A Phase 2, Multi-Arm Study of Niraparib Administered Alone and in Combination with a PD-1 Inhibitor in Patients with Non-Small Cell Lung Cancer

Sponsor:	TESARO, a GlaxoSmithKline Company 1000 Winter Street Suite 3300 Waltham, MA 02451 PPD
Medical Monitor:	PPD, MD Medical Director
Clinical Research Organization:	Syneos Health
Sponsor Protocol No.:	(TSO) 3000-02-001 / (GSK) 213352
IND No.:	134,426
Study Drug Names:	Niraparib, pembrolizumab, TSR-042 (also known as dostarlimab)
Development Phase:	2
Date of Original Protocol:	31 May 2017
Date of Amendment 1:	05 September 2017
Date of Amendment 2:	31 May 2018
Date of Amendment 3:	12 February 2021
Version of Protocol:	4.0

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

SPONSOR SIGNATURE PAGE

Declaration of Sponsor or Responsible Medical Officer

Title: A Phase 2, Multi-Arm Study of Niraparib Administered Alone and in Combination with a PD-1 Inhibitor in Patients with Non-Small Cell Lung Cancer

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

PPD

12 Feb 2021

PPD , **MD**
Medical Director
TESARO, a GSK company

Date

INVESTIGATOR'S AGREEMENT

Declaration of the Principal Investigator

Title: A Phase 2, Multi-Arm Study of Niraparib Administered Alone and in Combination with a PD-1 Inhibitor in Patients with Non-Small Cell Lung Cancer

I have read this study protocol, including all appendices. By signing this protocol, I agree to conduct the clinical study, following approval by an Independent Ethics Committee/Institutional Review Board, in accordance with the study protocol, the current International Council for Harmonisation Guideline for Good Clinical Practice, 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.

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Printed Name of Investigator

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Institution

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Signature of Investigator

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Date

Table 1: Summary of Changes for Amendment 3 (Version 4.0)

Section(s) Affected	Description of Change	Brief Rationale
Header, cover page, and Table 1: Summary of Changes for Amendment 3 (Version 4.0)	Cover page updated with new amendment and version number, and date of approval. Header updated with new amendment and version number, Table 1 created to include rationale for this version.	Updated per best documentation practices
Entire document	Included dostarlimab to TSR-042 nomenclature, ie, TSR-042 (dostarlimab)	Clarity
Entire document	Typographical corrections to address noted inconsistencies	Clarity
Entire document	Removed OS as a secondary endpoint	Sponsor decision based on portfolio prioritization following completion of the primary endpoint.
Synopsis – Study Period completion date	Revised from Q4 2019 to Q1 2021	Clarity
Synopsis – Duration of Treatment and Section 6.3.1.4	Describes option for patient on study to continue to receive niraparib treatment in an alternative study	Provisions for patients on study should study terminate
Synopsis – Methodology / Duration of Treatment / Section 3.1.1 / Section 9.3 / Section 9.5	Provided updated cohort status (completed/closed)	Clarification
Section 6.3.1.1, Table 5	Updated niraparib dose reduction/discontinuation guidelines for nonhematologic toxicities	Per Sponsor's recommended safety practices as documented in Global Data Sheet
Section 6.3.1.2, Table 6	Updated niraparib dose reduction/discontinuation guidelines for hematologic toxicities	Per Sponsor's recommended safety practices as documented in Global Data Sheet
Section 6.3.3. and Table 8	Updated treatment guidelines for irAEs	Per Sponsor's recommended safety practices
Section 6.7.4	Added new treatment guidelines for AE of uveitis	Per Sponsor's recommended safety practices
Section 7.1.2	Added definition of a SUSAR	Previously omitted in error

Table 1: Summary of Changes for Amendment 3 (Version 4.0) (Continued)

Section(s) Affected	Description of Change	Brief Rationale
Section 7.1.2.1 and Section 7.1.7	Explains no AESIs identified for TSR-042 (dostarlimab)	Clarification
Section 7.1.7.1	Removed pneumonitis and embryo-fetal toxicity as AESIs for niraparib	ADRs and pregnancy are tracked through other reporting mechanisms
Section 7.1.8	Added new monitoring requirements for hypertension	Updated per niraparib IB, Version 11
Section 7.1.9	Added new monitoring requirements for PRES	Updated per niraparib IB, Version 11
Section 7.1.10	Added new monitoring requirements for allergic reaction	Updated per niraparib IB, Version 11
Section 7.1.11	New monitoring requirements for potential photosensitivity	Updated per niraparib IB, Version 11
Table 15, Schedule of Events, Cohort 3	Added X (Cycle 1, Day 8 and 15) and footnote (14) to clarify monitoring requirement for vital signs Added footnote (15) to clarify monitoring requirement for CBC	New monitoring requirements for hypertension and CBC
Section 10.13	Explains that Sponsor has discretion to terminate study and will notify Investigators under this outcome	Clarification

Abbreviations: ADR=adverse drug reaction; AESI=adverse events of special interest; CBC=complete blood count; CSR=clinical study report; FDA=Food and Drug Administration; IB=Investigator's Brochure; irAE = immune-related adverse event; OS=overall survival; PRES=posterior reversible encephalopathy syndrome; SUSAR=suspected unexpected serious adverse reaction.

SYNOPSIS

Name of Sponsor/Company: TESARO, a GSK company	
Name of Investigational Product: Niraparib, pembrolizumab, and TSR-042 (also known as dostarlimab)	
Name of Active Ingredient: Niraparib, pembrolizumab, and TSR-042 (dostarlimab)	
Title of Study: A Phase 2, Multi-Arm Study of Niraparib Administered Alone and in Combination with a PD-1 Inhibitor in Patients with Non-Small Cell Lung Cancer	
Study Center(s): North America	
Study Period (years): Estimated date first patient enrolled: Q4 2017 Estimated date last patient completed: Q1 2021	**Phase of Development:** 2

Objectives:

Primary Objectives:

- To evaluate the efficacy of the combination of niraparib and a programmed cell death-1 (PD-1) inhibitor in chemotherapy-naïve and PD-1 inhibitor-naïve patients with locally advanced and metastatic non-small cell lung cancer (NSCLC) whose tumors have high programmed death ligand-1 (PD-L1) expression (Tumor Proportion Score [TPS] ≥ 50%), as assessed by objective response rate (ORR)
- To evaluate the efficacy of the combination of niraparib and a PD-1 inhibitor in chemotherapy-naïve and PD-1 inhibitor-naïve patients with locally advanced and metastatic NSCLC whose tumors express PD-L1 (TPS between 1 and 49%), as assessed by ORR
- To evaluate the efficacy of single agent niraparib in patients with locally advanced and metastatic squamous NSCLC (sqNSCLC) who have been previously treated with both platinum-based chemotherapy and either PD-1 or PD-L1 inhibitor, as assessed by ORR

Secondary Objectives:

- To evaluate the safety and tolerability of single agent niraparib and of the combination of niraparib and a PD-1 inhibitor
- To evaluate the following additional measures of clinical benefit of single agent niraparib and of the combination of niraparib and a PD-1 inhibitor:
  - Duration of response (DOR)
  - Disease control rate (DCR)
  - Progression-free survival (PFS)
- To evaluate the pharmacokinetics (PK) of niraparib following administration of single agent niraparib or the combination of niraparib and a PD-1 inhibitor

Exploratory Objectives:

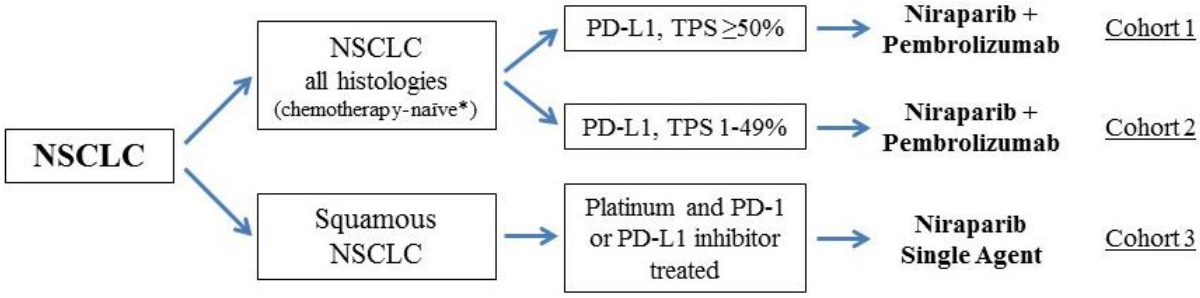
- To explore blood and tumor-based biomarkers that predict sensitivity or resistance to single agent niraparib and to the combination of niraparib and a PD-1 inhibitor

Methodology:

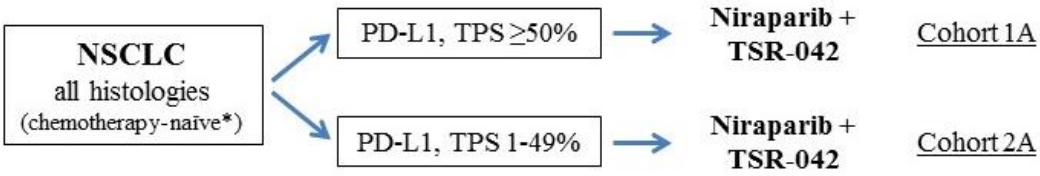
This is a multicenter, open-label, multi-arm Phase 2 study to evaluate the efficacy and safety of single agent niraparib in patients with locally advanced and metastatic sqNSCLC and of the combination of niraparib and a PD-1 inhibitor in locally advanced and metastatic NSCLC (all histologies) patients.

The study has 2 stages, each of which will evaluate separate cohorts of different cancer patients with a sample size that is deemed statistically significant to determine whether further examination may be warranted in the individual indications. In Stage 1, Cohorts 1 and 2 will receive niraparib plus the PD-1 inhibitor pembrolizumab, and Cohort 3 will receive niraparib alone. In Stage 2, Cohorts 1A and 2A will receive niraparib plus the PD-1 inhibitor TSR-042 (dostarlimab). (As of Amendment 2, following a cross-program review and decision to move forward with other studies, the Sponsor decided that Cohort 3 would close to further enrollment. As of Amendment 3, Cohort 1 and Cohort 2 had completed enrollment, Cohort 1A had closed after partial enrollment and Cohort 2A was not opened for enrollment.)

Stage 1:



Stage 2:



*Completion of treatment with chemotherapy and/or radiation as part of neoadjuvant/adjuvant therapy is allowed as long as therapy was completed at least 6 months prior to the diagnosis of metastatic disease

Abbreviations: NSCLC = non-small cell lung cancer; PD-1 = programmed cell death-1; PD-L1 = programmed death ligand-1; TPS = Tumor Proportion Score

Cohorts 1 and 1A: Locally advanced and metastatic NSCLC patients (all histologies) with no prior systemic chemotherapy or PD-1/PD-L1 inhibitor treatment, whose tumors have high PD-L1 expression (TPS ≥ 50%), and no known epidermal growth factor receptor (EGFR) sensitizing mutation and/or ROS-1 or anaplastic lymphoma kinase (ALK) translocations will receive combination of niraparib and a PD-1 inhibitor (pembrolizumab or TSR-042 (dostarlimab)). *Completion of treatment with chemotherapy and/or radiation as part of neoadjuvant/adjuvant therapy is allowed as long as therapy was completed at least 6 months prior to the diagnosis of metastatic disease.*

Cohorts 2 and 2A: Locally advanced and metastatic NSCLC patients (all histologies) with no prior systemic chemotherapy or PD-1/PD-L1 inhibitor treatment, whose tumors have PD-L1 expression (TPS between 1% and 49%) and no known EGFR-sensitizing mutation and/or ROS-1 or ALK translocations, will receive combination of niraparib and a PD-1 inhibitor (pembrolizumab or TSR-042 (dostarlimab)). *Completion of treatment with chemotherapy and/or radiation as part of neoadjuvant/adjuvant therapy is allowed as long as therapy was completed at least 6 months prior to the diagnosis of metastatic disease.*

Cohort 3: Locally advanced and metastatic sqNSCLC patients who have been previously treated with both platinum and either PD-1 or PD-L1 inhibitor will receive single agent niraparib.

This study will consist of a Screening Period (Day -21 to Day -1), a Treatment Period, an End of Treatment (EOT) Period occurring within 7 days of the decision to discontinue treatment for any reason, a Safety Follow-up Visit occurring 30 + 7 days after the last dose of study drug, and a Follow-up Assessment occurring every 90 ± 14 days, which will continue until death or the end of study data collection (a minimum of 6 months after the enrollment of the last patient, provided that this allows the opportunity for completion of all 90-day follow-up assessments).

Patients must have a baseline tumor assessment by computed tomography (CT) or magnetic resonance imaging (MRI) scans of the chest, abdomen, and other sites as clinically indicated. If the patient has had appropriate imaging scans (eg, routine clinical management) performed within 28 days prior to Cycle 1/Day 1, then the results of those scans may be used if they are of diagnostic quality. Subsequent postbaseline tumor assessments will be done in locations with tumor lesions identified at baseline only, unless clinically indicated.

Clinic visits will occur in each cycle (every 3 weeks [Q3W] ± 3 days). For follow-up tumor assessments in Cohorts 1, 1A, 2, and 2A, CT/MRI scans will be performed every 9 weeks ± 7 days from first treatment dose until Week 72 and every 12 weeks ± 7 days thereafter. For sqNSCLC patients in Cohort 3, follow-up tumor assessment CT/MRI scans will be performed every 6 weeks (Q6W) ± 7 days from the first dose until Week 24, then every 9 weeks ± 7 days until Week 52 (12 months) and every 12 weeks ± 7 days until disease progression.

Per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, complete response (CR) or partial response (PR) should be confirmed; tumor imaging for confirmation of response must be performed at the earliest 28 days after the first indication of response but no later than 35 days after the response. The subsequent scan after the confirmatory scan should be obtained per original schedule (9 weeks ± 7 days from confirmatory scan for Cohorts 1, 1A, 2 and 2A, and 6 weeks ± 7 days from confirmatory scan for Cohort 3).

For Cohorts 1, 1A, 2, and 2A (a PD-1 inhibitor and niraparib), patients with radiologic evidence of progressive disease (PD) who are clinically stable may continue treatment at the Investigator's discretion while awaiting confirmatory tumor imaging. Repeat imaging should be performed at ≥ 4 weeks. If repeat imaging shows stable disease (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 radiologic progression if the patient is clinically stable *and* the Investigator deems that the patient is deriving clinical benefit. This allowance to continue treatment despite radiologic 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.

For Cohort 3 (single agent niraparib), patients with radiologic evidence of PD should be discontinued from treatment.

Tumor assessment should occur according to study schedule regardless of whether study treatment is interrupted. If a patient discontinues treatment for a reason other than progression, death, withdrawal of consent, or lost to follow-up, scans should continue at the specified intervals until progression is confirmed or until the start of subsequent anticancer treatment.

Each patient will have an EOT visit within 7 days of the decision to discontinue treatment for any reason, a Safety Follow-up Visit occurring 30 + 7 days after the last dose of study drug, and a Follow-up Assessment every 90 ± 14 days, which will continue until death or the end of study data collection (a minimum of 6 months after the enrollment of the last patient, provided that this allows the opportunity for completion of all 90-day follow-up assessments).

Treatment with niraparib will continue until progression. Treatment with pembrolizumab or TSR-042 (dostarlimab) will continue for a maximum of 24 months in patients without disease progression or unacceptable toxicity.

For Cohorts 1, 1A, 2 and 2A, local assessment of PD-L1 is acceptable on either archival or fresh tissue. PD-L1 status will be confirmed retrospectively in a central immunohistochemistry laboratory using a Food and Drug Administration (FDA)-approved *in vitro* companion diagnostic indicated as an aid in identifying NSCLC patients for treatment with a PD-1 inhibitor.

