections detail specific guidance by type of AE.

- Pneumonitis
  - Treat with systemic corticosteroids, oral for Grade 2 (eg, 0.5 to 1 mg/kg/day of prednisone or equivalent) and IV for Grade 3 or 4 (eg, 1 to 2 mg/kg/day of prednisone or equivalent).
  - Administer additional anti-inflammatory measures, as needed.
  - Taper corticosteroids when symptoms improve to Grade $\leq$ 1 over $\geq$ 4 weeks.
  - If Grade 2 and no improvement or worsening over 2 weeks, treat as Grade 3 or 4.
  - Consider prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.
- Diarrhea/Colitis
  - Monitor carefully for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus).
  - All patients who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.

  - For Grade 2 diarrhea/colitis that persists > 3 days, administer oral corticosteroids (eg, 0.5 to 1.0 mg/kg/day of prednisone or equivalent). If symptoms persist or worsen with steroids, treat as Grade 3 or 4.
  - For Grade 3 or 4 diarrhea/colitis that persists > 3 days, treat with IV steroids (eg, 1 to 2 mg/kg/day of prednisone or equivalent) followed by high-dose oral steroids.
  - Taper corticosteroids when symptoms improve to Grade ≤ 1 over ≥ 4 weeks.
- Type 1 Diabetes Mellitus (T1DM) or Grade 3 or 4 Hyperglycemia
  - For T1DM and for Grade 3 or 4 hyperglycemia associated with metabolic acidosis or ketonuria, insulin replacement therapy is required.
- Hypophysitis
  - Treat with systemic corticosteroids, oral for Grade 2 (eg, 0.5 to 1 mg/kg/day of prednisone or equivalent) and IV for Grade 3 or 4 (eg, 1 to 2 mg/kg/day of prednisone or equivalent).
  - Taper corticosteroids when symptoms improve to Grade ≤ 1 over ≥ 4 weeks.
  - Replacement of appropriate hormones may be required as the steroid dose is tapered.
- Hyperthyroidism or Hypothyroidism
  - Thyroid disorders have been reported with other PD-1 inhibitors occurring at any time during treatment. Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.
  - Grade 2 HYPERthyroidism: Consider nonselective beta-blockers (eg, propranolol) as initial therapy.
  - Grade 3 or 4 HYPERthyroidism: Treat with an initial dose of IV corticosteroids followed by oral corticosteroids (eg, 0.5 to 1 mg/kg/day of prednisone or equivalent). Taper corticosteroids when symptoms improve to Grade ≤ 1 over ≥ 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
  - Grade 2 to 4 HYPOthyroidism: Thyroid hormone replacement therapy, with levothyroxine or liothyronine, is indicated per standard of care.
- Hepatitis
  - Treat with systemic corticosteroids, oral for Grade 2 (initial dose of 1 to 2 mg/kg/day of prednisone or equivalent) and IV for Grade 3 or 4 (1 to 2 mg/kg/day of prednisone or equivalent).

  - Taper corticosteroids when symptoms improve to Grade ≤ 1 over ≥ 4 weeks.

- Renal Failure or Nephritis
  - Treat with systemic corticosteroids, oral for Grade 2 (initial dose of 0.5 to 1 mg/kg/day of prednisone or equivalent) and IV for Grade 3 or 4 (1 to 2 mg/kg/day of prednisone or equivalent).
  - Taper corticosteroids when symptoms improve to Grade ≤ 1 over ≥ 4 weeks.
- Adrenal Insufficiency:
  - Start treatment with corticosteroids before other hormone replacement therapy to avoid adrenal crisis (hydrocortisone slowly titrating doses down according to symptoms or prednisone and fludrocortisone titrating up or down based on blood pressure, other symptoms, and laboratory results); patients with severe symptoms may require additional fluids (eg, saline >2 L).
  - Monitor for cortisol level (AM), comprehensive metabolic panel (Na, K, CO_2, glucose), and renin.
  - Ensure adequate evaluation (eg, endocrine consultation).
- Severe Exfoliative Dermatologic Events:
  - Suspected: Treat with high potency topical steroids to affected areas. Treat with oral prednisone or equivalent at an initial dose of 0.5 to 1 mg/kg/day and taper steroid when dermatitis is controlled. Ensure adequate evaluation (eg, urgent dermatology consultation) to confirm etiology and/or exclude other causes.
  - Confirmed: Administer 1 to 2 mg/kg/day IV methylprednisolone or equivalent and taper steroid when dermatitis is controlled.
- Severe Neurologic Events (Myasthenic Syndrome/Myasthenia Gravis, Guillain-Barré Syndrome, Transverse Myelitis)
  - Consider high dose corticosteroids and other therapies as needed.
  - It is highly recommended that Investigators discuss any AEs with the Sponsor before using infliximab.
  - Ensure adequate evaluation (eg, neurology consultation).
  - Consider MRI of brain and/or spine depending on symptoms.
  - Consider inpatient management as clinically indicated.
- Myocarditis
  - Administer high-dose corticosteroids (1 g/day of IV methylprednisolone) for 3 to 5 days, followed by oral prednisone taper over 4 to 6 weeks based on improvement in cardiac function and biomarkers.

- If no improvement in 24 hours, consider adding other potent immunosuppressive agents.
- Ensure adequate evaluation (eg, urgent cardiology consultation) to confirm etiology and/or exclude other causes.

9.2.3.2. Management of Infusion-related Reactions

Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Table 12 shows treatment guidelines for patients who experience infusion-related reactions associated with administration of dostarlimab (TSR-042).

CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.

9.2.4. Other Study Restrictions

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

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

9.3. Treatment Compliance

Compliance with inclusion and exclusion criteria will be assessed as outlined in Section 8.1 and Section 8.2, respectively.

Study treatment (niraparib and dostarlimab [TSR-042]) will be administered as detailed in Section 10.5.

Study treatment accountability will be monitored as detailed in Section 10.6.

9.4. Randomization and Blinding

Not applicable.

10. STUDY DRUG MATERIALS AND MANAGEMENT

10.1. Study Drug

10.1.1. Niraparib

Niraparib ([3S]-3-[4-{7-(aminocarbonyl)-2H-indazol-2-yl} phenyl] piperidine [tosylate monohydrate salt]) is an orally available, potent, highly selective PARP-1 and PARP-2 inhibitor. The excipients for niraparib are lactose monohydrate and magnesium stearate. Niraparib will be supplied as 100-mg capsules.

10.1.2. Dostarlimab (TSR-042)

Dostarlimab (TSR-042) is a humanized mAb of the IgG4/kappa isotype that binds with high affinity to PD-1, resulting in inhibition of binding to PD-L1 and PD-L2. Dostarlimab (TSR-042) for IV infusion will be supplied as a solution of 160 mg (20 mg/mL) or 500 mg (50 mg/mL) in a single-dose vial.

10.2. Study Drug Packaging and Labeling

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

Dostarlimab (TSR-042) will be provided as 8R (20 mg/mL) or 10 mL (50 mg/mL) Type I borosilicate clear glass vials, stoppered with a chlorobutyl elastomer stopper laminated with fluoropolymer and sealed with an aluminum overseal with a flip-off cap. Expiration dates are printed on the product label.

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

10.3. Study Drug Storage

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

10.4. Study Drug Preparation

The Pharmacy Manual contains information for specific instructions for the preparation of the dostarlimab (TSR-042) infusion and administration of the infusion solution.

10.5. Administration

10.5.1. Niraparib

Niraparib will be administered orally QD throughout each 21-day or 42-day cycle, in the absence of PD, unacceptable toxicity, patient withdrawal, Investigator's decision to withdraw, or death. On Day 1 of each cycle, niraparib will be administered after completion of the dostarlimab (TSR-042) infusion.