An archival formalin fixed paraffin embedded (FFPE) tumor tissue is required for exploratory biomarker analysis. If archival tissue is not available, a fresh biopsy is needed. Archival FFPE sample should be submitted within 30 days of patient's first dose. (*For Cohort 3 only*: if diagnosis was made by cytology and archival tissue is not available, patient will not need to provide tumor tissue.)

Number of Patients (Planned):

Stage 1: 59 (Cohort 1 = 16, Cohort 2 = 20, Cohort 3 = 23)

Stage 2: 83 (Cohort 1A = 36, Cohort 2A = 47)

(As of Amendment 2, following a cross-program review and decision to move forward with other studies, the Sponsor decided that Cohort 3 would close to further enrollment. As of Amendment 3, Cohort 1 and Cohort 2 had completed enrollment, Cohort 1A had closed after partial enrollment and Cohort 2A was not opened for enrollment).

Criteria for Inclusion:

General Inclusion Criteria:

1. At least 18 years of age
2. Histological or cytological proven advanced (unresectable) or metastatic NSCLC as defined as stage IIIB (positive supraclavicular lymph nodes) not amenable to definitive chemoradiotherapy or stage IV NSCLC
3. Measurable disease by RECIST v1.1
4. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1
5. Adequate organ function, defined as follows:

   Note: complete blood count (CBC) test should be obtained without transfusion or receipt of colony-stimulating factors within 4 weeks prior to the first dose of study treatment.

   a. Absolute neutrophil count (ANC) ≥1,500/μL
   b. Platelets ≥100,000/μL
   c. Hemoglobin ≥9 g/dL or ≥5.6 mmol/L

d. Serum creatinine ≤ 1.5× upper limit of normal (ULN) or creatinine clearance ≥ 50 mL/min (as calculated using the Cockcroft Gault equation or measured using 24-hour urine creatinine clearance) for patients with creatinine levels > 1.5 × institutional ULN
e. *Total* bilirubin ≤ 1.5× ULN except in patients with Gilbert's syndrome. Patients with Gilbert's syndrome may enroll if direct bilirubin ≤ 1.5 × ULN of the direct bilirubin.
f. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 × ULN unless liver metastases are present, in which case they must be ≤5 × ULN

6. Patient must have recovered to Grade 1 toxicity from prior cancer therapy (a patient with Grade 2 neuropathy or Grade 2 alopecia is an exception to this criterion and may qualify for this study).
7. Patient agrees to submit FFPE tumor tissue specimen, which may have been collected at any time prior to Screening. If no archival FFPE tumor tissue is available, patient agrees to undergo a tumor tissue biopsy before Cycle 1/Day 1. (*For Cohort 3 only*: if diagnosis was made by cytology and archival tissue is not available, patient will not need to provide tumor tissue).
8. Patient is able to take oral medications
9. Female 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 drug, and agrees to abstain from activities that could result in pregnancy from enrollment through 180 days after the last dose of study treatment or is of nonchildbearing potential; or

        Note: A urine pregnancy test may be performed if the serum pregnancy result is not available before dosing.

    b. Female patient is of nonchildbearing potential, other than medical reasons, defined as follows:
        i. ≥ 45 years of age and has not had menses for > 1 year
        ii. Amenorrheic for < 2 years without a hysterectomy and oophorectomy and a follicle-stimulating hormone (FSH) value in the postmenopausal range upon Screening evaluation
        iii. Post hysterectomy, bilateral oophorectomy, or tubal ligation. Documented hysterectomy or oophorectomy must be confirmed with medical records of the actual procedure or confirmed by an ultrasound. Tubal ligation must be confirmed with medical records of the actual procedure, otherwise the patient must be willing to use 2 highly effective contraception methods throughout the study, starting with the screening visit through 180 days after the last dose of study therapy. Please see Section 6.7.3 for a list of acceptable birth control methods. Information must be captured appropriately within the site's source documents

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

10. Male patient agrees to use an adequate method of contraception and not donate sperm starting with the first dose of study therapy through 120 days after the last dose of study therapy.

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

11. Patient is able to understand the study procedures and agree to participate in the study by providing written informed consent

Cohort-Specific Inclusion Criteria:

1. *Cohorts 1 and 1A* (combination of niraparib and a PD-1 inhibitor): patients must have tumors with high PD-L1 expression (TPS ≥ 50%) per local assessment, with no known EGFR-sensitizing mutation and/or ROS-1 or ALK translocation, and no prior systemic chemotherapy or PD-1/PD-L1 inhibitor treatment for metastatic NSCLC
2. *Cohorts 2 and 2A* (combination of niraparib and a PD-1 inhibitor): patients must have tumors with PD-L1 expression (TPS between 1% and 49%) per local assessment, with no known EGFR-sensitizing mutation and/or ROS-1 or ALK translocations, and no prior systemic chemotherapy or PD-1/PD-L1 inhibitor treatment for metastatic NSCLC (all histologies)
3. *Cohort 3* (single agent niraparib): patients must have metastatic sqNSCLC and have progressed after both prior platinum-based chemotherapy and prior PD-1 or PD-L1 inhibitor treatment

Criteria for Exclusion:

Exclusion Criteria for Cohorts 1, 1A, 2 and 2A:

1. Has received systemic therapy for the treatment of advanced stage NSCLC. Completion of treatment with chemotherapy and/or radiation as part of neoadjuvant/adjuvant therapy is allowed as long as therapy was completed at least 6 months prior to the diagnosis of metastatic disease
2. Prior therapy with an anti-PD-1, anti-PD-L1, or anti-programmed death-ligand 2 (anti-PD-L2) agent
3. Known hypersensitivity to the components of niraparib, pembrolizumab, TSR-042 (dostarlimab), or their excipients
4. Known EGFR (exon 19 and 21) mutations, ALK translocations, and/or ROS-1 translocations
5. Patient has a history or current condition (such as transfusion-dependent anemia or thrombocytopenia), therapy, or laboratory abnormality that might confound the study results, or interfere with the patient's participation for the full duration of the study treatment.
6. Known diagnosis of immunodeficiency or receiving systemic steroid therapy (*except as allowed in exclusion criterion #9 below*) or any other form of immunosuppressive therapy within 7 days prior to the first dose of study treatment
7. Patient is immunocompromised, in the opinion of the Investigator *(Note: patients with splenectomy are allowed)*
8. Current participation in a treatment study or past participation in a study of an investigational agent within 4 weeks before the first dose of study treatment
9. 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 SD for 28 days

10. Active autoimmune disease that 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
11. Major surgery within 3 weeks of starting the study or patient has not recovered from any effects of any major surgery
12. Other active concomitant malignancy that warrants systemic therapy
13. Poor medical risk due to a serious, uncontrolled medical disorder, nonmalignant systemic disease, or active, uncontrolled infection. Examples include, but are not limited to, uncontrolled ventricular arrhythmia, recent (within 90 days) myocardial infarction, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, uncontrolled hypertension, active uncontrolled coagulopathy, or any psychiatric disorder that prohibits obtaining informed consent
14. Known history of interstitial lung disease, drug-related pneumonitis, or radiation pneumonitis requiring steroid treatment
15. Patient is pregnant, breastfeeding, or expecting to conceive children while receiving study treatment and for 180 days (for pregnancy or conception) or 30 days (for breastfeeding) after the last dose of study treatment
16. Male patient is expecting to donate sperm or father children while receiving study drug or for 120 days after the last dose of study treatment
17. Known active hepatic disease (known hepatic cirrhosis, hepatitis B surface antigen-positive status, or suspected active hepatitis C infection)
18. Prior treatment with a known poly-(adenosine diphosphate-ribose) polymerase (PARP) inhibitor
19. Patient received a live vaccine within 30 days of planned start of study therapy
20. Known history of myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML)

Exclusion Criteria for Cohort 3:

1. Platinum-treated patient who progressed while on or within less than 8 weeks from the last day of platinum administration
2. Known hypersensitivity to the components of niraparib or excipients

3. Patient has a history or current condition (such as transfusion dependent anemia or thrombocytopenia), therapy, or laboratory abnormality that might confound the study results, or interfere with the patient's participation for the full duration of the study treatment.
4. Known diagnosis of immunodeficiency or receiving systemic steroid therapy (*except as allowed in exclusion criterion #6 below*) or any other form of immunosuppressive therapy within 7 days prior to the first dose of study treatment
5. Current participation in a treatment study or past participation in a study of an investigational agent within 4 weeks before the first dose of study treatment
6. Symptomatic uncontrolled brain or leptomeningeal metastases. (To be considered "controlled," 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 $\leq$ 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 SD for 28 days
7. Major surgery within 3 weeks of starting the study or patient has not recovered from any effects of any major surgery.
8. Other active concomitant malignancy that warrants systemic therapy
9. Poor medical risk due to a serious, uncontrolled medical disorder, nonmalignant systemic disease, or active, uncontrolled infection. Examples include, but are not limited to, uncontrolled ventricular arrhythmia, recent (within 90 days) myocardial infarction, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, uncontrolled hypertension, active uncontrolled coagulopathy, or any psychiatric disorder that prohibits obtaining informed consent
10. Known history of interstitial lung disease, drug-related pneumonitis, or radiation pneumonitis requiring steroid treatment
11. Patient is pregnant, breastfeeding, or expecting to conceive children, while receiving study treatment and for 180 days (for pregnancy or conception) or 30 days (for breastfeeding) after the last dose of study treatment
12. Male patient is expecting to donate sperm or father children while receiving study drug or for 120 days after the last dose of study treatment
13. Patient is immunocompromised, in the opinion of the Investigator *(Note: patients with splenectomy are allowed)*
14. Known active hepatic disease (known hepatic cirrhosis, hepatitis B surface antigen-positive status, or suspected active hepatitis C infection)
15. Prior treatment with a known PARP inhibitor
16. Known history of MDS or AML

Investigational Product, Dosage, and Mode of Administration:

Niraparib:

Niraparib will be administered orally once a day, continuously throughout the 21-day cycle. Two capsules of 100 mg strength (200 mg/day) will be taken at each dose administration. Patients will be instructed to take their niraparib dose in the morning at approximately the same time each day. Niraparib may be taken with or without food or water. Patients must swallow and not chew the capsules.

For those patients experiencing nausea and who are at Cycle 5 and beyond, bedtime administration may be a potential method for managing nausea. For those patients experiencing nausea who are not yet at Cycle 5, please seek approval from Medical Monitor to permit bedtime administration.

For Cohorts 1, 1A, 2, and 2A, niraparib will be administered upon completion of pembrolizumab or TSR-042 (dostarlimab) infusion per respective cohorts.

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

Niraparib dose may be escalated on or after Cycle 3/Day 1 from 200 mg daily (2 capsules) to 300 mg daily (3 capsules) if platelets ≥100,000/μL, hemoglobin ≥ 9 g/dL, and neutrophils ≥ 1,500/μL for all laboratory tests performed during the first 2 cycles after discussion with Medical Monitor or designee.

Dose interruption will be allowed for no longer than 28 days. In addition, dose reduction will be allowed based on treatment side effects. Dose reductions to 100 mg daily (1 capsule) will be allowed. No further dose reductions will be allowed. The timing of efficacy or safety evaluations should not be affected by dose interruptions or reductions.

Pembrolizumab:

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

Pembrolizumab will be administered at a dose of 200 mg IV 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, however, a window between - 5 minutes and + 10 minutes is permitted. Dose interruption will be allowed for no longer than 28 days.

Refer to United States Prescribing Information for specific instructions for the preparation of the pembrolizumab infusion and administration of the infusion solution.

TSR-042 (dostarlimab):

TSR-042 (dostarlimab) infusion will be administered before niraparib dose at the study site on Day 1 of each 21-day treatment cycle (Q3W) in Cycles 1 through 4 and on Day 1 of every other cycle (Q6W) thereafter, beginning on Cycle 5 Day 1 (ie, Cycle 5, Cycle 7, Cycle 9, etc.).

TSR-042 (dostarlimab) will be administered after all procedures and assessments have been completed, unless otherwise indicated. TSR-042 (dostarlimab) may be administered up to 3 days before or after the scheduled Day 1 of each cycle after Cycle 1 due to administrative reasons.

TSR-042 (dostarlimab) 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 thereafter, beginning on Cycle 5 Day 1, 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, however, a window between - 5 minutes and + 15 minutes is permitted. Dose interruption to manage adverse reactions will be allowed for no longer than 28 days.

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

Duration of Treatment:

Patients may continue treatment until disease progression, unacceptable toxicity, patient withdrawal, Investigator's decision, or death. Treatment with niraparib will continue until disease progression. Treatment with pembrolizumab or TSR-042 (dostarlimab) will continue for a maximum of 24 months in patients without disease progression or unacceptable toxicity.

Those patients deemed to derive clinical benefit from niraparib monotherapy treatment at the time of final analysis and who are no longer receiving a PD-1 inhibitor will have the option to continue treatment with niraparib through the extension "rollover" protocol, if available, and at the discretion of the Investigator and Sponsor.

Long-Term Follow-Up Assessment: Every 90 days, via telephone.

Planned study conduct duration:

- Stage 1: It may take 8 to 12 months to complete enrollment in each cohort. For each cohort, analysis will be done after the last patient enrolled in that cohort has discontinued treatment or completed 2 postbaseline tumor assessments (approximately 3 to 5 months from baseline), whichever occurs earlier.

  (As of Amendment 2, following a cross-program review and decision to move forward with other studies, the Sponsor decided that Cohort 3 would close to further enrollment. As of Amendment 3, Cohort 1 and Cohort 2 had completed enrollment, Cohort 1A had closed after partial enrollment and Cohort 2A was not opened for enrollment**.)**

- Stage 2: It may take 12 to 14 months to complete enrollment in each cohort. For each cohort, analysis will be done after the last patient enrolled in that cohort has discontinued treatment or completed 2 postbaseline tumor assessments (approximately 3 to 5 months from baseline), whichever occurs earlier.

Criteria for Evaluation:

Efficacy:

The primary endpoint is the ORR, which is defined as the proportion of patients with a confirmed best overall response of CR or PR in the analysis population. Tumor assessment will be done by the Investigator per RECIST v1.1.

Secondary efficacy endpoints include:

- DOR, defined as the time from first documented CR or PR until the subsequently documented disease progression or death, whichever occurs earlier.
- DCR defined as the proportion of patients with a best overall response of CR, PR, or SD.

- PFS is defined as the time from the date of first dose to the date of disease progression or death due to any cause, whichever occurs earlier.

Safety:

Safety and tolerability of single agent niraparib and of the combination of niraparib and a PD-1 inhibitor will be evaluated throughout the study, including assessment of treatment-emergent adverse events (AEs), discontinuations due to AEs, clinical laboratory assessments (CBC, serum chemistry, and urinalysis), vital signs, electrocardiograms, physical examination, and use of concomitant medications.

Pharmacokinetics:

The PK of niraparib when given alone and in combination with pembrolizumab or TSR-042 (dostarlimab) will be evaluated. Samples for PK determination will be collected from patients in plasma for single agent niraparib (Cohort 3) and serum and plasma for the combination of niraparib and pembrolizumab or TSR-042 (dostarlimab) (Cohorts 1, 1A, 2, and 2A).

Biomarkers:

Biomarker analysis will be carried out on tumor tissue and blood to include but not be limited to circulating tumor DNA (ctDNA) or circulating tumor cells (CTC) to identify prognostic or predictive biomarkers and to explore potential mechanisms of either *de nov*o or treatment-emergent resistance.

Biomarkers will be evaluated in archival or fresh tumor samples obtained during screening to confirm histology morphology, presence of tumor, and to conduct biomarker analysis. Archival FFPE sample should be submitted within 30 days of patient's first dose. (*For Cohort 3 only*: if diagnosis was made by cytology and archival tissue is not available, patient will not need to provide tumor tissue.)

Blood samples for the analysis of tumor-related circulating biomarkers such as CTC will be collected at Cycle 1/Day 1 predose. Blood samples for the analysis of ctDNA will be obtained at Screening, Cycle 2/Day 1 predose, as well as EOT.

Statistical Methods:

Data from Stage 1 will be used to determine whether further enrollment of Stage 2 patients is warranted. The criteria for continuing Stage 2 enrollment are provided in Section 9. For each cohort, if the number of responders by the end of Stage 1 is the same or less as defined by the criterion, the cohort will be terminated. Only cohorts with number of responders larger than that defined by the criteria will continue Stage 2 enrollment. (As of Amendment 2, following a cross-program review and decision to move forward with other studies, the Sponsor decided that Cohort 3 would close to further enrollment. As of Amendment 3, Cohort 1 and Cohort 2 had completed enrollment, Cohort 1A had closed after partial enrollment and Cohort 2A was not opened for enrollment.)

Number of responders, ORR, and its 80% and 95% binomial exact confidence interval will be reported by cohort and stage.

Results for DCR and PFS will be summarized in a descriptive manner. DCR will be analyzed using the same methods for ORR. Kaplan-Meier estimates including median and its 95% confidence interval will be tabulated for time-to-event variables. In addition, Kaplan-Meier curves will also be presented for time-to-event variables.

Pharmacokinetics:

PK parameters will be summarized by cohort and dose schedule using descriptive statistics. The concentration-time data for niraparib will be used to perform a population PK analysis. The

relationship between measures of niraparib exposure and measures of efficacy, including, but not limited to, ORR, PFS, DOR, and DCR, will be explored. The relationship between niraparib exposure and key safety variables, including, but not limited to, AEs of special interest in the population will be explored.

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

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

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

Table 2: Abbreviations and Specialist Terms

Abbreviation	Explanation
ADL	activity of daily living
ADP	adenosine diphosphate
AE	adverse event
AESI	adverse event of special interest
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
ATM	ataxia telangiectasia mutated
AUC	area under the concentration × time curve
AUC_{ss}	area under the concentration × time curve at steady state
BIW	biweekly
BP	blood pressure
BRCA	breast cancer (gene)
CBC	complete blood count
CI	confidence interval
CL	clearance
C_{max}	maximum concentration
$C_{max,ss}$	maximum concentration at steady state
C_{min}	minimum concentration
$C_{min,ss}$	minimum concentration at steady state
CNS	central nervous system
CR	complete response
CT	computed tomography
CTC	circulating tumor cell
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor DNA

Abbreviation	Explanation
CYP	cytochrome P450
DCR	disease control rate
DDR	DNA damage repair
DKA	diabetic ketoacidosis
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
DSB	double-stranded breaks
EC	endometrial cancer
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EGFR	epidermal growth factor receptor
ELISA	enzyme-linked immunosorbent assay
EOT	end of treatment
FAS	full analysis set
FDA	Food and Drug Administration
FFPE	formalin fixed paraffin embedded
FSH	follicle-stimulating hormone
FT3	free triiodothyronine
FT4	free thyroxine
gBRCAmut	germline breast cancer gene mutation
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
H_0	null hypothesis
H_a	alternative hypothesis
HR	hazard ratio
HRD	homologous recombination deficiency
HRR	homologous recombination repair
IB	Investigator Brochure
ICF	informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee

Abbreviation	Explanation
Ig	immunoglobulin
IHC	immunohistochemistry
irAEI	immune related adverse event of interest
IRB	Institutional Review Board
irRECIST	Immune-related Response Evaluation Criteria in Solid Tumors
ITIM	immunoreceptor tyrosine-based inhibition motif
ITSM	immunoreceptor tyrosine-based switch motif
ITT	intent-to-treat
IV	intravenous
mAb	monoclonal antibody
MDS	myelodysplastic syndrome
MRI	magnetic resonance imaging
MSI-H	microsatellite instability-high
NSCLC	non-small cell lung cancer
OAE	other significant adverse event
ORR	objective response rate
OS	overall survival
PARP	poly (ADP-ribose) polymerases
PD	progressive disease
PD-1	programmed cell death-1
PD-L1	programmed death-ligand 1
PD-L2	programmed death-ligand 2
PDX	patient-derived xenograft
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetics
PO	oral(ly)
PR	partial response
PTEN	phosphatase and tensin homolog
Q3W	every 3 weeks
Q6W	every 6 weeks
QD	once daily
RECIST	Response Evaluation Criteria in Solid Tumors

Abbreviation	Explanation
RNA	ribonucleic acid
RP2D	recommended Phase 2 dose
RR_s	standard of care response rate
RR_t	target response rate
SAE	serious adverse event
SAP	statistical analysis plan
SCLC	small cell lung cancer
SD	stable disease
sqNSCLC	squamous non-small cell lung cancer
SUSAR	suspected unexpected serious adverse reaction
T1DM	type 1 diabetes mellitus
T3	triiodothyronine
TCGA	The Cancer Genome Atlas
TEAE	treatment-emergent adverse event
TIL	tumor-infiltrating lymphocytes
TMB	tumor mutation burden
TPS	Tumor Proportion Score
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
US	United States
USPI	United States Prescribing Information
vs.	versus
WHO	World Health Organization

Trademark Information

Trademarks of the TESARO-GlaxoSmithKline group of companies	Trademarks not owned by the TESARO-GlaxoSmithKline group of companies
Zejula	None

1. INTRODUCTION

1.1. Background

1.1.1. Lung Cancer

Lung cancer is the most common cause of cancer mortality globally and the second most common cancer in both men and women. About 14% of all new cancers are lung cancers. In the United States (US), there are projected to be 222,500 new cases of lung cancer (116,990 in men and 105,510 in women) and 155,870 deaths from lung cancer (84,590 in men and 71,280 in women) in 2017.[1]

The 2 major forms of lung cancer are non-small cell lung cancer (NSCLC) and small cell lung cancer. NSCLC is a heterogeneous disease that consists of adenocarcinoma, large-cell carcinoma, and squamous cell carcinoma (sqNSCLC), and comprises approximately 80% to 85% of all lung cancers.[2] Despite advances in early detection and standard treatment, NSCLC is often diagnosed at an advanced stage, has poor prognosis, and is the leading cause of cancer deaths worldwide.

Platinum-based doublet therapy, maintenance chemotherapy, and anti-angiogenic agents in combination with chemotherapy have contributed to improved patient outcomes in advanced NSCLC.[3] The identification of point mutations (epidermal growth factor receptor [EGFR], BRAF), gene fusions due to chromosomal translocations (anaplastic lymphoma kinase [ALK], ROS-1), and gene amplifications (mesenchymal epithelial transition factor [MET]) as oncogenic drivers in a small subset of patients has led to the new era of personalized medicine, taking targeted therapy to the frontline setting for these patients.[4]

For most NSCLC patients without targetable oncogene drivers, first-line platinum-based chemotherapy was until recently the only standard treatment approach.[3] However, the recent understanding of the interactions between immune system and tumor growth has led to the development of a new class of immunotherapies. Approval of pembrolizumab in the US and European Union in 2016 and 2017, respectively, as the first-line treatment approach for NSCLC patients whose tumors express high programmed death ligand-1 (PD-L1) [Tumor Proportion Score, (TPS) ≥50%] led to a change in the lung cancer management paradigm.[5-7] Pembrolizumab was also approved for patients with PD-L1 TPS ≥ 1% as second-line treatment.[7] Other immunotherapies such as the programmed cell death-1 (PD-1) inhibitor nivolumab and the PD-L1 inhibitor atezolizumab were similarly approved for NSCLC patients following platinum-based chemotherapy.[8-10]

Squamous cell carcinoma of the lung accounts for 20% to 30% of NSCLC. Despite the differences in disease characteristics between squamous and nonsquamous, both have historically been treated similarly. However, clinical studies have shown poorer tolerability and efficacy of new therapeutic drugs in patients with squamous histology.[11,12]

Patients with sqNSCLC rarely have EGFR, BRAF, ALK, or ROS-1 alterations in their tumors, and molecular testing is not routine.

Until the recent approval of pembrolizumab, the standard first-line therapy for sqNSCLC consisted of 4 to 6 cycles of platinum-based doublet chemotherapy not containing

pemetrexed.[11,13,14] In the second-line setting, gemcitabine, docetaxel with or without ramucirumab, afatinib as well as the recently approved immunotherapies pembrolizumab, nivolumab, and atezolizumab[5-10] are considered the standard treatment options for patients.[15]

1.1.2. Overview of PARP and Homologous Recombination Deficiency

Normal cells repair up to 10,000 deoxyribonucleic acid (DNA) defects daily; single-strand breaks being the most common form of DNA damage. Cells unable to repair their DNA are susceptible to the accumulation of mutations that ultimately lead to cancer development.

Poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP)1 and PARP2 are zinc-finger DNA-binding-enzymes that play a crucial role in single-strand DNA repair.[16] Upon formation of DNA breaks, PARP binds at the end of broken DNA strands, a process that activates its enzymatic activity. Activated PARP catalyzes the addition of long polymers of ADP-ribose onto PARP and several other proteins associated with chromatin, including histones and various DNA repair proteins. This results in chromatin relaxation, fast recruitment of DNA repair proteins, and efficient repair of DNA breaks. In this manner, PARP plays a key role in sensing DNA damage and activating the base excision repair and single-strand break repair pathways.[16-18]

Niraparib is a potent, orally active PARP 1/2 inhibitor being developed as an agent for tumors with defects in the homologous recombination DNA repair pathway. PARP inhibitors prevent single-strand break repair leading to double-stranded breaks (DSB) and γH2AX foci formation. DSB repair occurs preferentially through the homologous recombination pathway.[17] This pathway is disrupted in several conditions, including ataxia telangiectasia mutated (ATM) deficiency (10%–15% prevalence in NSCLC), phosphatase and tensin homologue (PTEN) deficiency, Fanconi deficiency, and breast cancer gene 1 or 2 (BRCA1/2) deficiency.[19,20] BRCA deficient cells are highly sensitive to single-agent PARP inhibition.[17]

Treatment with PARP inhibitors represents a novel opportunity to selectively kill a subset of cancer cells by exploiting their deficiencies in DNA repair. For example, a tumor arising in a patient with a germline BRCA mutation (gBRCAmut) has a defective homologous recombination DNA repair pathway and would be increasingly dependent on the other DNA repair pathways for maintenance of genomic integrity.

1.1.2.1. Nonclinical Experience with PARP Inhibitors in NSCLC

Homologous recombination deficiencies, which render tumor sensitivity to PARP inhibitors, were evaluated across 15 different cancer types in The Cancer Genome Atlas (TCGA), showing that squamous cell carcinoma and adenocarcinoma of the lung were among the highest ranking cancer types with homologous recombination deficiencies.[21] Moreover, deficiency in the Fanconi anemia pathway, a major mechanism of homologous recombination DNA repair, was found in 22% of NSCLC cases studied.[22]

TESARO in-house analysis of TCGA data also showed that more than 10% of NSCLC patients harbor aberrations in BRCA1/2, ATM, or other genes in homologous recombination repair (HRR) while a study of BRCA1 protein levels using immunohistochemistry (IHC) showed that 11-19% of NSCLC patients are BRCA1 deficient.[23]

Synthetic lethality between PARP inhibitor and HRR deficiency was observed in several NSCLC *in vitro* models. One study showed that BRCA1-deficient NSCLC cells, generated by ribonucleic

acid (RNA) interference, were more sensitive to PARP-1 inhibition. This study also showed that BRCA-deficient, platinum-resistant cells were still sensitive to PARP inhibition.[23] Another study reported that lung cancer cells deficient in ERCC1, an endonuclease essential for HRR, were highly sensitive to PARP inhibitors.[24]

In an effort to evaluate the *in vivo* activity of niraparib in NSCLC models, a large panel of patient-derived xenograft models, comprising 35 adenocarcinomas and 28 squamous cell carcinomas, was treated with niraparib (50 mg/kg PO once daily [QD] for adenocarcinoma and 75 mg/kg PO 5-on/2-off for squamous cell carcinoma) or vehicle control (0.5% Methyl Cellulose, PO QD). The results showed that more than 50% tumor growth inhibition was achieved in 7 adenocarcinoma models (20%) and 7 squamous cell carcinoma models (25%) [Study E0322-U1502, Study E0322-U1505 (US), Study E0322-U1505 (China), Study P381B and Study 16079-64] (Study references on file).

1.1.2.2. Clinical Experience with PARP inhibitors

Clinical studies have shown that PARP inhibitors are active in recurrent ovarian cancer.[16,25-30] PARP inhibition appears to be most active in patients with gBRCAmut and in patients who are sensitive to platinum-containing therapy. However, clinical benefit has also been observed in gBRCA wild type.[26-29] Maintenance treatment of high-grade serous ovarian cancer patients with recurrent platinum sensitivity showed that the PARP1/2 inhibitor niraparib significantly improved progression-free survival (PFS) in gBRCAmut patients (21 months for niraparib vs. 5.5 months for control). Furthermore, in the gBRCA wild-type population, significantly improvement in PFS was observed for both HRD (homologous recombination deficient patients identified by myChoice HRD assay developed by Myriad) positive (12.9 months for niraparib versus (vs.) 3.8 months for placebo, hazard ratio [HR]=0.38, p=0.0001) and HRD negative (HRDneg) patients (9.3 months for niraparib vs. 3.9 months for placebo, HR=0.45, p<0.0001).[30,31] Niraparib has been recently approved in the US for the treatment of platinum-sensitive patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer.[32]

The use of PARP inhibitors in lung cancer may not be limited to alterations in the BRCA genes as in tumors carrying intrinsically high genomic instability, targeting PARP might induce a saturation of the systems controlling DNA damage, leading to uncontrolled accumulation of mutations and subsequent cell death.[33] Data from niraparib Phase 1 development program showed that clinical benefit was observed in 2 of 2 patients with NSCLC.[30] One patient with gBRCAmut was treated with 110 mg niraparib QD and had stable disease (SD) for 6 months, and another patient was treated with 40 mg niraparib QD and had SD for 11 months. Additionally, preliminary data from a randomized Phase 2 study in advanced NSCLC patients treated with carboplatin/paclitaxel or the combination of the PARP inhibitor veliparib plus chemotherapy demonstrated that addition of veliparib was associated with improvements in outcomes: 5.8 months vs. 4.2 months (PFS), 11.7 months vs. 9.1 months overall survival (OS) [HR= 0.56; 95% confidence interval (CI)=0.54-1.18; P=0.27]. Improvements in PFS and OS were more pronounced in squamous histology: 6.5 months vs. 4.1 months (PFS) [HR=0.54; 95% CI=0.26-1.12; P=0.098], 10.3 months vs. 8.4 months (OS) [HR= 0.73; 95% CI=0.43-1.24; P=0.24].[34] The reasons behind the efficacy in squamous histology may be related to the higher genomic instability observed in this patient population, which is more vulnerable to agents that enhanced DNA damage.[34-36] A Phase 3 trial in squamous and nonsquamous NSCLC have

completed enrollment. These findings indicate that PARP inhibitors may have a potential role in the treatment of NSCLC.