The starting dose of niraparib will be based on the patient's baseline actual body weight or platelet count (Table 13). Patients with a baseline actual body weight of ≥ 77 kg **and** baseline platelet count of ≥ 150,000/µL will take three capsules of 100 mg strength (300 mg/day) at each dose administration. Patients with a baseline actual body weight of < 77 kg **or** baseline platelet count of < 150,000/µL will take two capsules of 100 mg strength (200 mg) at each dose administration. Additional dose modifications will not be based upon changes in the patient's actual body weight during study participation.

For patients whose starting dose is 200 mg/day, the niraparib dose may be escalated on or after Cycle 3 Day 1 from 200 mg QD (2 capsules) to 300 mg QD (3 capsules) if the laboratory test results are within the specified limits (platelet count ≥ 100,000/µL, hemoglobin ≥ 9 g/dL, and neutrophil count ≥ 1,500/µL) during the first 2 cycles of treatment. This escalation will occur at the discretion of the Investigator, following discussion with the Sponsor's Medical Monitor or designee.

Table 13: Recommended Initial Starting Dose

	Baseline platelets ≥ 150,000/µL	**Baseline platelets < 150,000/µL**
Baseline weight ≥ 77 kg	300 mg (3 × 100 mg capsules) QD	200 mg (2 × 100 mg capsules) QD
Baseline weight < 77 kg	200 mg (2 × 100 mg capsules) QD	200 mg (2 × 100 mg capsules) QD

Abbreviation: QD = once daily

Patients will be instructed to take their niraparib dose QD or as instructed by the Investigator. Patients must swallow and not chew all capsules. The consumption of water and food is permissible. If a patient vomits or misses a dose of niraparib, a replacement dose should not be taken.

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

10.5.2. Dostarlimab (TSR-042)

Dostarlimab (TSR-042) infusion will be administered before the niraparib dose at the study site on Day 1 of each 21-day treatment cycle (Q3W) in Cycles 1 through 4 and every 6 weeks thereafter, beginning on Cycle 5 Day 1. Dostarlimab (TSR-042) treatment may continue for up to 3 years or until PD, unacceptable toxicity, withdrawal of consent, Investigator's decision, or death. Continued treatment with dostarlimab (TSR-042) beyond 3 years may be considered following discussion between the Sponsor and the Investigator.

Dostarlimab (TSR-042) may be administered up to 3 days before or after the scheduled Day 1 of each cycle after Cycle 1 due to administrative reasons. If dostarlimab (TSR-042) is administered on Day 1 of the cycle, it will be administered after all procedures and assessments have been completed, unless otherwise indicated. If dostarlimab (TSR-042) is administered earlier or later than Day 1 of the cycle, patients will continue to take niraparib as scheduled.

Dostarlimab (TSR-042) will be administered at a dose of 500 mg IV Q3W in Cycles 1 through 4 and at a dose of 1,000 mg IV Q6W, starting in Cycle 5, for the rest of the

treatment using a 30-minute infusion. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. Given the variability of infusion pumps from site to site, infusion durations of 25 to 45 minutes are permitted.

The Pharmacy Manual contains information for specific instructions for the preparation of the dostarlimab (TSR-042) infusion and administration of the infusion solution.

10.6. Study Drug Accountability

The Investigator or designee is responsible for maintaining accurate dispensing records of the study treatments throughout the clinical study. Study drug accountability for niraparib should be maintained by each site based on capsules dispensed vs. returned to the clinic at each visit and the number of days since the last visit.

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

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

10.6.1. Continued Access to Study Treatment Following Final DCO

Following the final DCO date, for patients continuing study treatment, the dispensing and ordering of study treatment will be done outside of the Rave Randomisation and Trial Suppy Management Interactive Response Technology (RAVE RTSM IRT) system. At the usual clinic visits, the patients will return used and unused medication, and a thorough drug accountability assessment will be performed at the site. Drug dispensing and accountability information will be recorded in the patient notes for as long as the patients continue to receive study treatment. Details of manual ordering are provided in the Pharmacy Manual.

10.7. Study Drug Handling and Disposal

At the end of study, when all patients have stopped protocol treatment, complete drug reconciliation per batch should be available at the site for verification in order to allow drug destruction or return procedure. After receiving Sponsor approval in writing, the investigational site is responsible for destruction of study drug according to local regulations. If a site does not have the capability for onsite destruction, the Sponsor will provide a return for destruction service through a third party. Both the unused and expired study treatment must be destroyed, upon authorization of the Sponsor, according to local regulations and procedures, and a copy of the destruction form must be filed in the study binder.

The medication provided for this study is to be used only as indicated in this protocol and only for the patients entered in this study.

11. ASSESSMENT OF EFFICACY

11.1. Primary Efficacy Endpoint

The primary efficacy endpoint is Investigator-assessed confirmed ORR, which is defined as the proportion of patients who have achieved confirmed CR or PR. Tumor response will be evaluated using RECIST v.1.1 (Appendix 2). The primary analysis population will be the intent-to-treat (ITT) population, consisting of all patients who receive at least 1 complete dose of either study drug and who have measurable disease at baseline. Analyses will be performed overall (including all patients in the ITT population) and in the subset of patients with PD-L1 positive tumors.

11.1.1. Evaluation of Tumor Response

The efficacy of the treatment combination will be evaluated by assessment of tumor response according to RECIST v.1.1 per the Investigator's assessment.

Tumor imaging (chest, abdomen, and pelvis) should be performed by CT with IV contrast (preferred, if no contraindication to IV contrast). MRI should only be used if clinically appropriate, when CT is contraindicated, or for imaging of the head, but the same imaging technique should be used in a patient throughout the study, unless this is not feasible. CT scan is the more commonly used modality and is preferred for the majority of patients. Positron emission tomography/CT may be used according to RECIST v.1.1 guidelines. If the chest or head CT/MRI is clear at screening, repeat imaging of these areas is not required in the absence of clinical indication requiring follow-up. Bone scans should be conducted per standard of care.

When the Investigator reports that the patient has progressed, all imaging and supportive clinical data will be submitted for central review, in order to allow evaluation of the secondary endpoints of ORR as assessed by independent review.

11.1.2. Timing of Radiographic Evaluations

All patients will undergo serial radiographic assessments to assess tumor response. Initial tumor imaging at screening must be performed within 28 days prior to the date of the first dose of study treatment. Scans performed prior to the signing of the ICF as part of routine clinical management are acceptable for use as initial tumor imaging if they are of diagnostic quality and performed within 28 days prior to the date of first dose.

Radiographic evaluations to assess extent of disease will be conducted every 9 weeks (63 ± 7 days) from Cycle 1 Day 1 for the first year, independent of cycle delays or dose interruptions, or at any time when PD is suspected. After 1 year of radiographic assessments (week 54), imaging will be performed every 12 weeks (84 ± 14 days).

Per RECIST v.1.1, CR or PR should be confirmed; tumor imaging for confirmation of response must be performed at the earliest 28 days after the first indication of PR or CR but no later than 35 days after the response. The subsequent tumor imaging after the confirmatory scan should be obtained per original schedule (9 weeks ± 7 days from confirmatory scan during the first year of study treatment and every 12 weeks thereafter).

Radiographic evaluations will continue until PD, start of alternate anticancer therapy, withdrawal of consent to study participation, becoming lost to follow-up, death, or end of the study. If a patient discontinues treatment for a reason other than radiographic progression, death, withdrawal of consent, loss to follow-up, or the end of the study, radiographic evaluation should continue at the specified intervals (ie, every 9 weeks for the first year of study treatment and every 12 weeks thereafter until PD). Also, clinically stable patients should not be discontinued until progression is confirmed. If a patient discontinues treatment for clinical progression and does not meet RECIST criteria for progression, scans should continue at the specified intervals until progression is confirmed or until the start of subsequent anticancer treatment.