1.1.3. Overview of PD-1 Inhibitors

The recognition of tumors by the immune system has been appreciated for multiple decades and provides an impetus to utilize the immune system to control tumor growth. Studies have reported the presence of tumor-infiltrating lymphocytes (TILs) as a positive prognostic feature in multiple tumors supporting a role for the immune system in limiting tumor growth. Despite evidence of immune reactivity, tumors are able to grow in the presence of an immune system suggesting a suboptimal immune response.[37-39]

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control.[40] The normal function of PD-1, expressed on the cell surface of activated T cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an immunoglobulin superfamily member related to CD28 and CTLA-4, which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands. PD-1 is expressed on activated lymphocytes, including peripheral CD4+ and CD8+, T cells, B cells, Tregs, and natural killer cells.[41] Expression has also been shown during thymic development on CD4-/CD8- (double-negative), T cells, as well as subsets of macrophages and dendritic cells.[42-44]

The ligands for PD-1 (PD-L1 and programmed death-ligand 2 [PD-L2]) are constitutively expressed or can be induced in a variety of cell types.[45] PD-L1 is expressed at low levels on various nonhematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is predominantly expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments.[45] The binding of PD-1 ligands to PD-1 inhibits T cell activation triggered through the T cell receptor. PD-L2 is thought to control immune T cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T cell function in peripheral tissues. While healthy organs express little (if any) PD-L1, a variety of cancers were shown to express abundant levels,[46,47] which, via its interaction with the receptor plays a critical role in immune evasion by tumors.[48] As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in cancer.[49]

1.1.3.1. Clinical Experience with PD-1/PD-L1 Inhibitors in NSCLC

Lung cancer had been considered a poorly immunogenic malignancy, however, in recent years, immune checkpoint inhibitors have emerged as promising therapeutic agents in NSCLC. There are currently three PD-1/PD-L1 inhibitors available for the treatment of lung cancer: nivolumab, pembrolizumab and atezolizumab.[5-10,50] Keynote-024 Study showed that treatment with PD-1 inhibitor pembrolizumab achieved statistically significant clinical benefits in terms of progression free survival, OS and objective responses in advanced NSCLC patients whose tumors express high PD-L1 (TPS $\geq$ 50%), which led to the approval of pembrolizumab as the first-line treatment for that patient population. Pembrolizumab was approved as second-line treatment in advanced NSCLC PD-L1 positive patients [TPS $\geq$ 1%] who progressed during or after platinum-based therapy. The PD-1 inhibitor nivolumab and the PD-L1 inhibitor atezolizumab were also approved as second-line treatment for advanced NSCLC after showing

significant improvement in OS compared to docetaxel during or after first-line platinum treatment.

1.1.3.2. Clinical Experience with TSR-042 (Dostarlimab)

As of April 2018, there were 4 ongoing Phase 1 studies with TSR-042: Study 4010-01-001 (TSR-042 monotherapy), Study 4020-01-001 (TSR-042 combination therapy), Study 3000-01-002 (TSR-042 combination therapy), and Study 4040-01-001 (TSR-042 combination therapy).

1.1.3.2.1. TSR-042 (Dostarlimab) Monotherapy

GARNET (Study 4010-01-001) is an ongoing, first-in-human Phase 1 study of TSR-042 (dostarlimab) that aims to evaluate the safety and tolerability, PK, pharmacodynamics (PDy), and clinical activity of TSR-042 (dostarlimab) in patients with recurrent or advanced solid tumors. A total of 21 subjects 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 (Q2W) and a maximum tolerated dose (MTD) was not identified. No dose-limiting toxicities (DLTs) were observed. In Part 2A of the study, the safety and tolerability of TSR-042 (dostarlimab) was evaluated at 2 fixed dosing schedules: 500 mg every 3 weeks (Q3W) and 1,000 mg every 6 weeks (Q6W). For both doses, the mean last measurable concentration (C_{last}) was approximately 40 μg/mL, which is approximately 16-fold higher than the lowest TSR-042 (dostarlimab) serum concentration at which maximal receptor occupancy has been observed. These results led to a proposed TSR-042 (dostarlimab) recommended Phase 2 dose (RP2D) regimen of 500 mg Q3W for 4 cycles, followed by 1,000 mg Q6W for all subsequent cycles, which is being evaluated in expansion cohorts for microsatellite instability-high (MSI-H) and microsatellite stable (MSS) endometrial cancer (EC), non-small cell lung cancer (NSCLC), and non-endometrial MSI-H or polymerase ε-mutated cancer in Part 2B of study.

As of 21 January 2018, 135 subjects with heavily pretreated advanced solid tumors have been treated with TSR-042 (dostarlimab) in GARNET. Preliminary data indicate that the majority of these subjects (92.6%) reported at least 1 treatment-emergent adverse event (TEAE), with events of fatigue, nausea, and decreased appetite being the most frequently reported. Study drug-related TEAEs of Grade ≥ 3 were reported in 13 subjects (9.6%). The majority of these events occurred in only 1 subject each, with the exception of aspartate aminotransferase increased (3 subjects), alanine aminotransferase increased (2 subjects), and fatigue (2 subjects). Serious adverse events (SAEs) occurred in 38 subjects (28.1%), for 5 of these subjects the event was considered study drug-related. Eight subjects had an adverse event (AE) leading to study drug discontinuation. Six subjects had an AE leading to study drug discontinuation which was considered study drug-related. Three subjects had an AE leading to death. None of the AEs leading to death were considered to be related to the study drug.

Preliminary efficacy data from 15 subjects with MSI-H EC and 24 subjects with NSCLC who had at least 1 tumor assessment were presented at AACR (April 2018). Responses were assessed by Investigators using immune-related Response Evaluation Criteria in Solid Tumors (irRECIST). Among the 15 subjects with MSI-H EC, the objective response rate (ORR) was 47% and consisted of all partial responses (PRs), 20% with SD and 33% had disease progression (PD). Among the 24 subjects with NSCLC, the ORR was 29% and consisted of all PRs, 42% had

SD and 17% had PD. Although preliminary, efficacy data from subjects with NSCLC treated with TSR-042 (dostarlimab) appears to be comparable to the reported efficacy of other PD-(L)1 inhibitors in the advanced and recurrent population, including nivolumab (ORR 19-20%),[8,51] pembrolizumab (ORR 19%)[50] and atezolizumab (ORR 14%).[52]

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

In addition to the GARNET TSR-042 (dostarlimab) monotherapy, three additional studies involving TSR-042 (dostarlimab) and other therapeutic agents are being conducted.

Study 4020-01-001 is an open-label, first-in-human Phase 1 study of another mAb, TSR-022 - anti-TIM3, that is being conducted in 2 parts in patients with advanced solid tumors. In Part 1C of this study, TSR-042 (dostarlimab) will be administered in combination with TSR-022.

Study 3000-01-002 is an open-label, Phase 1b study of TSR-042 (dostarlimab) that is being conducted in 4 parts in patients with advanced or metastatic cancer. The study will evaluate DLTs, safety, and tolerability of TSR-042 (dostarlimab) in combination with niraparib with or without bevacizumab or carboplatin and paclitaxel with or without bevacizumab.

Study 4040-01-001 is an open-label, first-in-human Phase 1 study of another mAb, TSR-033 - anti-LAG3, that is being conducted in 2 parts in patients with advanced solid tumors. In Part 1C, TSR-042 (dostarlimab) 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 plus TSR-022 with or without TSR-042 (dostarlimab) will be evaluated in patients with advanced solid tumors.

As of 21 January 2018, a total of 51 subjects with heavily pretreated advanced solid tumors have received TSR-042 (dostarlimab) in combination with other therapeutic agents. The majority (80.4%) of subjects receiving TSR-042 (dostarlimab) combination therapy reported at least 1 TEAE, with events of fatigue and dyspnoea being the most frequently reported. One DLT (Grade 3 aspartate aminotransferase increased) was reported in a subject in Part B of Study 3000-01-002. Serious AEs occurred in 14 subjects, none of these events were considered study drug-related. One subject had at least 1 AE leading to study drug discontinuation (alanine aminotransferase increased and aspartate aminotransferase increased). Both events were considered study drug-related. No subject had an AE leading to death.

Given the encouraging clinical activity in patients with diverse tumor types and the manageable safety profile of TSR-042 (dostarlimab), the benefit-risk profile for TSR-042 (dostarlimab) as a treatment for patients with advanced cancers appears positive.

1.1.4. Combination of PARP Inhibitors and PD-1 Inhibitors

1.1.4.1. Nonclinical Experience Combining PARP inhibitors and PD-1 Inhibitors

Multiple lines of evidence suggest that the combination of PARP inhibitors with anti-PD-1 agents may provide additional benefits. PARP inhibitors have been shown to elevate PD-L1 expression, in a cell-autonomous fashion, and to enhance the antitumor activity of an anti-PD-1 antibody in preclinical syngeneic breast cancer models.[53] Additionally, there is reason to believe that PARP inhibition could potentially synergize with anti-PD-1/anti-PD-L1 therapy by enhancing local immune surveillance in the tumor microenvironment via induction of DNA

damage. The intracellular accumulation of self DNA fragments resulting from inefficient DNA repair and/or genomic instability has been linked to activation of innate immunity pathway. Multiple molecular mechanisms have been elucidated by which both tumor and immune cells could be leveraged to sense the accumulated cytosolic DNA fragments and subsequently enable innate immune responses via production of type I interferons.[54-58] Elevated type I interferon level within tumor immune microenvironment promotes immune surveillance by engaging and enhancing immune cell functions to exert antitumor activities.[59] The resulting immune-stimulating tumor microenvironment will adaptively induce PD-L1 expression to counteract antitumor immune responses which can be blocked by targeting PD-1/PD-L1 signaling. By suppressing the enzymatic activity of PARP1/2, PARP inhibitor impairs the base excision repair process, resulting in accumulation of DNA damages within the cells, which in turn may promote immune surveillance through elevation of interferon-α production.

The efficacy and tolerability of the combination of niraparib and anti-PD-1 inhibitor was evaluated in several preclinical models. The combination was well-tolerated in all of these studies. Given the lack of syngeneic model in homologous recombination deficient NSCLCs, the combination was first tested in a homologous recombination deficient ovarian cancer model derived from BRCA-null genetic background, where PARP inhibition has been shown to increase immune cell infiltration.[60,61] In this study, niraparib (50 mg/kg PO QD) and an anti-PD-1 antibody (5 mg/kg intravenously [IV] biweekly [BIW]) were administered either alone or in combination. The combination was well tolerated, with no treatment-related death. Almost all the tumors achieved complete regression upon niraparib, anti-PD-1 antibody, and the combination treatment in the study. Complete regression was first observed on treatment day 16, in 2 of 6, 1 of 6 and 4 of 6 mice from niraparib, anti-PD-1, or the combination group, respectively, suggesting that the therapeutic approach of combining niraparib with an anti-PD-1 agent may provide additional benefit for patients with homologous recombination deficient tumors (CrownBio BRKRAS, Study reference on file).

The combination of niraparib and PD-1 inhibitor was also evaluated in several syngeneic models representing BRCA1/2-wild type tumors, one of which was the breast cancer model LPA1-T22. In this study niraparib and an anti-PD-1 antibody were administered either alone or in combination for 15 days. While the tumors were slightly responsive to niraparib or anti-PD-1 antibody alone, with average tumor growth inhibition around 50% for niraparib and 30% for PD-1 antibody, synergistic antitumor activity with near complete tumor growth inhibition (> 95%) was achieved with the combination (G. Mills report, Study reference on file). In a similar study using 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-1antibody alone (30.5%) (Pharmaron KLN205, Study reference on file). Together, these data support the therapeutic approach of combining niraparib with an anti-PD-1 agent in either BRCA1/2-mutant or wild type tumors.

1.1.4.2. Clinical Experience Combining Niraparib and Pembrolizumab

TOPACIO (Study 3000-PN162-01-001) is an open-label, single-arm Phase 1/2 study evaluating the safety and efficacy of the combination of niraparib and pembrolizumab in patients with advanced triple-negative breast cancer or ovarian cancer. TOPACIO was initiated in April 2016 and is currently ongoing. In the Phase 1 portion of the study, 14 patients were enrolled in Dose

Level 1 (200 mg) or Dose Level 2 (300 mg). Based on Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, 4 of 8 patients with ovarian cancer responded, 3 of whom were gBRCA wild type; 4 patients with ovarian cancer had SD (range 3-6 cycles), and 1 patient with breast cancer had SD for 10 cycles. Dose limiting toxicity was myelosuppression (neutropenia, anemia and predominantly thrombocytopenia) consistent with the known adverse events (AEs) associated with single agent niraparib (Section 1.2.1). The recommended Phase 2 dose was determined as niraparib 200 mg PO daily and pembrolizumab 200 mg IV on day 1 of each 21-day cycle. This dose was implemented in the ongoing Phase 2 portion of the study.

As of January 2018, 60 of 62 patients in the recurrent ovarian cancer cohort were evaluable for response assessment with ≥ 1 on-study scan; the ORR was 25%, and the disease control rate (DCR) was 68%. Among the 11 tumor BRCA mutation evaluable patients, the ORR and DCR were 45% and 73%, respectively. The most common Grade ≥ 3 TEAEs were anemia (19%) and thrombocytopenia (9%). In the metastatic triple-negative breast cancer cohort, 45 patients were evaluable with ≥ 1 on-study scan; the ORR was 29%, and the DCR was 49%, including 3 (7%) patients with complete response (CR), 10 (22%) patients with PR, 9 (20%) patients with SD, and 23 (51%) patients with progressive disease (PD). Ten of 13 responders have ongoing responses. Results from the 12 patients with BRCA mutations included 1 CR, 7 PRs, 1 SD, and 3 PDs. Median PFS in the BRCA mutation group is 8.1 months. ORR in any BRCA status was 33% in PD-L1-postive patients (combined proportion score ≥ 1%) versus 15% in PD-L1-negative patients. Treatment-related Grade ≥ 3 AEs occurred in 27 patients (50%), most common were thrombocytopenia (13%) and anemia (11%). No new safety signals were identified with this combination in either of the 2 cohorts.

1.1.4.3. Clinical Experience Combining Niraparib and TSR-042 (Dostarlimab)

Study 3000-01-002 is a Phase 1b dose-finding study of niraparib, niraparib/bevacizumab, carboplatin/paclitaxel, or carboplatin-paclitaxel/bevacizumab in combination with TSR-042 (dostarlimab) in patients with advanced or metastatic cancer. The study was initiated on 12 October 2017 and is the first to assess TSR-042 (dostarlimab) and niraparib combination treatment. In Part A of this study, the objectives are to evaluate the DLTs of TSR-042 (dostarlimab) and niraparib combination treatment during the first cycle of treatment, to establish an RP2D of niraparib in combination with TSR-042 (dostarlimab), and to evaluate the safety and tolerability of TSR-042 (dostarlimab) and niraparib combination treatment. An initial cohort of 12 patients was enrolled at niraparib dose level 1 (200 mg), which has been determined to be safe. Niraparib dose level 2 (300 mg) is currently open for enrollment of an additional cohort of 6 to 12 patients. Study 3000-01-002 is currently ongoing, and no results have been made available yet.

1.2. Study Treatments

1.2.1. Niraparib

Niraparib is an orally available, potent, and highly selective PARP 1/2 inhibitor. The crystalline tosylate monohydrate salt of niraparib is being developed as a monotherapy agent for tumors with defects in the homologous recombination DNA repair pathway, as a sensitizing agent in combination with cytotoxic agents and radiotherapy, and in combination with immune-oncology

biologics. Zejula™ (niraparib) has been recently approved for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or PR to platinum-based chemotherapy. For more details, refer to Zejula United States Prescribing Information (USPI).[32]

Nonclinical data, including cell-derived and patient-derived xenograph studies demonstrating response to niraparib in both BRCA mutated and BRCA wild-type tumors, are discussed in detail in Section 1.1.2.1 and in the Investigator Brochure (IB).

There are 3 ongoing Phase 3 niraparib studies: Study PR-30-5010-C (BRAVO), Study PR-30-5017-C (PRIMA), and Study PR-30-5011-C (NOVA). There is also 1 ongoing Phase 1/2 study (Study 3000-PN162-01-001 [TOPACIO]) and 1 ongoing Phase 2 study (Study PR-30-5020-C [QUADRA]).

NOVA is a double-blind, placebo-controlled study in patients with platinum-sensitive ovarian cancer who have received at least 2 platinum-based regimens.[31] A total of 553 patients were categorized according to the presence or absence of a gBRCAmut (gBRCA cohort and non-gBRCA cohort) and the type of non-gBRCA mutation, and were randomly assigned in a 2:1 ratio to receive niraparib (300 mg) or placebo QD. The primary end point was PFS. The study enrolled 203 patients in the gBRCAmut cohort and 350 patients in the non-BRCAmut cohort. Among the 350 patients in the non-gBRCAmut cohort, 162 had tumors that were defined as HRD-positive (HRDpos) and 134 had tumors that were HRDneg. HRD status was not determined for 54 patients.

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

Table 3: Progression-Free Survival in Ovarian Cancer Patients in NOVA

	gBRCAmut cohort		**Non-gBRCAmut cohort (regardless of HRD status)**		**HRDpos (within non-gBRCAmut cohort)**	
	Niraparib (N=138)	**Placebo (N=65)**	**Niraparib (N=234)**	**Placebo (N=116)**	**Niraparib (N=106)**	**Placebo (N=56)**
PFS median (95% CI)	21.0 (12.9, NR)	5.5 (3.8, 7.2)	9.3 (7.2, 11.2)	3.9 (3.7, 5.5)	12.9 (8.1, 15.9)	3.8 (3.5, 5.7)
p-value	<0.0001		<0.0001		<0.0001	
Hazard ratio (Nir:Plac) (95% CI)	0.27 (0.173, 0.410)		0.45 (0.338, 0.607)		0.38 (0.243, 0.586)	

Abbreviations: CI = confidence interval; gBRCAmut = germline breast cancer gene mutation; HRD = homologous recombination deficiency; HRDpos = homologous recombination deficiency-positive; Nir = niraparib; NR = not reported; PFS = progression-free survival; Plac = placebo
PFS is defined as the time in months from the date of first dose to progression or death
Source: Zejula USPI.[32]

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

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

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

Myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) are potential adverse class effects associated with PARP inhibitors.[62] MDS and AML therefore represent a potential risk to patients receiving niraparib. In the Phase 3 NOVA study, the incidence of MDS/AML in patients who received niraparib (5 of 367; 1.4%) was similar to its incidence in patients who received placebo (2 of 179; 1.1%). Guidance on monitoring patients for new events of MDS/AML and the follow-up of patients with suspected MDS/AML is provided in Section 7.1.14 and Section 8.2.7.

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

1.2.2. Pembrolizumab

Pembrolizumab is a potent humanized IgG4 monoclonal antibody (mAb) with high specificity of binding to PD-1 receptor, thus inhibiting its interaction with PD-L1 and PD-L2 ligands. Based on preclinical *in vitro* data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1.

Pembrolizumab (KEYTRUDA) is in clinical development as an IV immunotherapy for numerous advanced malignancies. In NSCLC, pembrolizumab demonstrated a statistically significant improvement in PFS when compared to chemotherapy and has been approved as first-line treatment for metastatic NSCLC patients with no EGFR or ALK genomic tumor aberrations and whose tumors express high PD-L1 (TPS ≥ 50%).[6] Pembrolizumab is also indicated for patients with metastatic NSCLC with no EGFR or ALK genomic tumor aberrations, whose tumors express PD-L1 (TPS ≥ 1%) with disease progression on or after platinum-containing chemotherapy.[5,7]

The safety of pembrolizumab was determined in patients with advanced NSCLC who had documented disease progression following treatment with platinum-based chemotherapy. A total of 991 patients received pembrolizumab 2 mg/kg (n=339) or 10 mg/kg (n=343) every 3 weeks or docetaxel (n=309) at 75 mg/m^2 every 3 weeks. Adverse reactions leading to interruption of pembrolizumab occurred in 23% of patients; and the profile was similar for the 2 mg/kg and 10 mg/kg dose. The most common AEs were (≥1%) were diarrhea (1%), fatigue (1.3%), pneumonia (1%), liver enzyme elevation (1.2%), decreased appetite (1.3%), and pneumonitis (1%). Other clinically important adverse reactions were fatigue (25%), diarrhea (14%), asthenia (11%), and pyrexia (11%). For more details refer to KEYTRUDA USPI.

1.2.3. TSR-042 (Dostarlimab)

TSR-042 (dostarlimab) is an IgG4 humanized mAb that binds with high affinity to PD-1, resulting in inhibition of binding to PD-L1 and 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 TSR-042 (dostarlimab) was confirmed in a mixed lymphocyte reaction assay, demonstrating enhanced interleukin-2 (IL 2) production upon addition of TSR-042 (dostarlimab).

TSR-042 (dostarlimab) has shown an acceptable clinical and nonclinical safety profile. No signals have been identified in the clinical and nonclinical studies. A 1-month toxicity and TK study in cynomolgus monkeys showed no TSR-042 (dostarlimab)-related effects on any parameters evaluated, including neurological examinations, electrocardiography, blood pressure, and respiration.

As of 21 January 2018, a total of 186 patients have received at least 1 dose of TSR-042 (dostarlimab). Additional safety data are presented in the current TSR-042 (dostarlimab) IB.

1.3. Rationale for Current Study

Given that preclinical data suggest a possible synergistic interaction between immune checkpoint inhibitors and PARP inhibitors along with a potential overlap for PD-l- and PARP-sensitive patient populations, this study is designed to evaluate the combination of niraparib and a PD-1

inhibitor in a treatment-naïve NSCLC population with PD-L1 tumor expression (Cohorts 1, 1A, 2, and 2A).

Although substantial advances have been made in the management of nonsquamous NSCLC, an unmet need exists for effective treatment of sqNSCLC. Niraparib is being explored in this study as a potential treatment option for patients with sqNSCLC who previously achieved clinical benefit from platinum chemotherapy (Cohort 3).

2. STUDY OBJECTIVES AND PURPOSE

2.1. Primary Objectives

The primary objectives of this study are:

- To evaluate the efficacy of the combination of niraparib and a PD-1 inhibitor in chemotherapy-naïve and PD-1 inhibitor-naïve patients with locally advanced and metastatic NSCLC whose tumors have high PD-L1 expression (TPS ≥ 50%), as assessed by ORR
- To evaluate the efficacy of the combination of niraparib and a PD-1 inhibitor in chemotherapy-naïve and PD-1inhibitor-naïve patients with locally advanced and metastatic NSCLC whose tumors express PD-L1 (TPS between 1 and 49%) as assessed by ORR
- To evaluate the efficacy of single agent niraparib in patients with metastatic sqNSCLC who have been previously treated with both platinum-based chemotherapy and either PD-1 or PD-L1 inhibitor, as assessed by ORR

2.2. Secondary Objectives

The secondary objectives of the study are as follows:

- To evaluate the safety and tolerability of single agent niraparib and of the combination of niraparib and a PD-1 inhibitor
- To evaluate the following additional measures of clinical benefit of single agent niraparib and of the combination of niraparib and a PD-1 inhibitor:
  - Duration of response (DOR)
  - DCR
  - PFS
- To evaluate the pharmacokinetics (PK) of niraparib following administration of single agent niraparib or the combination of niraparib and a PD-1 inhibitor

2.3. Exploratory Objectives

- To explore blood and tumor-based biomarkers that predict sensitivity or resistance to single agent niraparib and to the combination of niraparib and a PD-1 inhibitor

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design and Plan

3.1.1. Overview

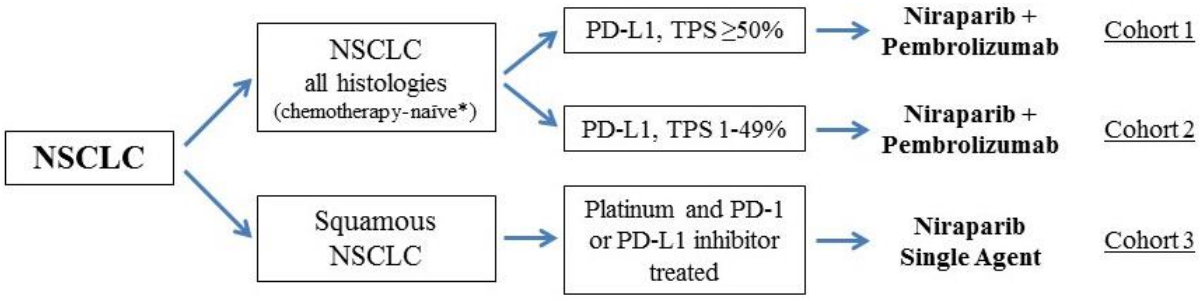
This is a multicenter, open-label, multi-arm Phase 2 study to evaluate the efficacy and safety of single agent niraparib in patients with locally advanced and metastatic sqNSCLC and of the combination of niraparib and a PD-1 inhibitor in locally advanced and metastatic NSCLC (all histologies) patients.

The multi-arm design will evaluate separate cohorts of different cancer patients with enough statistical power to determine whether further examination may be warranted in the individual indications. A 2-stage design will be used for all cohorts. In Stage 1, Cohorts 1 and 2 will receive niraparib plus the PD-1 inhibitor pembrolizumab, and Cohort 3 will receive niraparib alone. In Stage 2, Cohorts 1A and 2A will receive niraparib plus the PD-1 inhibitor TSR-042 (dostarlimab). (As of Amendment 2, following a cross-program review and decision to move forward with other studies, the Sponsor decided that Cohort 3 would close to further enrollment. As of Amendment 3, Cohort 1 and Cohort 2 had completed enrollment, Cohort 1A had closed after partial enrollment and Cohort 2A was not opened for enrollment. In Amendment 3, OS was removed as a secondary endpoint, following completion of the primary endpoint and Sponsor review of portfolio prioritization.) Enrollment in Stage 2 must not begin until the clinical study site has received the necessary approval of this amendment from the ethics committee of record for that site. Enrollment in Stage 2 will not be allowed under previous versions of the protocol.

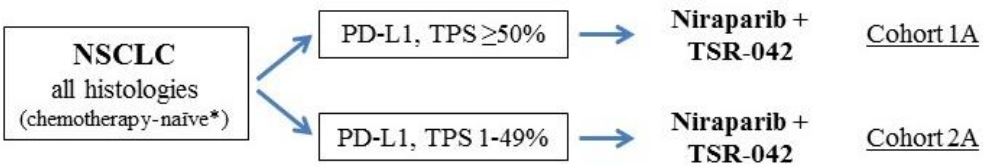
Figure 1 presents an overview of the study design. The schedule of events for the study is provided in Table 13 and Table 14.

Figure 1: Study Design

Stage 1:



Stage 2:



*Completion of treatment with chemotherapy and/or radiation as part of neoadjuvant/adjuvant therapy is allowed as long as therapy was completed at least 6 months prior to the diagnosis of metastatic disease

Abbreviations: NSCLC = non-small cell lung cancer; PD-1 = programmed cell death-1; PD-L1 = programmed death ligand-1; TPS = tumor progression score.

Cohorts 1 and 1A: Locally advanced and metastatic NSCLC patients (all histologies) with no prior systemic chemotherapy or PD-1/PD-L1 inhibitor treatment, whose tumors have high PD-L1 expression (TPS ≥ 50 %), and no known EGFR-sensitizing mutation and/or ROS-1 or ALK translocations will receive combination of niraparib and a PD-1 inhibitor (pembrolizumab or TSR-042 (dostarlimab)). *Completion of treatment with chemotherapy and/or radiation as part of neoadjuvant/adjuvant therapy is allowed as long as therapy was completed at least 6 months prior to the diagnosis of metastatic disease.*

Cohorts 2 and 2A: Locally advanced and metastatic NSCLC patients (all histologies) with no prior systemic chemotherapy or PD-1/PD-L1 inhibitor treatment, whose tumors have PD-L1 expression (TPS between 1 % and 49 %), and no known EGFR sensitizing mutation and/or ROS-1 or ALK translocation, will receive combination of niraparib and a PD-1 inhibitor (pembrolizumab or TSR-042 (dostarlimab)). *Completion of treatment with chemotherapy and/or radiation as part of neoadjuvant/adjuvant therapy is allowed as long as therapy was completed at least 6 months prior to the diagnosis of metastatic disease.*

Cohort 3: Locally advanced and metastatic sqNSCLC patients who have been previously treated with both platinum and either PD-1 or PD-L1 inhibitor will receive single agent niraparib.

Data from Stage 1 will be used to determine whether further enrollment of Stage 2 patients is necessary. The criteria for continuing Stage 2 enrollment are provided in Statistical Analysis Section 9.

3.1.2. General Study Conduct

This study will consist of a Screening Period (Day -21 to Day -1), a Treatment Period, an End of Treatment (EOT) Period occurring within 7 days of the decision to discontinue treatment for any reason, a Safety Follow-up Visit occurring 30 + 7 days after the last dose of study medication, and a Follow-up Assessment Period occurring every 90 ± 14 days, which will continue until death or the end of study data collection (a minimum of 6 months after the enrollment of the last patient, provided that this allows the opportunity for completion of all 90-day follow-up assessments).

Following informed consent, all patients will undergo screening procedures within 21 days prior to the first dose of study treatment to determine eligibility for study entry. Screening procedures include medical, surgical, cancer, smoking, and medication history; complete physical examination, including vital signs, height, and weight; Eastern Cooperative Oncology Group (ECOG) performance status; clinical laboratory assessments (complete blood count [CBC], serum chemistry, and urinalysis); pregnancy test for women of childbearing potential (a urine pregnancy test may be performed if the serum pregnancy result is not available before dosing); and electrocardiogram (ECG).

Patients must have a baseline tumor assessment by computed tomography (CT, preferred method) or magnetic resonance imaging (MRI, if clinically indicated) of the chest, abdomen, and other sites as clinically indicated, to determine extent of disease and confirm presence of measurable disease. If the patient has had appropriate imaging scans (eg, routine clinical

management) performed within 28 days prior to Cycle 1/Day 1, then the results of those scans may be used if they are of diagnostic quality. Subsequent postbaseline tumor assessments will be done in locations with tumor lesions identified at baseline only, unless clinically indicated. Response will be assessed as per RECIST v1.1 by the Investigator.

In Stage 1, patients will begin treatment with niraparib and pembrolizumab (Cohorts 1 and 2) or niraparib monotherapy (Cohort 3) on Cycle 1/Day 1. In Stage 2, patients will begin treatment with niraparib and TSR-042 (dostarlimab) (Cohorts 1A and 2A) on Cycle 1/Day 1. Patients enrolled during Stage 1 will continue with their original study treatment until discontinuation from treatment. Clinic visits will occur in each cycle (every 3 weeks ± 3 days). Additional on-treatment assessments will be conducted on Days 8 and 15 of Cycle 1 and on Day 1 of all subsequent cycles. Safety assessments conducted throughout the Treatment Period include symptom-directed physical examination, vital signs, ECOG performance status, clinical laboratory assessments (CBC, serum chemistry, and urinalysis) (Table 13 and Table 14).

For follow-up tumor assessments, CT/MRI scans will be performed every 9 weeks ± 7 days from the date of first dose until Week 72, and every 12 weeks ± 7 days thereafter for Cohorts 1, 1A, 2, and 2A. For sqNSCLC patients in Cohort 3, follow- up tumor assessment CT/MRI scans will be performed every 6 weeks ± 7 days from the date of first dose until Week 24, then every 9 weeks ± 7 days until Week 52 (12 months), and every 12 weeks ± 7 days until progression. The same modality (CT or MRI) should be used throughout the study for a given patient.

Per RECIST v1.1, 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 response but no later than 35 days after the response. The subsequent scan after the confirmatory scan should be obtained per original schedule (9 weeks ± 7 days from confirmatory scan for Cohorts 1, 1A, 2 and 2A, and 6 weeks ± 7 days from confirmatory scan for Cohort 3).

For Cohorts 1, 1A, 2, and 2A (a PD-1 inhibitor and niraparib), patients with radiologic evidence of PD who are clinically stable may continue treatment at the Investigator's discretion 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 radiologic progression if the patient is clinically stable (Section 7.3.1.2) *and* the Investigator deems that the patient is deriving clinical benefit. This allowance to continue treatment despite radiologic 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. Before making a decision to continue treatment after radiological progression, the Investigator will discuss with the patient that this is not considered standard in the treatment of cancer and will discuss alternative treatment options including available approved therapies and other clinical trials. The Investigator will document this discussion in the source documents.

For Cohort 3 (single agent niraparib), patients with radiologic evidence of PD should be discontinued from treatment.

Tumor assessment should occur according to study schedule regardless of whether study treatment is interrupted.

If a patient discontinues treatment for a reason other than progression, death, withdrawal of consent, or lost to follow-up, scans should continue at the specified intervals (ie, every 9 weeks for the first 72 weeks and every 12 weeks thereafter for Cohorts 1, 1A, 2, and 2A; every 6 weeks for the first 24 weeks, every 9 weeks until Week 52 [12 months], and then every 12 weeks until progression for Cohort 3) until radiological progression is confirmed or until the start of subsequent anticancer treatment.