There is accumulating evidence indicating clinical benefit in a subset of patients treated with immunotherapy despite initial evidence of PD.[53] Patients with PD may continue study treatment at the Investigator's discretion only after discussion with the Sponsor, until the Investigator has determined that the patient is no longer experiencing clinical benefit or until study treatment is no longer tolerated by the patient.

11.2. Secondary Efficacy Endpoints

Secondary efficacy endpoints will be analyzed overall (including all patients in the ITT population) and in the subset of patients with PD-L1 positive tumors.

11.2.1. Duration of Response

DOR based on Investigator/independent review committee assessment is defined as the time from first documentation of response (CR or PR) until the time of first documentation of disease progression by RECIST v.1.1 based on Investigator/independent review committee assessment or death by any cause in the absence of progression by RECIST v.1.1.

11.2.2. Progression-free Survival

PFS based on Investigator/independent review committee assessment is defined as the time from the date of the first dose of study treatment to the earlier date of assessment of progression by RECIST v.1.1 based on Investigator/independent review committee assessment or death by any cause in the absence of progression by RECIST v.1.1.

11.2.3. Overall Survival

OS is defined as the time from the date of the first dose of study treatment to the date of death by any cause. Following the End of Treatment Visit, survival status will be collected for all patients using acceptable means, including telephone contact. Patients without documented death at the time of the final analysis will be censored at the last date they were known to be alive.

11.2.4. Disease Control Rate

DCR based on Investigator/independent review committee assessment is defined as the percentage of patients who have achieved best overall response (BOR) of CR, PR, or SD per RECIST v.1.1 based on the Investigator/independent review committee assessment.

11.2.5. Objective Response Rate Based on Independent Review Committee Assessment

ORR based on independent review committee assessment is defined as the percentage of patients who have achieved confirmed CR or PR per RECIST v1.1 based on the independent review committee assessment.

11.3. Exploratory Efficacy Endpoints

11.3.1. Duration of Disease Control

Duration of disease control is defined as the time from the date of the first dose of study treatment to the earlier date of assessment of progression by RECIST v.1.1 based on the Investigator/independent review committee assessment or death by any cause in the absence of progression by RECIST v1.1 among patients whose BOR is CR, PR or SD.

11.3.2. Functional Assessment of Cancer Therapy – Ovarian Symptom Index

The Functional Assessment of Cancer Therapy – Ovarian Symptom Index (FOSI) is a validated 8-item measure of symptom response to treatment for ovarian cancer[54] based on a subset of questions from the Functional Assessment of Cancer Therapy – Ovarian Cancer questionnaire (Appendix 5). Patients respond to their symptom experience over the past 7 days using a 5-point Likert scale ranging from PPD to PPD. For items 1 through 6 and item 8, the score used for calculating the total score is the difference between the patient's response and 4. For item 7, the score used for calculating the total score is the patient's response. The total score is calculated by multiplying the sum of all items scored by 8 and dividing the result by the number of responses. If 5 or more responses are recorded, the FOSI can be scored; otherwise, the FOSI score is recorded as missing. The FOSI score range is PPD to PPD.

11.3.3. Efficacy in BRCAwt population

Efficacy endpoints will also be evaluated in the BRCAwt population.

11.3.4. Disease-Related or Treatment-Related Biomarkers

- Disease-related or treatment-related biomarkers (eg, homologous recombination repair pathway deficiency and PD-L1 expression) may be assessed to explore the correlations with responses to the combination of niraparib and dostarlimab (TSR-042).

12. ASSESSMENT OF SAFETY

12.1. Safety Parameters

Safety parameters evaluated during this study will include AEs, vital signs, symptom-directed physical examination findings, and clinical laboratory values (including hematology, serum or plasma chemistry, coagulation, and thyroid function).

All safety parameters will be performed in accordance with the schedule of events (Table 10).

12.1.1. Demographic

Demographic and baseline characteristics consist of those variables that are assessed at screening/baseline. Patient demographics consist of age at screening, race, ethnicity, and sex.

12.1.2. Disease History

The following information regarding disease history will be recorded:

- Date of first diagnosis
- Tumor type
- Stage at time of initial diagnosis
- Histology and grade of disease at diagnosis and most recent biopsy if additional biopsy performed
- Information on first anticancer therapy:
  - Intent (adjuvant, neoadjuvant, curative, and palliative)
  - Date of start of first treatment
  - Agents used in first treatment
  - Date of last dose of first treatment
- Information on second and subsequent anticancer therapies:
  - Intent (adjuvant, neoadjuvant, curative, and palliative)
  - Dates of start of all subsequent treatments
  - Agents in all subsequent treatments
  - Dates of last dose of all subsequent treatments
- Best response and reason for treatment discontinuation (including PD and toxicities) for each prior anticancer therapy
- Date of PD for each prior anticancer therapy
- Genotyping, such as gBRCA or, if known, tBRCA status

12.1.3. Medical and Surgical History

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

12.1.4. Previous and Concomitant Medications

Previous and concomitant medications will be documented as described in Section 9.2. Medications will be coded using World Health Organization (WHO) Anatomical Therapeutic Chemical classification.

12.1.5. Vital Signs

Vital signs will be measured in all patients and include blood pressure, heart rate (pulse), and temperature. Temperature, blood pressure, and heart rate (pulse) will be measured at screening, on Day 1 of each treatment cycle, and on Day 22 of Cycles 5 and 6. Blood pressure and heart rate (pulse) should also be measured weekly (Day 8 and Day 15) during the first 8 weeks (Cycles 1 through 3) and on Day 29 ±7 days in Cycles 7 through 11, and entered as an unscheduled visit if abnormal. Any abnormal vital signs assessed as clinically significant should be recorded as an AE or SAE. If SAE criteria are met or the abnormality is an AESI (see Section 12.2.1.4), the event should be recorded and reported according to the SAE reporting process (see Section 12.2.6).

12.1.6. Weight and Height

Weight and height will be measured in accordance with the schedule of events (Table 10).

Height will be measured at screening only. Weight will be measured at screening and at every visit.

12.1.7. Physical Examination

Physical examinations, including height (screening only), weight, and vital signs (blood pressure, pulse rate, and temperature), will be performed in accordance with the schedule of events (Table 10).

Any physical examination or vital sign abnormalities assessed as clinically significant should be recorded as an AE or SAE. If SAE criteria are met or the abnormality is an AESI (see Section 12.2.1.4), the event should be recorded and reported according to the SAE reporting process (see Section 12.2.5).

12.1.8. Electrocardiogram

All patients will undergo ECGs at screening (Table 10). Patients will be supine or in a semirecumbent position (about 30 degrees of elevation) and rested for approximately 2 minutes before ECGs are recorded.

12.1.9. Laboratory Assessments

The following laboratory variables will be determined in accordance with the schedule of events (Table 10).

These tests will be performed by the local laboratory at the investigational site.

Any abnormal laboratory value assessed as clinically significant should be recorded as an AE. If SAE criteria are met or the abnormality is an AESI (see Section 12.2.1.4), the event should be recorded and reported according to the SAE reporting process (see Section 12.2.6).

Hematologic testing may occur more frequently than is specified in the schedule of events, if additional testing is medically indicated per the Investigator's judgment or if the event meets the criteria for study treatment dose adjustment (see Section 7.4). Additional tests may be performed at a laboratory facility other than the study site, but the test results must be reported to the study site, the study site must keep a copy of test results with the patient's study file, as well as laboratory normal ranges for the facility used, and the results must be entered into the eCRF.

Any suspected case of MDS/AML reported while a patient is receiving treatment or followed for post-treatment assessments must be referred for evaluation to a local hematologist to perform bone marrow aspirate and biopsy as per local practice. The study site must receive a copy of the hematologist's report of aspirate/biopsy findings, which must include a classification according to WHO, and other sample testing reports related to MDS/AML. Report data will be entered in the appropriate eCRF pages, and the site must keep a copy of all reports with the patient's study file.