Each patient will have an EOT assessment within 7 days of the decision to discontinue treatment for any reason, a Safety Follow-up Visit occurring 30 + 7 days after the last dose of study drug, and a Follow-up Assessment every 90 ± 14 days, which will continue until death or the end of study data collection (a minimum of 6 months after the enrollment of the last patient, provided that this allows the opportunity for completion of all 90-day follow-up assessments).

Blood samples will be collected prior to, during, and after treatment to evaluate PK of niraparib when given alone and in combination with a PD-1 inhibitor in accordance with Section 7.4 and Section 8.1. Plasma samples will be collected from patients receiving single agent niraparib (Cohort 3), and serum and plasma will be collected from patients treated with the combination of niraparib and pembrolizumab (Cohorts 1 and 2) or niraparib and TSR-042 (dostarlimab) (Cohorts 1A and 2A).

Blood samples for the analysis of tumor-related circulating biomarkers such as circulating tumor cells (CTC) will be collected at Cycle 1/Day 1 predose. Blood samples for the analysis of circulating tumor DNA (ctDNA) will be obtained at Screening, Cycle 2/Day 1 predose, as well as EOT.

PD-L1 status must be available for patients in Cohorts 1, 1A, 2, and 2A. Local assessment of PD-L1 is acceptable on either archival or fresh tissue (see Laboratory Manual for details on sample collection and management). PD-L1 status will be confirmed retrospectively in a central IHC laboratory using a Food and Drug Administration (FDA)-approved *in vitro* companion diagnostic indicated as an aid in identifying NSCLC patients for treatment with a PD-1 inhibitor.

An archival formalin fixed paraffin embedded (FFPE) tumor tissue is required for exploratory biomarker analysis and will be obtained during screening to confirm histology morphology, presence of tumor, and to conduct biomarker analysis. If archival tumor tissue is not available, a fresh biopsy is needed. Archival FFPE sample should be submitted within 30 days of patient's first dose. (*For Cohort 3 only*: if diagnosis was made by cytology and archival tissue is not available, patient will not need to provide tumor tissue).

All patients will undergo an EOT assessment within 7 days of the decision to discontinue treatment for any reason and a Safety Follow-up Visit occurring 30 + 7 days post-treatment. Thereafter, all patients will enter the post-Treatment Period for telephone assessment of survival status every 90 ± 14 days.

Treatment with niraparib will continue until disease progression. Treatment with a PD-1 inhibitor (pembrolizumab or TSR-042 (dostarlimab)) will continue for a maximum of 24 months in patients without disease progression or unacceptable toxicity.

All AEs will be collected and recorded for each patient from the day of signing the informed consent form (ICF) until 30 days after last study drug administration (Section 7.1.4); SAEs are required to be captured at least through 90 days after cessation of study treatment (or to a

minimum of 30 days post-treatment if the patient starts alternate anticancer therapy), and any pregnancies are to be captured through 180 days post-treatment (Section 7.1.6). Adverse events of special interest (AESIs), as well as study-drug-related SAEs, will be collected until study closeout or as otherwise indicated in Section 7.1.7 . AESIs must be reported as soon as the Investigator becomes aware of them. All AEs and SAEs experienced by a patient, irrespective of the suspected causality, will be monitored until the AE or SAE has resolved, until abnormal laboratory values have returned to baseline or normalized, until stabilized and there is a satisfactory explanation for the changes observed, until the patient is lost to follow-up, or until the patient has died.

4. SELECTION AND WITHDRAWAL OF SUBJECTS

4.1. Subject Inclusion Criteria

4.1.1. General Inclusion Criteria

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

1. At least 18 years of age
2. Histological or cytological proven advanced (unresectable) or metastatic NSCLC as defined as stage IIIB (positive supraclavicular lymph nodes) not amenable to definitive chemoradiotherapy or stage IV NSCLC
3. Measurable disease by RECIST v1.1
4. ECOG performance status of 0 to 1
5. Adequate organ function, defined as follows:

   Note: CBC test should be obtained without transfusion or receipt of colony-stimulating factors within 4 weeks prior to the first dose of study treatment.

   a. Absolute neutrophil count (ANC) ≥1,500/µL
   b. Platelets ≥100,000/µL
   c. Hemoglobin ≥9 g/dL or ≥5.6 mmol/L
   d. Serum creatinine ≤ 1.5× upper limit of normal (ULN) or creatinine clearance ≥50 mL/min (as calculated using the Cockcroft Gault equation or measured using 24-hour urine creatinine clearance) for patients with creatinine levels > 1.5 × institutional ULN (Appendix A)
   e. *Total* bilirubin ≤1.5 × ULN except in patients with Gilbert's syndrome. Patients with Gilbert's syndrome may enroll if direct bilirubin ≤1.5 × ULN of the *direct* bilirubin.
   f. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 × ULN unless liver metastases are present, in which case they must be ≤5 × ULN
6. Patient must have recovered to Grade 1 toxicity from prior cancer therapy (a patient with Grade 2 neuropathy or Grade 2 alopecia is an exception to this criterion and may qualify for this study).
7. Patient agrees to submit FFPE tumor tissue specimen, which may have been collected at any time prior to Screening. If no archival FFPE tumor tissue is available, patient agrees to undergo a tumor tissue biopsy before Cycle 1/Day 1. (*For Cohort 3 only*: if diagnosis was made by cytology and archival tissue is not available, patient will not need to provide tumor tissue).
8. Patient is able to take oral medications
9. Female 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 drug, and agrees to abstain from

activities that could result in pregnancy from enrollment through 180 days after the last dose of study treatment or is of nonchildbearing potential; or

Note: A urine pregnancy test may be performed if the serum pregnancy result is not available before dosing.

b. Female patient is of nonchildbearing potential, other than medical reasons, defined as follows:
   i. ≥45 years of age and has not had menses for >1 year
   ii. Amenorrheic for < 2 years without a hysterectomy and oophorectomy and a follicle-stimulating hormone (FSH) value in the postmenopausal range upon screening evaluation
   iii. Post hysterectomy, bilateral oophorectomy, or tubal ligation. Documented hysterectomy or oophorectomy must be confirmed with medical records of the actual procedure or confirmed by an ultrasound. Tubal ligation must be confirmed with medical records of the actual procedure; otherwise, the patient must be willing to use 2 highly effective contraception methods throughout the study, starting with the screening visit through 180 days after the last dose of study therapy. Please see Section 6.7.3 for a list of acceptable birth control methods. Information must be captured appropriately within the site's source documents

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

10. Male patient agrees to use an adequate method of contraception and not donate sperm starting with the first dose of study therapy through 120 days after the last dose of study therapy (please see Section 6.7.3 for a list of acceptable birth control methods). *Note: Abstinence is acceptable if this is the established and preferred contraception method for the patient.*
11. Patient is able to understand the study procedures and agree to participate in the study by providing written informed consent

4.1.2. Cohort-Specific Inclusion Criteria

1. *Cohorts 1 and 1A* (combination of niraparib and a PD-1 inhibitor): patients must have tumors with high PD-L1 expression (TPS ≥ 50%) per local assessment; with no known EGFR sensitizing mutation and/or ROS-1 or ALK translocations, and no prior systemic chemotherapy or PD-1/PD-L1 inhibitor treatment for metastatic NSCLC
2. *Cohorts 2 and 2A* (combination of niraparib and a PD-1 inhibitor): patients must have tumors with PD-L1 expression (TPS between 1% and 49%) per local assessment, with no known EGFR-sensitizing mutation and/or ROS-1 or ALK translocation, and no prior systemic chemotherapy or PD-1/PD-L1 inhibitor treatment for metastatic NSCLC
3. *Cohort 3* (single agent niraparib): patients must have metastatic sqNSCLC and have progressed after both prior platinum-based chemotherapy and prior PD-1 or PD-L1 inhibitor treatment

4.2. Subject Exclusion Criteria

4.2.1. Exclusion Criteria for Cohorts 1, 1A, 2, and 2A

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

1. Has received systemic therapy for the treatment of advanced stage NSCLC. Completion of treatment with chemotherapy and/or radiation as part of neoadjuvant/adjuvant therapy is allowed as long as therapy was completed at least 6 months prior to the diagnosis of metastatic disease
2. Prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent
3. Known hypersensitivity to the components of niraparib, pembrolizumab, TSR-042 (dostarlimab), or their excipients
4. Known EGFR (exon 19 and 21) mutations, ALK translocations, and/or ROS-1 translocations
5. Patient has a history or current condition (such as transfusion dependent anemia or thrombocytopenia), therapy, or laboratory abnormality that might confound the study results, or interfere with the patient's participation for the full duration of the study treatment.
6. Known diagnosis of immunodeficiency or receiving systemic steroid therapy (*except as allowed in exclusion criterion #9 below*) or any other form of immunosuppressive therapy within 7 days prior to the first dose of study treatment
7. Patient is immunocompromised, in the opinion of the Investigator (*Note: patients with splenectomy are allowed*)
8. Current participation in a treatment study or past participation in a study of an investigational agent within 4 weeks before the first dose of study treatment
9. 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 $\leq$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 SD for 28 days
10. Active autoimmune disease that 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

11. Major surgery within 3 weeks of starting the study or patient has not recovered from any effects of any major surgery
12. Other active concomitant malignancy that warrants systemic therapy
13. Poor medical risk due to a serious, uncontrolled medical disorder, nonmalignant systemic disease, or active, uncontrolled infection. Examples include, but are not limited to, uncontrolled ventricular arrhythmia, recent (within 90 days) myocardial infarction, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, uncontrolled hypertension, active uncontrolled coagulopathy, or any psychiatric disorder that prohibits obtaining informed consent
14. Known history of interstitial lung disease, drug-related pneumonitis, or radiation pneumonitis requiring steroid treatment
15. Patient is pregnant, breastfeeding, or expecting to conceive children while receiving study treatment and for 180 days (for pregnancy or conception) or 30 days (for breastfeeding) after the last dose of study treatment
16. Male patient is expecting to donate sperm or father children while receiving study drug or for 120 days after the last dose of study treatment
17. Known active hepatic disease (known hepatic cirrhosis, hepatitis B surface antigen-positive status, or suspected active hepatitis C infection)
18. Prior treatment with a known PARP inhibitor
19. Patient received a live vaccine within 30 days of planned start of study therapy
20. Known history of MDS or AML

4.2.2. Exclusion Criteria for Cohort 3

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

1. Platinum-treated patient who progressed while on or within less than 8 weeks from the last day of platinum administration
2. Known hypersensitivity to the components of niraparib or excipients
3. Patient has a history or current condition (such as transfusion dependent anemia or thrombocytopenia), therapy, or laboratory abnormality that might confound the study results, or interfere with the patient's participation for the full duration of the study treatment.
4. Known diagnosis of immunodeficiency or receiving systemic steroid therapy (*except as allowed in exclusion criterion #6 below*) or any other form of immunosuppressive therapy within 7 days prior to the first dose of study treatment
5. Current participation in a treatment study or past participation in a study of an investigational agent within 4 weeks before the first dose of study treatment
6. Symptomatic uncontrolled brain or leptomeningeal metastases. (To be considered "controlled," 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 SD for 28 days

7. Major surgery within 3 weeks of starting the study or patient has not recovered from any effects of any major surgery
8. Other active concomitant malignancy that warrants systemic therapy
9. Poor medical risk due to a serious, uncontrolled medical disorder, nonmalignant systemic disease, or active, uncontrolled infection. Examples include, but are not limited to, uncontrolled ventricular arrhythmia, recent (within 90 days) myocardial infarction, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, uncontrolled hypertension, active uncontrolled coagulopathy, or any psychiatric disorder that prohibits obtaining informed consent
10. Known history of interstitial lung disease, drug-related pneumonitis, or radiation pneumonitis requiring steroid treatment
11. Patient is pregnant, breastfeeding, or expecting to conceive children, while receiving study treatment and for 180 days (for pregnancy or conception) or 30 days (for breastfeeding) the last dose of study treatment
12. Male patient is expecting to donate sperm or father children while receiving study drug or for 120 days after the last dose of study treatment
13. Patient is immunocompromised, in the opinion of the Investigator (*Note: patients with splenectomy are allowed*)
14. Known active hepatic disease (known hepatic cirrhosis, hepatitis B surface antigen-positive status, or suspected active hepatitis C infection)
15. Prior treatment with a known PARP inhibitor
16. Known history of MDS or AML

4.3. Subject Withdrawal Criteria

4.3.1. Discontinuation from Treatment

Patients may be discontinued from study treatment at any time. Specific reasons for discontinuing all study treatments include the following:

- Unacceptable toxicity that cannot be managed by dose modification
- Disease progression per RECIST v1.1 (see Section 7.3.1)
- It is in the best interest of the patient as judged by the Investigator and/or Sponsor
- Severe noncompliance with the protocol as judged by the Investigator and/or Sponsor

- Withdrawal of consent

  Note: All reasonable efforts should be made to encourage patients to remain on study even if they withdraw from treatment.
- Patient becomes pregnant
- Sponsor decision to terminate study
- Death
- Confirmed CR in a patient who was treated for at least 24 weeks with study treatment and had at least 2 cycles of treatment beyond the date when the initial CR was declared

Details of required niraparib dose modifications, including interruptions, dose reductions, and permanent discontinuations, related to toxicity, are provided in Section 6.3.1.

Details of required pembrolizumab dose interruptions and permanent discontinuation related to toxicity are provided in Section 6.3.2.

Details of required TSR-042 (dostarlimab) dose modifications, including interruptions, dose reductions, and permanent discontinuations, related to toxicity, are provided in Section 6.3.3.

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

Patients who discontinue from all study treatments will continue to receive follow-up assessments (Table 13 and Table 14) as part of the study unless they are discontinued from the study (Section 4.3.2).

4.3.2. Discontinuation from the Study

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

- Withdrawal of consent by the patient, who is at any time free to discontinue their participation in the study
- Death from any cause
- Loss to follow-up
- Sponsor decision to terminate study

Patients who withdraw from study drug will be asked to continue the study visits and assessments as outlined in the schedule of procedures (Section 8, Table 13 and Table 14). If a patient is lost to follow-up, attempts should be made to contact the patient to determine the reason for discontinuation. For patients who are lost to follow-up, at least 3 documented attempts, including one via certified mail, should be made to contact the patient before considering the patient lost to follow-up.

4.3.3. Replacement of Patients

If a patient discontinues study treatment due to withdrawal of consent prior to the first assessment of disease (either scheduled radiological assessment at 9 [Cohorts 1, 1A, 2, and 2A] or 6 weeks [Cohort 3] post-treatment initiation), the patient may be replaced for the purposes of efficacy analysis after consultation between the Sponsor and Investigator. The analysis population will include all patients who received any study medication and did not withdraw consent prior to having at least 1 postbaseline tumor assessment.

4.4. Patient Identification and Randomization

4.4.1. Patient Identification

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

4.4.2. Randomization Scheme

Not applicable.

5. TREATMENT OF SUBJECTS

5.1. Description of Study Drug

Table 4: Investigational Product

	Investigational Product		
Product Name:	Niraparib	Pembrolizumab	TSR-042 (dostarlimab)
Dosage Form:	100 mg capsule	infusion	infusion
Unit Dose	2 capsules of 100 mg each (200 mg/day) Administered once daily 21-day cycle	200 mg infusion Administered over 30 minutes Day 1 of each 21-day cycle	500 mg or 1,000 mg infusion Administered over 30 minutes 500 mg: Day 1 of each 21-day cycle (Q3W) for the first 4 cycles 1,000 mg: Day 1 of every other 21-day cycle (Q6W) for the rest of treatment, beginning on Cycle 5
Route of Administration	PO	IV	IV
Physical Description	capsule	powder or solution	solution for intravenous infusion in single-use vial

Abbreviations: IV = intravenous; PO = oral; Q3W = every 3 weeks; Q6W = every 6 weeks

6. STUDY DRUG MATERIALS AND MANAGEMENT

6.1. Study Drug

6.1.1. Niraparib

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

6.1.2. Pembrolizumab

Pembrolizumab is a potent and highly selective humanized mAb of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Pembrolizumab for injection may be supplied as 50-mg lyophilized powder single-use vials or 100 mg/4 mL (25 mg/mL) solution in a single-dose vial.

6.1.3. TSR-042 (Dostarlimab)

TSR-042 (dostarlimab) 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. TSR-042 (dostarlimab) for IV infusion is supplied as a solution of 160 mg (20 mg/mL) or 500 mg (50 mg/mL) in a single-dose vial.

6.2. Administration

6.2.1. Niraparib

Niraparib will be supplied as 100-mg capsules and will be administered PO QD continuously starting on Cycle 1/Day 1. The starting dose of 2 capsules of 100-mg strength (200 mg/day) will be taken at each dose administration. Patients will be instructed to take their niraparib dose in the morning at approximately the same time each day, except for days when PK sampling will be performed. On these days, patients will be instructed to hold their niraparib dose until the pre-dose PK sample has been taken. Niraparib may be taken with or without food or water. Patients must swallow and not chew the capsules.

For those patients experiencing nausea and who are at Cycle 5 and beyond, bedtime administration may be a potential method for managing nausea. For those patients experiencing nausea who are not yet at Cycle 5, please seek approval from Medical Monitor to permit bedtime administration.

On days where a PD-1 inhibitor is administered (Cohorts 1, 1A, 2, and 2A), niraparib will be administered upon completion of PD-1 inhibitor infusion on Day 1 of each cycle.

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

6.2.2. Pembrolizumab

Pembrolizumab infusion will be administered before niraparib dose at the study site on Day 1 of each 21-day treatment cycle after all procedures and assessments have been completed as detailed in Table 13 and Table 14. Pembrolizumab may be administered up to 3 days before or after the scheduled Day 1 of each cycle after Cycle 1 due to administrative reasons.

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

Refer to USPI for specific instructions for the preparation of the pembrolizumab infusion and administration of the infusion solution.

6.2.3. TSR-042 (Dostarlimab)

TSR-042 (dostarlimab) 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 on Day 1 of every other cycle (Q6W) thereafter, beginning on Cycle 5 Day 1 (ie, Cycle 5, Cycle 7, Cycle 9, etc.).

TSR-042 (dostarlimab) will be administered after all procedures and assessments have been completed, unless otherwise indicated. TSR-042 (dostarlimab) may be administered up to 3 days before or after the scheduled Day 1 of each cycle after Cycle 1 due to administrative reasons.

TSR-042 (dostarlimab) 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, however, a window between - 5 minutes and + 15 minutes is permitted.

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

6.3. Dose Modification

Study treatment dosing interruptions are permitted in the case of medical/surgical events or logistical reasons not related to study therapy (eg, surgery, unrelated medical events, patient vacation, or holidays). Patients should be placed back on study therapy within 28 days of the scheduled interruption, unless otherwise discussed with the Sponsor.

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

6.3.1. Niraparib

Dose interruption of niraparib may be implemented at any time per the Investigator's judgment. See the following sections for permitted duration of interruption prior to required discontinuation from treatment.

Niraparib dose reduction will be allowed based on treatment side effects. Dose reductions to 1 capsule daily (100 mg) will be allowed (Table 5). No further dose reductions will be allowed.

The timing of efficacy or safety evaluations should not be affected by dose interruptions or reductions.

6.3.1.1. Niraparib Dose Modifications for Nonhematologic Toxicity

Treatment with niraparib must be interrupted for any treatment-related nonhematologic Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or 4 event unless it is deemed by the Investigator to be pembrolizumab-related Table 7), in which case treatment with niraparib may continue without interruption. If toxicity is appropriately resolved to Grade 1 or less within 28 days of interruption, the patient may restart treatment with niraparib with a dose level reduction according to Table 5 unless prophylaxis is considered feasible. If the event recurs at a similar or worse grade, treatment should be interrupted.

If the toxicity requiring dose interruption has not resolved to CTCAE Grade 1 or less during a maximum 4-week (28-day) dose interruption period, or the patient has already undergone a dose reduction (to a minimum dose of 100 mg QD), or both, the patient must permanently discontinue treatment with niraparib. Once the dose of niraparib has been reduced, any re-escalation must be discussed with the Sponsor. Note that treatment with pembrolizumab may continue if discontinuation criteria as outlined in Section 6.3.2 have not been met.

Table 5: Niraparib Dose Reductions for Nonhematologic Toxicity

Event	Dose
Nonhematalogic NCI CTCAE Grade ≥3 TEAE or SAE where treatment or prophylaxis is not considered feasible or TEAE persists despite treatment or prophylaxis.	Withhold niraparib for a maximum of 28 days or until resolution of TEAE. Resume niraparib at 100 mg QD
NCI CTCAE Grade ≥3 TEAE or SAE ≥ lasting more than 28 days while the patient is administered niraparib 100 mg QD	Discontinue niraparib
NCI CTCAE Grade ≥2 Posterior Reversible Encephalopathy Syndrome (PRES) (see Section 7.1.9)	Discontinue niraparib

Abbreviations:, NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; QD = once daily; PRES=Posterior Reversible Encephalopathy Syndrome; SAE = serious adverse event; TEAE = treatment emergent adverse event

6.3.1.2. Niraparib Dose Modifications for Hematologic Toxicity

The dose interruption/modification criteria for niraparib for hematologic toxicities will be based on blood counts and are outlined in Table 6.

Table 6: Management of Hematologic Toxicities

Laboratory Abnormality	Intervention
Weekly CBC is to be obtained for the first 4 weeks from the start of niraparib treatment, followed by assessment at least every 4 weeks for the first year. If niraparib requires a dosing hold or dose reduction, weekly CBC is to be performed for the 4 weeks following restart of niraparib. If patients have not recovered within 28 days or have persistent cytopenia following dose modification, further investigations including bone marrow analysis and blood sample for cytogenetics must be done in addition to monthly monitoring, and consideration given as to whether to discontinue niraparib treatment.	
Platelet count < 100,000/μL	Niraparib must be interrupted until platelet count is ≥ 100,000/μL with twice-weekly CBC monitored until recovery. After recovery, niraparib may then be resumed at same or reduced dose (Table 5); with monitoring of blood counts once weekly for 4 weeks. If nadir platelet count was <75,000/μL, resume niraparib at a reduced dose after recovery.
Second occurrence of platelet count < 100,000/μL	Niraparib must be interrupted until platelet count is ≥ 100,000/μL with twice-weekly CBCs monitored until recovery. Niraparib may then be resumed at a reduced dose (Table 5); after recovery, blood counts are monitored once weekly for 4 weeks to ensure the safety of the new dose level. (Dose not to be decreased below 100 mg daily). 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 once daily.
Platelet count < 25,000/μL	Niraparib must be interrupted until platelet count is ≥ 100,000/μL with twice-weekly CBCs monitored until recovery. Niraparib may then be resumed at a reduced dose (Table 5); after recovery, blood counts are monitored once weekly for 4 weeks to ensure the safety of the new dose level. 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 once daily.
Neutrophil < 1,000/μL	Niraparib must be interrupted until neutrophil counts are ≥ 1,500/μL with twice-weekly CBCs monitored until recovery. Niraparib may then be resumed at a reduced dose (Table 5); after recovery, blood counts once weekly for 4 weeks to ensure the safety of the new dose level. (Dose not to be decreased below 100 mg daily)
Hemoglobin ≤ 8 g/dL	Niraparib must be interrupted until hemoglobin is ≥ 9 g/dL with once- or twice-weekly CBCs monitored until recovery. Niraparib may then be resumed at a reduced dose (Table 5); after recovery, blood counts once weekly for 4 weeks to ensure the safety of the new dose level

Laboratory Abnormality	Intervention
Hematologic adverse reaction requiring transfusion	For patients with platelet count ≤ 10,000/µL, prophylactic platelet transfusion per guidelines should be considered. [60,61] If there are other risk factors such as coadministration of anticoagulation or antiplatelet drugs, consider interrupting these drugs and/or prophylactic transfusion at a higher platelet count. RBC transfusion is at the discretion of the Investigator Resume niraparib at a reduced dose (dose not to be decreased below 100 mg daily).
Confirmed diagnosis of MDS/AML	Permanently discontinue niraparib.

Abbreviations: AML=acute myeloid leukemia; CBC = complete blood count; MDS=myelodysplastic syndrome; RBC=red blood cell. Note: If blood counts do not recover within 28 days to normal values (ie, platelets ≥ 100,000/µL, hemoglobin ≥ 9g/dL, neutrophils ≥ 1,500/µL) niraparib should be discontinued.

If clinically indicated, use of granulocyte colony-stimulating factor (G-CSF) is allowed according to current American Society of Clinical Oncology (ASCO) guidelines.[63] If clinically indicated, red blood cell transfusions are allowed according to institutional guidelines.

If the hematologic toxicity does not recover to the specified level within 4 weeks (28 days) of dose interruption and/or the patient has already undergone 1 dose reduction (to a minimum dose of 100 mg QD), then niraparib should be discontinued.

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

Once the dose of study treatment has been reduced, any re-escalation must be discussed with the Sponsor's Medical Monitor or designee.

It is strongly recommended that the patient be referred to a hematologist for further evaluation (1) if transfusions are required on more than 1 occasion or (2) if the treatment-related hematologic toxicities have not recovered to CTCAE ≤ Grade 1 within 4 weeks. If a diagnosis of MDS/AML is confirmed by a hematologist, the patient must permanently discontinue niraparib.

Note that treatment with pembrolizumab may continue following discussion with the Sponsor's Medical Monitor or designee if discontinuation criteria as outlined in Section 6.3.2 have not been met.

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

6.3.1.3. Niraparib Dose Escalation

Niraparib dose may be escalated on or after Cycle 3/Day 1 from 200 mg daily (2 capsules) to 300 mg daily (3 capsules) if platelets ≥100,000/µL, hemoglobin ≥9 g/dL, and neutrophils ≥1,500/µL for all laboratory tests performed during the first 2 cycles after discussion with Medical Monitor or designee.

6.3.1.4. Niraparib Extended Treatment

Those patients deemed to derive clinical benefit from niraparib monotherapy treatment at the time of final analysis and who are no longer receiving their study-assigned PD-1 inhibitor will have the option to continue treatment with niraparib through the extension "rollover" protocol, if available, and at the discretion of the Investigator and Sponsor .

Eligibility to receive continued niraparib treatment through the extension "rollover" protocol will be at the discretion of the Investigator and Sponsor and will follow review of the enrolling study's inclusion criteria and completion of the required screening assessments. Continued treatment in the study will be based on documented evidence of clinical benefit determined by local standard of care disease assessment frequency.

6.3.2. Pembrolizumab

AEs (both nonserious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These AEs may occur shortly after the first dose or several months after the last dose of treatment. Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs per Table 7. See also Section 7.1.7.

Table 7 provides detailed information for dose interruptions and discontinuations related to toxicity for pembrolizumab. No dose reductions of pembrolizumab are permitted. Note that treatment with niraparib may continue following discussion with the Sponsor's Medical Monitor or designee if discontinuation criteria as outlined in Section 6.3.1 have not been met.

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

Table 7: Pembrolizumab Dose Modifications for Nonhematologic Toxicities

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

Table 7: Pembrolizumab Dose Modifications for Nonhematologic Toxicities (Continued)

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

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; T1DM = type 1 diabetes mellitus.
Note: Permanently discontinue for any severe or Grade 3 (Grade 2 for pneumonitis) drug-related AE that recurs or any life-threatening event.
[a] For patients with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by greater than or equal to 50% relative to baseline and lasts for at least 1 week then patients should be discontinued
[b] If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (eg, from 100 mL/h to 50 mL/h). Otherwise dosing will be held until symptoms resolve, and the subject should be premedicated for the next scheduled dose; refer to Section 6.7.4 Infusion Treatment Guidelines for further management details
[c] Patients with intolerable or persistent Grade 2 drug-related AE may hold study medication at physician discretion. Permanently discontinue study drug for persistent Grade 2 adverse reactions for which treatment with study drug has been held that do not recover to Grade 0-1 within 12 weeks of the last dose

6.3.3. TSR-042 (Dostarlimab)

AEs (both nonserious and serious) associated with TSR-042 (dostarlimab) 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, TSR-042 (dostarlimab) 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; TSR-042 (dostarlimab) will be permanently discontinued for any drug-related Grade 4 AE. TSR-042 (dostarlimab) must be permanently discontinued for certain irAEIs as described in Table 8. This guideline does not include a complete list of all irAEs associated with immune checkpoint inhibitor therapy. The recent joint ASCO and NCCN guideline for diagnosis and management of immune related adverse events treated with immune checkpoint inhibitor therapy may be used as a supplement to Table 8 and may be applied in association with local guidelines.[64]

The specific immune-related AEs typically observed with anti-PD-1 antibodies will be managed according to the guidelines summarized below.

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

Table 8: Guidelines for Treatment of Immune-related Adverse Events of Interest

Toxicity	Withhold Treatment for AE Grade	Restarting Treatment/Discontinuation
Diarrhea/colitis	2 or 3	Withhold dose. Restart dosing when toxicity resolves to Grade 0 or 1.
	4	Permanently discontinue.
AST, ALT, or increased bilirubin	2 (AST or ALT >3 and ≤5× ULN or total bilirubin >1.5 and ≤3× ULN)	Withhold dose Restart dosing when toxicity resolves to Grade 0 or 1.
	3 or 4 (AST or ALT >5× ULN or total bilirubin >3× ULN)	Withhold dose. Permanently discontinue (see exception below).[a]
T1DM or hyperglycemia	3 or 4 hyperglycemia or T1DM (associated with metabolic acidosis or ketonuria)	Withhold dose. Restart dosing in appropriately managed, clinically and metabolically stable patients; insulin replacement therapy is required.
Immune-related encephalitis	Any grade	Permanently discontinue.
Uveitis	Symptomatic any grade	Withhold dose. Restart the treatment when toxicity resolves to normal. For any recurrent uveitis or uveitis resistant to topical steroids, permanently discontinue treatment.

Toxicity	Withhold Treatment for AE Grade	Restarting Treatment/Discontinuation
Myositis	2 or 3	Withhold dose. Restart the treatment when toxicity resolves to Grade 1 or normal.
Hypophysitis	2 to 4	For Grade 2 to 3 AEs, withhold until hormonal therapy results in return to adequate levels by laboratory values and restart dosing when toxicity resolves to Grade 0 to 1. For recurrence or worsening of Grade ≥2 hypophysitis after corticosteroid taper has been completed and patient is on adequate hormone replacement therapy, permanently discontinue. For Grade 4 AEs, permanently discontinue.
Adrenal insufficiency	2 or 3	Withhold dose. Hold until hormonal therapy results in return to adequate levels by laboratory values and restart dosing when toxicity resolves to Grade 0 or 1. For recurrent or worsening ≥Grade 2 adrenal insufficiency while adequate hormonal replacement is continuing, permanently discontinue study drug.
	4	Permanently discontinue.
Hypo- and hyperthyroidism	3	Withhold dose until hormonal therapy results in return to adequate levels by laboratory values and restart dosing when toxicity resolves to Grade 0 or 1.
	4	Permanently discontinue.
Infusion-related reaction	2[b]	Withhold dose. Restart dosing when toxicity resolves to Grade 0 or 1.
	3 or 4	Permanently discontinue.
Pneumonitis	2	Withhold dose. Restart dosing when toxicity resolves to Grade 0 or 1. If Grade 2 recurs, permanently discontinue.
	3 or 4	Permanently discontinue.
Immune-related rash	3	Withhold dose. Restart dosing when toxicity resolves to Grade 0 or 1.
	4	Permanently discontinue.
Renal failure or nephritis	2	Withhold dose. Restart dosing when toxicity resolves to Grade 0 or 1.
	3 or 4	Permanently discontinue.
Recurrence of AEs after resolution to Grade ≤1	3 or 4	Permanently discontinue.