Any suspected case of secondary cancer (new malignancies other than MDS/AML) reported while a patient is receiving treatment or followed for post-treatment assessments must be investigated, including obtaining and documenting a histological diagnosis. Testing completed as part of standard of care is sufficient as long as the methods are deemed acceptable after consultation with the Sponsor's Medical Monitor.

12.1.9.1. Hematology

The following hematologic parameters will be determined in accordance with the schedule of events (Table 10):

- Complete blood count:
  - hemoglobin
  - platelet count
  - white blood cell count
  - differential white blood cell count
- Coagulation factors:
  - international normalized ratio
  - activated partial thromboplastin time

12.1.9.2. Blood Chemistry

The following blood chemistry parameters will be measured in accordance with the schedule of events (Table 10):

- Serum or plasma chemistry:
  - sodium
  - potassium
  - chloride
  - calcium
  - magnesium
  - glucose
  - total bilirubin
  - ALP
  - AST
  - ALT
  - total protein
  - albumin
  - creatinine
  - urea or blood urea nitrogen
  - amylase

12.1.9.3. Urinalysis

The following urinalysis parameters will be measured in accordance with the schedule of events (Table 10):

- specific gravity
- leukocyte esterase
- nitrite
- blood
- glucose
- ketones
- microscopy (if clinically indicated)

12.1.9.4. Thyroid Panel

The following thyroid parameters (or equivalent tests) will be measured in accordance with the schedule of events (Table 10):

- thyroid-stimulating hormone
- triiodothyronine or free triiodothyronine
- free thyroxine

12.1.9.5. Hepatitis B and Hepatitis C Testing

Hepatitis C virus and hepatitis B virus testing will be done at screening if clinically indicated.

12.1.9.6. Tumor Marker

CA-125 will be obtained at screening and at Day 1 of each cycle. If a patient discontinues treatment for a reason other than radiographic progression, death, withdrawal of consent, loss to follow-up, or the end of the study, CA-125 testing should continue every 9 weeks for the first year of study treatment and every 12 weeks thereafter until PD. If a patient discontinues treatment for clinical progression and does not meet RECIST criteria for progression, CA-125 testing should continue at the specified intervals until progression is confirmed or until the start of subsequent anticancer treatment.

12.1.9.7. Pregnancy Screen

Niraparib and dostarlimab (TSR-042) are known to have properties that require the patient to use a highly selective contraception measure and may have adverse effects on a fetus in utero. For females of childbearing potential, negative serum or urine pregnancy test is required within 72 hours prior to Cycle 1 Day 1. Urine pregnancy testing will be performed on Day 1 of each subsequent cycle and at the Safety Follow-Up Visit (30 ± 7 days after the last dose of study treatment) for females of childbearing potential. If the clinic standard is to do a serum or urine pregnancy test more frequently, that is acceptable with the protocol as written.

Patients should start using birth control as outlined in Appendix 1 from screening throughout the study period up to 180 days after the last dose of study treatment. If there is any question that a patient will not reliably comply with the contraception requirements, they should not be enrolled in the study, and any patient who becomes pregnant should be withdrawn from the study. Any pregnancies that occur within 180 days post-treatment discontinuation are to be reported as described in Section 12.2.11.

12.1.10. ECOG Performance Status

Performance status will be assessed using the ECOG scale (see Appendix 3) in accordance with the schedule of events (Table 10).

12.2. Adverse Events and Special Situations

12.2.1. Definitions

12.2.1.1. Adverse Event

Any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and that does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of study treatment, whether or not considered related to the study treatment.

AEs may include the onset of new illness and the exacerbation of pre-existing medical conditions. An AE can include an undesirable medical condition occurring at any time after the time of treatment assignment, including baseline or washout periods, even if no study treatment has been administered. (See Section 12.2.3 for information about AE collecting and recording.)

12.2.1.2. Serious Adverse Event

Any untoward medical occurrence that, at any dose

- Results in death;
- Is life-threatening (ie, an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe);
- Requires inpatient hospitalization* or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity;
- Is a congenital anomaly/birth defect; or
- Is an important medical event**

*Exception: Preplanned (at time of informed consent) hospitalization for elective procedures, for protocol compliance or social reasons, or for observation will not be considered criteria for an SAE. The reason for the planned hospitalization should be captured in medical history section in the eCRF. Complications experienced during these hospitalizations must be reported as AEs (or SAEs, if hospitalization is prolonged due to the AE).

**Medical and scientific judgment should be exercised in determining whether situations or events should be considered SAEs: an important medical event may not be immediately life threatening or result in death or require hospitalization but may jeopardize the patient or require intervention to prevent one of the above outcomes. Examples of such events are allergic bronchospasm, blood dyscrasias, or convulsions that may require intensive treatment in an emergency room or at home but do not result in hospitalization; development of drug dependency or drug abuse; and transmission of disease associated with the administration of the study treatment. (See Section 12.2.5 for information about SAE reporting.)

12.2.1.3. Treatment-Emergent Adverse Event

Any event that was not present prior to the initiation of study treatment or any event already present that worsens in either intensity or frequency following exposure to study treatment.

12.2.1.4. Adverse Event of Special Interest

Any AE (serious or nonserious) that is of scientific and medical concern specific to the study treatment, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor is appropriate. The AESIs for this study are MDS, AML, and secondary cancers (new malignancies other than MDS or AML).

12.2.1.5. Special Situations: Abuse, Misuse, Medication Errors, Overdose, and Accidental or Occupational Exposure

- **Abuse:** is the persistent or sporadic, intentional excessive use of the study treatment, which is accompanied by harmful physical or psychological effects.
- **Misuse:** medicinal product is intentionally and inappropriately used not in accordance with the authorized/approved product information.
- **Medication error:** is any preventable incident that may cause or lead to inappropriate study treatment use or patient harm while the study treatment is in the control of the health care professionals or patients. Such incident may be due to health care professional practice, product labeling, packaging and preparation, procedures for administration, and systems, including the following: prescribing, order communication, nomenclature, compounding, dispensing, distribution, administration, education, monitoring, and use.
- **Overdose:** is a deliberate or accidental administration of study treatment to a study patient at a dose greater than that which was assigned to that patient per the study protocol and under the direction of the Investigator. If an overdose occurs, the Investigator and the Sponsor should be notified immediately, and the patient should be observed closely for AEs. Associated AEs should be treated and monitored by the Investigator. The dosage of study treatment administered, any associated AEs, or treatment provided to the patient because of the overdose should be documented on the applicable sections within the eCRF. An overdose (including an AE or SAE resulting from the overdose, if any) will be reported as described in Section 12.2.5.
- **Accidental/Occupational exposure:** is the unintentional exposure to a study treatment as a result of one's professional or nonprofessional occupation, or accidental exposure to a nonprofessional to whom exposure was not intended (ie, study product given to wrong patient).

Reporting Special Situations: All occurrences of abuse, misuse, medication error, overdose, and accidental or occupational exposure with any study treatment must be reported on an SAE Report Form [or designated Special Form] to the Sponsor regardless of whether or not an AE or SAE has occurred. If the abuse, misuse, medication error, overdose, or accidental / occupational exposure is associated with an SAE, an SAE report

form must be submitted to the Sponsor within 24 hours of awareness. If there is no AE or SAE, the occurrence must be submitted on the designated Special Form (indicate "no AE has occurred") as soon as possible.

12.2.2. Assessment of Adverse Events

12.2.2.1. Severity Assessment

All AEs will be assessed by the Investigator for severity* according to CTCAE v4.03: 14 June 2010; National Institutes of Health (NIH), NCI. The CTCAE severity grades 1 through 5 provide unique clinical descriptions of severity of each AE. The CTCAE v4.03 is available on the NCI/NIH website.

*Please note that there is a distinction between **serious** and **severe** AEs: Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 12.2.1.2. For example, a mild degree of gastrointestinal bleeding requiring an overnight hospitalization for monitoring purposes may be considered an SAE but is not necessarily severe.

12.2.2.2. Relationship to Study Intervention

The Investigator must provide a causality assessment regarding the relationship of the event with the study treatment or study procedure for all AEs. One of the following categories should be selected based on medical judgment, considering all contributing factors:

- Related: A causal relationship between the medicinal product (or study procedures) and AE is a reasonable possibility. For example, the occurrence of the AE cannot be explained by other causative factors. The AE, however, can be explained by pharmacological effect of the medicinal product such as a similar event having been reported previously, alteration of the dose effect, or the timing or seriousness of the AE, etc. Positive rechallenge/dechallenge is supportive.
- Not Related: A causal relationship between the medicinal product (or study procedures) and AE is not a reasonable possibility: there is no temporal relationship between the medicinal product and event, or an alternative etiology is more reasonable.

12.2.2.3. Expectedness

The Sponsor will be responsible for determining whether an AE is "expected" or "unexpected." An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information provided in the Reference Safety Information of the effective study treatment Investigator's Brochure or local approved product label.

12.2.3. Collection and Recording of Adverse Events

AEs may be volunteered spontaneously by the study subject or discovered by the study staff during physical examinations or by asking an open, nonleading question such as,

"How have you been feeling since your last study visit?" The Investigator will document the nature of the AE, date of onset of the AE (and time, if known), date of outcome of the AE (and time, if known), severity of the AE, action taken with study treatment as a result of the AE, assessment of the seriousness of the AE, and assessment of the causal relationship of the AE to study treatment or study procedure.

AEs, including laboratory abnormalities that are assessed as clinically significant or require intervention, should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be recorded as a separate AE.

All SAEs will be collected from the signing of the ICF for this study through the Survival Follow-up Visit (90 ± 14 days after the last dose of study treatment or until alternate anticancer treatment has been initiated, whichever occurs earlier) and recorded in the eCRF. SAEs will also be reported on an SAE form as described in Section 12.2.5 of this protocol. SAEs considered by the Investigator to be related to study treatment are reported throughout the Survival Assessment Period.

All AEs, regardless of the source of identification (eg, physical examination, laboratory assessment, or reported by subject), will be collected and recorded in the eCRF for each subject from the day of signed informed consent through the Survival Follow-up Visit (90 ± 14 days after the last dose of study treatment or until alternate anticancer treatment has been initiated, whichever occurs earlier).

Concomitant illnesses that existed before entry into the study will not be considered AEs unless the illness worsens during the Treatment Period. Pre-existing conditions will be recorded as Medical History in the eCRF and on the SAE Report Form.

Disease progression is an efficacy criterion and is therefore not considered an AE or SAE (even if fatal). Disease progression should be reported within the eCRF. If AEs/SAEs occur in relation to disease progression that are not consistent with the natural progression of the subject's disease, these AEs/SAEs must be reported per AE/SAE reporting requirements described in Section 12.2.5

12.2.4. Follow-Up of Adverse Events

All AEs experienced by a subject, regardless of the suspected causality, will be monitored until the AE or SAE has resolved, until any abnormal laboratory values have returned to baseline or normal levels, until stabilized with a satisfactory explanation for the changes observed, until the subject is lost to follow-up, or until the subject has died.

If an Investigator becomes aware of an SAE after the specified follow-up period and considers the SAE related to the study treatment, the Investigator should report the SAE to the Sponsor according to timelines for reporting SAEs described in Section 12.2.5.

12.2.5. Reporting

The Investigator must report all SAEs and all follow up information to the Sponsor on an SAE Report Form within 24 hours of becoming aware of the initial event or follow-up information. SAEs are to be reported per the SAE Form Completion Instructions within the Investigator Site File. The Investigator must provide a causality assessment and must sign and date all SAE Report Forms.

It is the responsibility of the Investigator to review source documentation and describe pertinent information on the SAE Report Form. If supporting documentation is requested (eg, hospital reports, consultant reports, death certificates, autopsy reports), the Investigator should highlight all relevant and pertinent information within such documents, ensure that any subject's personal identifiers (including Medical Record number) are removed, and submit the documents with the SAE Form to the Sponsor. The Sponsor (or designee) will return a confirmation of receipt for all email reports (if received from other than a "no reply" domain) within 1 business day.

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

12.2.6. Submission and Distribution of Serious Adverse Event Reports

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to Investigators, as necessary.

In addition, the SUSAR will be distributed to the Investigators/investigational sites, utilizing a Council for International Organizations of Medical Sciences report form, or the MedWatch 3500A form). The Investigator/site will submit a copy of the report to their respective Institutional Review Board (IRB) or Independent Ethics Committee (IEC) per the governing institutional requirements and in compliance with local laws and guidelines.

12.2.7. Adverse Events of Special Interest

AESIs for niraparib are the following:

- MDS and AML
- Secondary cancers (new malignancies other than MDS or AML)

All occurrences of AESIs must be reported. If the AESI is serious, follow the SAE reporting outlined in Section 12.2.5. If the AESI is nonserious , it should be reported on the designated AESI Form and submitted it to the Sponsor by email or fax within 5 calendar days of awareness of the event.

No AESIs have been reported to date for dostarlimab (TSR-042).

12.2.8. Hypertension, Including Hypertensive Crisis

Hypertension, including hypertensive crisis, has been reported with the use of niraparib. Pre-existing hypertension should be adequately controlled before starting niraparib treatment. While receiving treatment, hypertension should be medically managed with antihypertensive medicinal products with or without niraparib dose adjustment.

Blood pressure and heart rate should be monitored at least weekly for the first 2 months of niraparib treatment in the maintenance setting, then monthly for the first year and periodically thereafter during treatment with niraparib. Niraparib should be discontinued in case of hypertensive crisis or if medically significant hypertension cannot be adequately controlled with antihypertensive therapy.

12.2.9. Posterior Reversible Encephalopathy Syndrome

There have been rare reports of niraparib-treated patients developing signs and symptoms that are consistent with posterior reversible encephalopathy syndrome (PRES). PRES is a rare neurologic disorder that can present with the following signs and symptoms including seizures, headache, altered mental status, visual disturbance, or cortical blindness, with or without associated hypertension. A diagnosis of PRES requires confirmation by brain imaging, preferably magnetic resonance imaging. In patients developing PRES, treatment of specific symptoms including control of hypertension is recommended, along with discontinuation of niraparib. The safety of reinitiating niraparib therapy in patients previously experiencing PRES is not known.

12.2.10. Allergic Reaction

Niraparib capsules contain tartrazine, which may cause allergic-type reactions.

12.2.11. Pregnancy

The Investigator must report all pregnancies and the outcomes to the Sponsor. The Sponsor has the responsibility to monitor the outcome of all pregnancies reported during the clinical study.

Each pregnancy must be reported by the Investigator to the Sponsor on an Initial Pregnancy Report Form within 24 hours of becoming aware of the pregnancy. Pregnancy is not an AE and therefore does not need to be reported as an AE in the eCRF unless there is a suspicion that the study treatment may have interfered with the effectiveness of a contraceptive medication. The Investigator must follow-up all pregnancies, document the course and the outcome, and report this information to the Sponsor on a Pregnancy Outcome Report Form within 24 hours of becoming aware—even if the subject was withdrawn from the study or the study has finished.

An elective abortion without complications should not be regarded as an AE; however, it should be reported as the outcome to the pregnancy on the Pregnancy Outcome Report Form. Therapeutic abortions should be reported as a treatment procedure; the reason for the therapeutic abortion should be reported on the Pregnancy Outcome Report Form and as an AE in the eCRF. Hospitalization for normal delivery of a healthy newborn should not be considered an SAE.

Any SAE that occurs during pregnancy must be recorded on the Pregnancy Outcome Report Form, reported as an SAE on the SAE Report Form (eg, maternal serious complications, therapeutic abortion, ectopic pregnancy, stillbirth, neonatal death, congenital anomaly, birth defect) and reported to the Sponsor within 24 hours. Hospitalization for normal delivery of a healthy newborn should not be considered an SAE.

12.2.12. Special Situations

All occurrences of abuse, misuse, medication error, overdose, and accidental or occupational exposure to any study treatment must be reported on a Special Situations Report Form to the Sponsor within 5 calendar days of becoming aware of the occurrence, regardless of whether it is categorized as an AE. If the occurrence is associated with an

SAE, an SAE Report Form, along with the Special Situations Report Form, must be submitted to the Sponsor within 24 hours of awareness.

12.3. Safety Monitoring For Continuation of Treatment After Final DCO

After the final DCO date, all SAEs, AESIs (as defined in Section 12.2.7), AEs leading to discontinuation, overdoses, and pregnancies must be reported as detailed in Section 12.2.5 to the Sponsor within 24 hours of becoming aware of a new event or of new (follow up) information on a previously reported event and signed by the Investigator or Sub-Investigator. This information should be collected on paper forms and submitted to the Sponsor via email [Email: PPD]. The Sponsor retains the right to request additional information for patients with ongoing SAE(s)/AESI(s) at the end of the study, if judged necessary. As described in Section 12.2.3 and Section 12.2.5, SAE, AESI, AEs leading to discontinuation and overdose reporting should continue during the treatment period and for 90 ± 14 days after the last dose of study treatment or until alternate anticancer treatment has been initiated, whichever occurs earlier. Any pregnancies that occur within 180 days post-treatment are to be reported. If an investigator learns of any SAEs, including death, at any time after a patient has completed the study, and he/she considers there is a reasonable possibility that the event is causally related to study treatment, the investigator should notify the Sponsor (see Section 12.2.5). Additionally, as stated in Section 12.2.4, any SAE or non-serious AE that is ongoing at the time of the final DCO must be followed up to resolution unless the event is considered by the investigator to be unlikely to resolve, or the patient is lost to follow up.

13. STATISTICS

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

13.1. Sample Size Determination

A sample size of approximately 150 patients overall will provide sufficient precision for assessment of the primary endpoint of ORR in the overall and PD-L1 positive populations. No inferential testing will be performed, and no adjustments will be made for multiplicity. Primary analysis will be based on the ORR point estimate and the corresponding 95% exact CI. The PD-L1 positive population will be defined in the SAP prior to performance of any PD-L1 assays on patient samples.

Standard of care treatment options in the BRCAwt population include single-agent chemotherapy, such as paclitaxel, doxorubicin, topotecan, and gemcitabine. The described ORR with these agents is 10% to 20% in first or second relapse.[5,8,9,19,20] Therefore, a target ORR of 25% (with sufficient precision such that the lower 95% confidence bound exceeds 15%) in the described study population (patients with BRCAwt PROC previously treated with bevacizumab with 1 to 3 prior lines of therapy) with durable response would be considered clinically meaningful.

Table 14 shows 95% CIs at different observed ORR rates (ranging from 20% to 50%) with 150 patients. If the true ORR is 25%, there is an 87% chance that the lower bound of the 95% CI will exceed 15%.

Assuming the prevalence of PD-L1 positive disease is 50% in this study population, it is expected that approximately 75 patients with PD-L1 positive tumors will be enrolled and dosed. Table 15 shows 95% CIs at different observed ORR rates (ranging from 20% to 49.3%) for 75 patients with PD-L1 positive tumors. If the true ORR is 30%, there is an 84% chance that the lower bound of the 95% CI will exceed 15%.

Table 14: Estimates and 95% CIs with 150 Patients

Sample Size	Number of Responders	ORR (%)	Lower 95% Confidence Limit	Upper 95% Confidence Limit
150	30	20.0	13.9	27.3
	32	21.3	15.1	28.8
	37	24.7	18.0	32.4
	45	30.0	22.8	38.0
	52	34.7	27.1	42.9
	60	40.0	32.1	48.3
	67	44.7	36.6	53.0
	75	50.0	41.7	58.3

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

Table 15: Estimates and 95% CIs with 75 Evaluable Patients with PD-L1 Positive Tumors

Sample Size	Number of Responders	ORR (%)	Lower 95% Confidence Limit	Upper 95% Confidence Limit
75	15	20.0	11.7	30.8
	19	25.3	16.0	36.7
	23	30.7	20.5	42.4
	26	34.7	24.0	46.5
	30	40.0	28.9	52.0
	34	45.3	33.8	57.3
	37	49.3	37.6	61.1

Abbreviations: CI = confidence interval; ORR = objective response rate; PD-L1 = programmed cell death ligand 1.

13.2. Analysis Populations

Three analysis populations will be defined as follows:

- Safety (SAF) Population: All patients who receive any amount of study treatment.
- ITT Population: All patients who receive at least 1 complete dose of either study drug and who have measurable disease at baseline. Measurable disease at baseline is defined by the existence of at least 1 target lesion at baseline tumor assessment by RECIST v1.1 criteria.
- Efficacy-Evaluable (EE) Population: All patients who receive at least 1 complete dose of either study drug and who have measurable disease at baseline and do not have protocol deviations with the potential to significantly impact the interpretation of efficacy results. Patients who withdraw without obtaining a post-baseline tumor assessment due to withdrawal of consent, loss to follow-up, or non-compliance will also be excluded from the EE population.

13.3. Patient Disposition

Patient disposition will be tabulated and will include the number of screened patients (who have signed informed consent) and the number of patients in each study population for analysis, the number of patients who have discontinued treatment and the reasons for treatment discontinuation, and the number of patients who have discontinued study and the reasons for study discontinuation.

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

Demographics, baseline characteristics, concomitant medications, and medical history information will be summarized using descriptive statistics.

13.5. Efficacy Analyses

All analyses will include summary statistics, including number and percentage for categorical variables and number of patients, mean, standard deviation, median, minimum, and maximum for continuous variables. Time-to-event analyses will be performed using Kaplan-Meier methods. All efficacy analyses will be performed using the ITT population, overall (including all patients in the ITT population) and in the subset of patients with PD-L1 positive tumors. The primary analysis population is the ITT population. Additional supportive analyses may be performed using the EE population.

The specific criteria for PD-L1 positive and negative status will be predefined in the SAP prior to any PD-L1 samples being analyzed from the study.

13.5.1. Primary Efficacy Parameter

The primary efficacy endpoint is Investigator-assessed confirmed ORR, which is defined as the proportion of patients whose BOR is a confirmed CR or PR. Tumor response will be evaluated using RECIST v.1.1 (Appendix 2).

The primary efficacy analyses will be performed on the ITT population. Patients who have no post-baseline evaluable tumor assessments will be considered non-responders.

BOR will be summarized by number and percentage. The ORR and 2-sided 95% CI, using the exact (Clopper-Pearson) method, will be provided.

13.5.2. Secondary Efficacy Parameters

DOR is defined as the time from first documentation of response (CR or PR) until the time of first documentation of disease progression by RECIST v.1.1 based on Investigator/independent review committee assessment or death by any cause in the absence of progression by RECIST v.1.1. DOR will be evaluated in the subset of patients who have achieved a BOR of confirmed CR/PR.

PFS is defined as the time from the date of the first dose of study treatment to the earliest date of assessment of progression by RECIST v.1.1 based on Investigator/independent review committee assessment or death by any cause in the absence of progression by RECIST v.1.1. PFS will be evaluated in the ITT population.

Table 16 provides a summary of censoring rules to be used in the DOR and PFS analysis.

Table 16: Censoring Rules Used in DOR and PFS Survival Analysis

Situation	Date of Event or Censoring	Outcome
No baseline tumor assessments[a]	First dose date	Censored
No post-baseline tumor assessments and no death[a]	First dose date	Censored
Start of subsequent anticancer therapy without a prior documented radiographic progression or death	Date of last post-baseline radiographic tumor assessment prior to or on the date of initiation of the subsequent anticancer therapy	Censored
Free of radiographic progression and no subsequent anticancer therapy started and no death	Date of last post-baseline radiographic tumor assessment	Censored
Documented radiographic progression or death after 2 or more consecutive missing radiographic assessments	Date of last post-baseline radiographic tumor assessment prior to the missed radiographic assessment	Censored
Documented radiographic progression or death	Earliest date of radiographic PD or death	Event

Abbreviations: DOR = duration of response; PD = progression of disease; PFS = progression-free survival.
[a] Not applicable for DOR

OS is defined as the time from the date of the first dose of study treatment to the date of death by any cause. OS will be evaluated in the ITT population.

DOR, PFS and OS will be presented through use of summary statistics using Kaplan-Meier methods, to include 25th, 50th (median), and 75th percentiles and associated 2-sided 95% CIs, number of events and number of censored observations.

DCR is defined as the percentage of patients who have achieved BOR of confirmed CR, PR, or SD per RECIST v.1.1 based on the Investigator/independent review committee assessment. Given that the protocol-scheduled tumor assessment interval is every 9 weeks (63 ± 7 days) for the first year of treatment, the minimum criteria for SD duration is that it should be met at least once at least 8 weeks from the date of the first dose of study treatment.

The point-estimate and corresponding 2-sided 95% exact CI will be provided for DCR. DCR will be evaluated in the ITT and EE populations. ORR based on independent review will be analyzed using similar methodology as described for the primary endpoint.

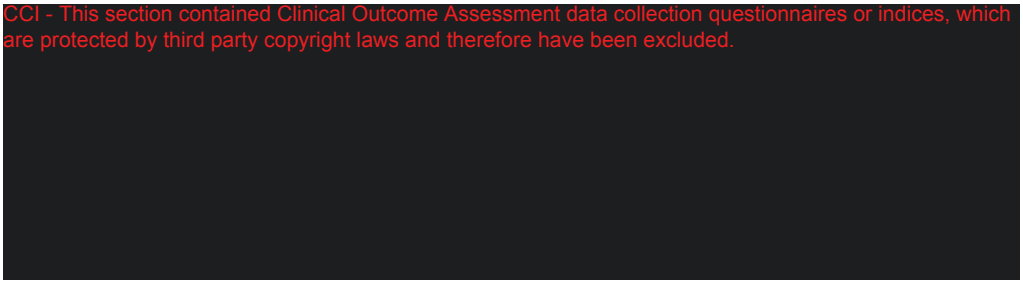
In addition, changes from baseline in tumor burden will be summarized by time-point.

13.5.3. Exploratory Analyses

Descriptive, exploratory subgroup analysis will be performed by baseline characteristics and biomarker status.

Descriptive summary statistics will be used to assess changes from baseline in overall FOSI score. Kaplan-Meier methodology will be used to summarize time to symptom worsening on the overall FOSI score, defined as the time from treatment assignment to

the first FOSI assessment with a worsening score compared to its baseline score using minimally important difference (MID) thresholds (defined as 2-point change[54]), which will be categorized as follows:



Duration of disease control will be summarized using Kaplan-Meier methodology.

Analyses of ORR, DOR, PFS, OS, and DCR based on Investigator assessment using RECIST v1.1 will be repeated in the BRCAwt population.

Additional exploratory analyses to explore the correlation of clinical activity with biomarker subpopulations and other baseline disease characteristics may be performed. Analyses to identify the optimal PD-L1 level relative to ORR to inform other dostarlimab (TSR-042) ovarian cancer studies will be performed and will be further described in the SAP.

13.6. Safety Analyses

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

The occurrence of dose interruption and dose modification will also be tabulated.

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

Additional safety summaries will be provided for vital signs, symptom-directed physical examination findings, and clinical laboratory tests.

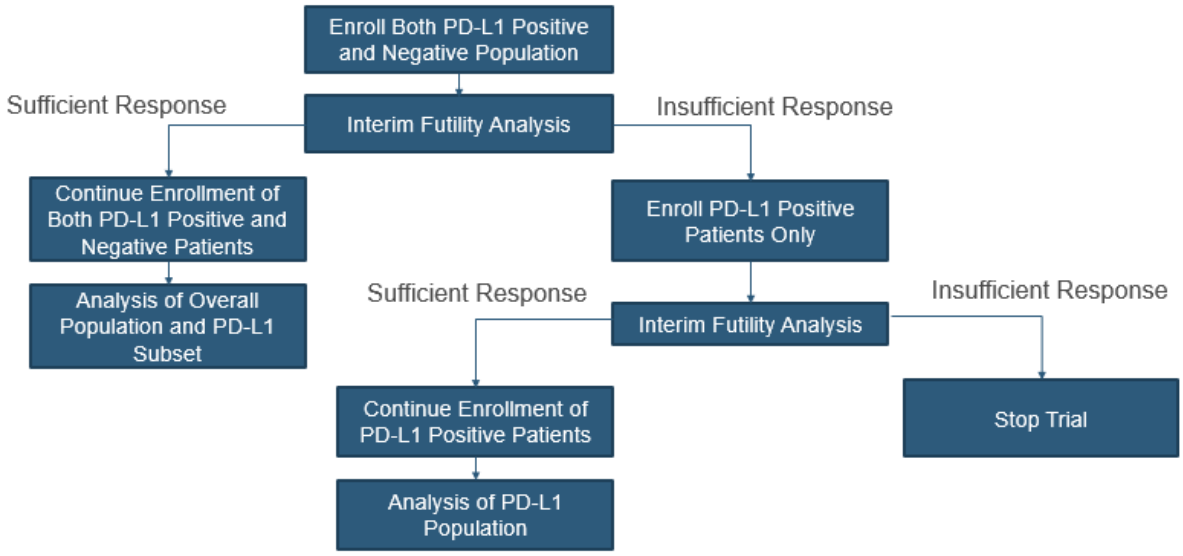
13.7. Biomarker/Interim Futility Analysis

An interim futility analysis will be performed on the overall population after the first 40 patients (regardless of PD-L1 status) have had the opportunity for at least 1 scan (approximately 9 weeks of treatment). Eligible patients with a non-evaluable scan will not be included. Interim futility analysis will be performed considering confirmed and unconfirmed responses that have the potential to be confirmed with additional follow-up. Enrollment will continue at the discretion of the Sponsor while obtaining response data on the first 40 patients.

The nonbinding rule for futility criteria is ≤5 in 40 responses. The probability of early termination is 79% and 43% when the true ORR is 10% and 15%, respectively.

In the event that the interim analysis demonstrates futility, the protocol may be amended as a result to enroll patients with PD-L1 positive tumors only (Figure 2). A cutoff verified assay may need to be in place to enroll patients with PD-L1 positive tumors.

Figure 2: Interim Futility Analysis Flowchart



Abbreviations: PD-1 = programmed cell death-1.

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

14.1. Study Monitoring

Before an investigational site can enter a patient into the study, a representative of the Sponsor will visit the investigational study site to:

- Determine the adequacy of the facilities to support the clinical study, including, but not limited to, clinical sample collection and management as per the laboratory manual.
- Discuss with the Investigator(s) and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of the Sponsor or its representatives. This will be documented in a Clinical Study Agreement between the Sponsor and the Investigator.

During the study, a monitor from the Sponsor or representative will have regular contact with the investigational site, for the following:

- Provide information and support to the Investigator(s).
- Confirm that facilities remain acceptable and that clinical samples are being appropriately managed.
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the CRFs, and that investigational product accountability checks are being performed.
- Perform source data verification. This includes a comparison of the data in the case report forms with the patient's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each patient (eg, clinic charts).
- Record and report any protocol deviations not previously sent to the Sponsor.
- Confirm AEs and SAEs have been properly documented on CRFs and confirm any SAEs have been forwarded to the Sponsor and those SAEs that met criteria for reporting have been forwarded to the IRB.

The monitor will be available between visits if the Investigator(s) or other staff needs information or advice.

14.2. Audits and Inspections

Authorized representatives of the Sponsor, a regulatory authority, an IEC, or an IRB may visit the site to perform audits or inspections, including source data verification. The purpose of a Sponsor audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice (GCP) guidelines of the International Council for Harmonisation (ICH), and any applicable regulatory requirements. The Investigator should contact the Sponsor immediately if contacted by a regulatory agency about an inspection.

14.3. Institutional Review Board

The Principal Investigator must obtain IRB or IEC approval, as appropriate, for the investigation. Initial IRB/IEC approval, and all materials approved by the IRB/IEC for this study including the patient consent form and recruitment materials must be maintained by the Investigator and made available for inspection.

15. QUALITY CONTROL AND QUALITY ASSURANCE

To ensure compliance with GCP and all applicable regulatory requirements, the Sponsor may conduct a quality assurance audit. Please see Section 14.2 for more details regarding the audit process.

16. ETHICS

16.1. Ethics Review

The final study protocol, including the final version of the ICF, must be approved or given a favorable opinion in writing by an IRB or IEC as appropriate. The Investigator must submit written approval to the Sponsor before he or she can enroll any patient into the study.

The Principal Investigator is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all advertising used to recruit patients for the study. The protocol must be re-approved by the IRB or IEC upon receipt of amendments and annually, as local regulations require.

The Principal Investigator is also responsible for providing the IRB with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product. The Sponsor will provide this information to the Principal Investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB or IEC according to local regulations and guidelines.

16.2. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki (please see Appendix 4) and are consistent with ICH/GCP guidelines, applicable regulatory requirements and the Sponsor's policy on Bioethics.

16.3. Written Informed Consent

The Principal Investigator(s) at each center will ensure that the patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Patients must also be notified that they are free to discontinue from the study at any time. The patient should be given the opportunity to ask questions and allowed time to consider the information provided.

The patient's signed and dated informed consent must be obtained before conducting any study procedures.

The Principal Investigator(s) must maintain the original, signed ICF. A copy of the signed ICF must be given to the patient.

17. DATA HANDLING AND RECORDKEEPING

17.1. Inspection of Records

The Sponsor will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, patient charts and study source documents, and other records relative to study conduct.

17.2. Retention of Records

The Principal Investigator must maintain all documentation relating to the study for a period of 2 years after the last marketing application approval, or if not approved 2 years following the discontinuance of the test article for investigation. If it becomes necessary for the Sponsor or the Regulatory Authority to review any documentation relating to the study, the Investigator must permit access to such records.

18. PUBLICATION POLICY

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

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20. APPENDICES

APPENDIX 1. CONTRACEPTION GUIDELINES

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[b] That Have Low User Dependency Failure rate of <1% per year when used consistently and correctly.
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)[c]
• Bilateral tubal occlusion
• Azoospermic partner (vasectomized or due to a to medical cause) Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days. Note: documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Highly Effective Methods [b] That Are User Dependent Failure rate of <1% per year when used consistently and correctly.
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] – oral – intravaginal – transdermal – injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation[c] – oral – injectable
• Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention.*

The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant
a. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. b. Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. c. Male condoms must be used in addition to hormonal contraception. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action. Note: Periodic abstinence (calendar, sympto-thermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception. Male condom and female condom should not be used together (due to risk of failure from friction)

APPENDIX 2. RESPONSE EVALUATION CRITERIA IN SOLID TUMORS V.1.1

Response Criteria by RECIST v.1.1

Evaluation of Target Lesions

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

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

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

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

Evaluation of Non-Target Lesions

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

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

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

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

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

Evaluation of Best Overall Response

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

Table 17: 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 8 wks. from first dose of study medication**
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; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease.
* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.[55]
** 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 18: 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; SD = stable disease.
*Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

APPENDIX 3. EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS

CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.

APPENDIX 4. WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and amended by the:

- 29th WMA General Assembly, Tokyo, Japan, October 1975
- 35th WMA General Assembly, Venice, Italy, October 1983
- 41st WMA General Assembly, Hong Kong, September 1989
- 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
- 52nd WMA General Assembly, Edinburgh, Scotland, October 2000
- 53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)
- 55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
- 59th WMA General Assembly, Seoul, Republic of Korea, October 2008
- 64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human patients, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human patients to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."
4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.
5. Medical progress is based on research that ultimately must include studies involving human patients.
6. The primary purpose of medical research involving human patients is to understand the causes, development, and effects of diseases and improve

preventive, diagnostic and therapeutic interventions (methods, procedures, and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility, and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human patients and protect their health and rights.
8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research patients.
9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research patients. The responsibility for the protection of research patients must always rest with the physician or other health care professionals and never with the research patients, even though they have given consent.
10. Physicians must consider the ethical, legal, and regulatory norms and standards for research involving human patients in their own countries, as well as applicable international norms and standards. No national or international ethical, legal, or regulatory requirement should reduce or eliminate any of the protections for research patients set forth in this Declaration.
11. Medical research should be conducted in a manner that minimizes possible harm to the environment.
12. Medical research involving human patients must be conducted only by individuals with the appropriate ethics and scientific education, training, and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.
13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.
14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic, or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research patients.
15. Appropriate compensation and treatment for patients who are harmed as a result of participating in research must be ensured.

Risks, Burdens, and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human patients may only be conducted if the importance of the objective outweighs the risks and burdens to the research patients.

17. All medical research involving human patients must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimize the risks must be implemented. The risks must be continuously monitored, assessed, and documented by the researcher.

18. Physicians may not be involved in a research study involving human patients unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify, or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices, or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human patients must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human patients must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for patients, and information regarding provisions for treating and/or compensating patients who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance, and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the Sponsor, and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed, as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research patients set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research patients and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as patients in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.
26. In medical research involving human patients capable of giving informed consent, each potential patient must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study, and the discomfort it may entail, post-study provisions, and any other relevant aspects of the study. The potential patient must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential patients, as well as to the methods used to deliver the information.

After ensuring that the potential patient has understood the information, the physician or another appropriately qualified individual must then seek the potential patient's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research patients should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential patient is in a dependent relationship with the physician or may consent under duress. In such situations the informed

consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research patient who is incapable of giving informed consent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential patient, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.
29. When a potential research patient who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential patient's dissent should be respected.
30. Research involving patients who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances, the physician must seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving patients with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the patient or a legally authorized representative.
31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.
32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage, and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens, and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention

is necessary to determine the efficacy or safety of an intervention and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers, and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human patients must be registered in a publicly accessible database before recruitment of the first patient.
36. Researchers, authors, sponsors, editors, and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human patients and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive, as well as positive results, must be published or otherwise made publicly available. Sources of funding, institutional affiliations, and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

Source: World Medical Association. World medical association declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA. 2013;310(20).

APPENDIX 5. SAMPLE FUNCTIONAL ASSESSMENT OF CANCER THERAPY – OVARIAN SYMPTOM INDEX (FOSI)