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; T1DM = type 1 diabetes mellitus; PO = orally; ULN = upper limit of normal.

[a] For patients 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 study treatment 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 to 50 mL/h). Otherwise, study treatment will be withheld until symptoms resolve, and the patient should be premedicated for the next scheduled dose with diphenhydramine 50 mg PO (or equivalent dose of antihistamine) and acetaminophen 500 to 1,000 mg PO (or equivalent dose of antipyretic) for the next

scheduled dose. Patients who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study treatment administration.

In addition to the irAEs listed in Table 8, treatment with dostarlimab may be associated with other irAEs, including events that may be less commonly associated with PD-1 or PD-L1 inhibitors but can similarly result from activation of cellular immune response (eg, 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.
- Withhold 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 1 mg/kg/day of prednisone or equivalent) must be administered.
- Withhold treatment 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 AEs 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.

6.4. Study Drug Packaging, Labeling, and Storage

Niraparib 100-mg capsules may be packed in high-density polyethylene bottles with child-resistant closures or in blister cards.

Pembrolizumab is obtained from commercial sources according to local practice standards, and it is provided as a commercially available dosage formulation. Pembrolizumab is an approved treatment for Cohort 1; it is expected that pembrolizumab will be supplied as standard of care for this cohort. Please refer to pembrolizumab USPI for instructions and precautions regarding preparation.

TSR-042 (dostarlimab) for injection is supplied in vials containing either 160 mg at a concentration of 20 mg/mL or 500 mg at a concentration of 50 mg/mL.

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 nonpatient-specific.

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

6.5. 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 should be maintained by each site based on capsules dispensed vs. returned to the clinic at each visit and the number days since 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 to reconcile the study treatment accountability log. The pharmacist will dispense study treatment for each patient according to the protocol and Pharmacy Manual, if applicable.

6.6. 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 on-site destruction, the Sponsor will provide a return for destruction service to a third party. Both the unused and expired study medication 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 drug provided for this study is to be used only as indicated in this protocol and only for the patients entered in this study.

6.7. Previous and Concomitant Medications

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

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

Niraparib weakly induces cytochrome P450 (CYP) 1A2 *in vitro* and is an insensitive substrate for P-glycoprotein; therefore, investigators should be advised to use caution with drugs that are sensitive substrates for CYP1A2 with a narrow therapeutic range, ie, theophylline and tizanidine.

The niraparib safety profile includes risk for thrombocytopenia; therefore, the Investigators should be advised to use caution with anticoagulation and antiplatelet drugs (Table 6).

6.7.1. Prohibited Medications

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

- Antineoplastic systemic chemotherapy or biological therapy
- Chemotherapy or immunotherapy not specified in this protocol
- Investigational agents other than niraparib, pembrolizumab, or TSR-042 (dostarlimab)
- Cohorts 1, 1A, 2, and 2A only: Live vaccines within 30 days prior to the first dose of study treatment and while participating in the study. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, Bacille Calmette-Guerin, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed. However, intranasal influenza vaccines (eg, Flu-Mist) are live attenuated vaccines and therefore are not allowed.
- Prophylactic cytokines (G-CSF) should not be administered in the first cycle of the study but may be administered in subsequent cycles according to current ASCO guidelines.[63]
- Systemic glucocorticoids for any purpose other than to manage symptoms of suspected irAEIs. (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 TSR-042 (dostarlimab).

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

6.7.2. Radiation Therapy

Radiation therapy to pre-existing small areas of painful metastases that cannot be managed with local or systemic analgesics is allowed as long as no evidence of disease progression is present. The patient must have clear measurable disease outside the radiated field.

6.7.3. Contraception

Pembrolizumab, TSR-042 (dostarlimab), and niraparib are known to have properties that require the patient to use contraception. For details on niraparib and TSR-042 (dostarlimab), please refer to the respective IBs.

The study drugs may have adverse effects on a fetus in utero. Furthermore, it is not known if pembrolizumab and niraparib have transient adverse effects on the composition of sperm. Therefore, nonpregnant, nonbreastfeeding women may only be enrolled if they are willing to use 2 highly effective contraception methods or are considered highly unlikely to conceive. Highly unlikely to conceive is defined as (1) surgically sterilized; (2) postmenopausal (a woman who is ≥ 45 years of age and has not had menses for > 1 year will be considered postmenopausal); (3) amenorrheic for < 2 years without a hysterectomy and oophorectomy and a follicle stimulating hormone (FSH) value in the postmenopausal range upon screening evaluation; or (4) not heterosexually active for the duration of the study. Female patients should start using birth control from screening throughout the study period up to 180 days after the last dose of study treatment (Table 9). See Appendix D for a list of acceptable contraceptive methods.

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

Male patients must use an adequate method of contraception and not donate sperm starting with the first dose of study treatment through 120 days after the last dose of study treatment (Table 9). Abstinence is acceptable if this is the established and preferred contraception for the patient.

Table 9: Timing of Contraception and Sperm Donation

Parameter	Timeframe
Contraception use, female patients	Starting with the screening visit through 180 days after the last dose of study treatment
Contraception use, male patients	Starting with the first dose of study treatment through 120 days after the last dose of study treatment
Sperm donation	Starting with the first dose of study treatment through 120 days after the last dose of study treatment

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

Patients should receive appropriate supportive care measures as deemed necessary by the treating Investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined below. Note that several courses of steroid tapering may be necessary, as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the Investigator determines the events to be related to pembrolizumab.

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

The following text details specific guidance by type of AE.

- **Pneumonitis:**
  - For Grade 2 events, treat with systemic corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

- For Grade 3 to 4 events, immediately treat with IV steroids. Administer additional anti-inflammatory measures, as needed.
- Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.

- **Diarrhea/Colitis:**
  - Patients should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, and with or without fever) and of bowel perforation (such as peritoneal signs and ileus).
    - All patients who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. For Grade 2 or higher diarrhea, consider gastrointestinal consultation and endoscopy to confirm or rule out colitis.
    - For Grade 2 diarrhea/colitis that persists greater than 3 days, administer oral corticosteroids.
    - For Grade 3 or 4 diarrhea/colitis that persists > 1 week, treat with IV steroids followed by high-dose oral steroids.
    - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- **Type 1 diabetes mellitus (if new onset, including diabetic ketoacidosis) or ≥ Grade 3 hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis:**
  - For Type 1 diabetes mellitus or Grade 3 to 4 hyperglycemia
    - Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3 to 4 hyperglycemia associated with metabolic acidosis or ketonuria.
    - Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.
- **Hypophysitis:**
  - For Grade 2 events, treat with corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
  - For Grade 3 to 4 events, treat with an initial dose of IV corticosteroids followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

- **Hyperthyroidism or hypothyroidism:**
  - Thyroid disorders can occur at any time during treatment. Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.
    - Grade 2 hyperthyroidism events (and Grade 2 to 4 hypothyroidism):
      - In hyperthyroidism, nonselective beta-blockers (eg, propranolol) are suggested as initial therapy.
      - In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyronine, is indicated per standard of care.
    - Grade 3 to 4 hyperthyroidism
      - Treat with an initial dose of IV corticosteroids followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
- **Hepatic:**
  - For Grade 2 events, monitor liver function tests more frequently until returned to baseline values (consider weekly).
    - Treat with IV or oral corticosteroids.
  - For Grade 3 to 4 events, treat with IV corticosteroids for 24 to 48 hours.
  - When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.
- **Renal failure or nephritis:**
  - For Grade 2 events, treat with corticosteroids.
  - For Grade 3 to 4 events, treat with systemic corticosteroids.
  - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- **Uveitis:**
  - Symptomatic (any grade): Hold treatment and consult ophthalmologist for treatment with corticosteroid eye drops. Restart dosing after resolution of symptoms.
  - Recurrent symptomatic uveitis or symptomatic uveitis unresponsive to topical corticosteroids: Permanently discontinue.
- **Management of infusion reactions**:

  Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Table 10

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

Table 10: Pembrolizumab Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the Investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 h	**Stop infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the Investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (eg, from 100 mL/h to 50 mL/h). Otherwise dosing will be held until symptoms resolve and the patient should be premedicated for the next scheduled dose. **Patients who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study treatment administration.**	Patient may be premedicated 1.5 hour (± 30 minutes) prior to infusion of pembrolizumab with: Diphenhydramine 50 mg PO (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg PO (or equivalent dose of antipyretic).
Grades 3 or 4 Grade 3: Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may be included but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the Investigator. Hospitalization may be indicated. **Patient is permanently discontinued from further study treatment administration.**	No subsequent dosing

Abbreviations: IV=intravenous; CTCAE = Common Terminology Criteria for Adverse Events; NCI = National Cancer Institute; NSAID = nonsteroidal anti-inflammatory; PO = oral.
Note: Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.

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

During treatment with TSR-042 (dostarlimab), 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. 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.[65] 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 ≤1 over ≥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 or Grade 3 or 4 Hyperglycemia

  - For type 1 diabetes mellitus 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.

6.7.5.1. 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 11 shows treatment guidelines for patients who experience infusion-related reactions associated with administration of TSR-042 (dostarlimab).

Table 11: TSR-042 (Dostarlimab) Infusion Reaction Treatment Guidelines

CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the Investigator.	None.
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, or IV fluids); prophylactic medications indicated for ≤24 hours	Stop infusion and monitor symptoms. Additional appropriate medical therapy may include but is not limited to: • IV fluids • Antihistamines • NSAIDs • Acetaminophen • Narcotics Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the Investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (eg, from 100 mL/h to 50 mL/h). Otherwise, dosing will be withheld until symptoms resolve, and the patient should be premedicated for the next scheduled dose. **Patients who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study treatment administration.**	Patient may be premedicated 1.5 hours (± 30 min) prior to infusion of TSR-042 (dostarlimab) with the following: • Diphenhydramine 50 mg PO (or equivalent dose of antihistamine) • Acetaminophen 500 to 1000 mg PO (or equivalent dose of antipyretic)

CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 3: Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates) **Grade 4:** Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to the following: • IV fluids • Antihistamines • NSAIDs • Acetaminophen • Narcotics • Oxygen • Pressors • Corticosteroids • Epinephrine Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the Investigator. Hospitalization may be indicated. **Patient is permanently discontinued from further study treatment administration.**	No subsequent dosing.

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; IV = intravenous; NSAID = nonsteroidal anti-inflammatory drug; PO = orally.
Note: Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of study treatment administration.

6.7.6. 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.

7. ENDPOINTS AND METHODS OF ASSESSMENT

7.1. Safety Endpoints

Safety parameters evaluated during this study will include AEs, discontinuations due to AEs, clinical laboratory values (CBC, serum chemistry, thyroid function [Cohorts 1, 1A, 2, and 2A only], and urinalysis), vital signs, ECGs, physical examination findings, and use of concomitant medications.

All safety parameters will be performed in accordance with the schedules of events presented in each cohort-specific supplement.

7.1.1. Definitions

7.1.1.1. Adverse event (AE)

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

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, including baseline or washout periods, even if no study treatment has been administered.

Disease progression will not be recorded as an AE.

7.1.1.2. Serious adverse event (SAE)

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

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

- Is a congenital anomaly or birth defect
- Is an important medical event(s)
  - 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 hospitalization but may jeopardize the patient or require intervention to prevent one of the above outcomes. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse. See Section 7.1.6.1 for information about SAE reporting.

7.1.1.3. Treatment-emergent adverse event

A TEAE is 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.

7.1.2. Suspected Unexpected Serious Adverse Reaction

A suspected unexpected serious adverse reaction is a serious adverse reaction, the nature and severity of which are not consistent with the information about the medicinal product set out in the Investigator's Brochure, Reference Safety Information section.

7.1.2.1. Adverse event of special interest

Any AE (serious or non-serious) 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 niraparib are MDS, AML, and second primary cancers (new malignancies other than MDS/AML).

To date, no AESIs have been identified for TSR-042 (dostarlimab).

7.1.2.2. 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.
- **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).

  See Section 7.1.12.1 for information about special situations reporting.

7.1.3. Assessment of Adverse Events

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

7.1.3.1. Expectedness

Expectedness (whether an AE is "expected" or "unexpected") will be determined by the Sponsor. 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 for niraparib and TSR-042 (dostarlimab) in the respective IBs and for pembrolizumab in the USPI.

7.1.3.2. Intensity

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

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated; easily tolerated
- Grade 2: Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADLs). (Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, or managing money.)
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL. (Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.)
- Grade 4: Life-threatening consequences; urgent intervention indicated
- Grade 5: Death related to AE

A distinction should be made between **serious** and **severe** AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria above in Section 7.1.1. For example, a mild degree of gastrointestinal bleeding requiring an overnight hospitalization for monitoring purposes may be considered an SAE but is not necessarily severe. Similarly, an AE that is severe in intensity is not necessarily an SAE. For example, alopecia may be assessed as severe in intensity but may not be considered an SAE.

7.1.3.3. Causality

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

- Definitely related: A clinical event, including laboratory test abnormality, that occurs in a plausible time relationship to treatment administration and that concurrent disease or other drugs or chemicals cannot explain. The response to withdrawal of the treatment should be clinically plausible.
- Possibly related: A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the treatment, unlikely to be attributed to concurrent disease or other drugs or chemicals.
- Unlikely related: A clinical event, including laboratory test abnormality, with a temporal relationship to treatment administration that makes a causal relationship improbable, or in which other drugs, chemicals or underlying disease provide likely explanations.
- Unrelated: A clinical event, including laboratory test abnormality, with little or no temporal relationship with treatment administration. Typically explained by extraneous factors (eg, concomitant disease, environmental factors, or other drugs or chemicals).

7.1.4. Collecting and Recording Adverse Events

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

All AEs, SAEs, and drug-related SAEs will be collected and recorded in the eCRF for each patient from the day of signed informed consent until the time points outlined in Table 12. All AEs and SAEs experienced by a patient, irrespective of the suspected causality, will be monitored until the AE or SAE has resolved, any abnormal laboratory values have returned to baseline or normal levels, until the event has stabilized and there is a satisfactory explanation for the changes observed, until the patient is lost to follow-up, or until the patient has died.

Table 12: Collecting and Reporting Adverse Events, Pregnancy, and Survival

Parameter	Timepoint
AEs	Through 30 days after cessation of study treatment
SAEs	Through 90 days after cessation of study treatment (or to a minimum of 30 days post-treatment if the patient starts alternate anticancer therapy)
Pregnancy	180 days following the last dose of study treatment (applies to female patients and female partners of male patients)
Drug-related SAEs	Until study closeout
AESIs	Until study closeout
Survival	Until study closeout

Abbreviations: AE = adverse event; SAE = serious adverse event; AESI = adverse event of special interest.
Note: Collection and reporting will begin on the day of informed consent.

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

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

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

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

7.1.5. Reporting Disease Progression

The event of disease progression is an efficacy criterion and is therefore not considered an AE. Disease progression should be reported within the eCRF. If AEs/SAEs occur in relation to disease progression, the AEs/SAEs must be reported per AE/SAE reporting requirements described in Section 7.1.4 and Section 7.1.6.

7.1.6. Serious Adverse Events

7.1.6.1. Reporting Serious Adverse Events

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. 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 document and describe pertinent information on the SAE Report Form. If supporting documentation is requested (eg, hospital reports, consultant reports, death certificates, and autopsy reports), the Investigator should highlight all relevant and pertinent information within such documents, ensure that any patient's personal identifiers (including medical record number) are removed, and submit the documents with the SAE Report Form to the Sponsor. The Sponsor (or designee) will return a confirmation of receipt of 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.

7.1.6.2. Submission and Distribution of Serious Adverse Events

Per regulatory requirements, if an event is assessed by the Sponsor as a suspected unexpected serious adverse reaction (SUSAR), it is the responsibility of the Sponsor to submit the SUSAR to regulatory authorities according to applicable regulations. In addition, the SUSAR will be distributed to the Investigators/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) as per the governing institutional requirements and in compliance with local laws and guidelines.

7.1.7. Adverse Events of Special Interest

Selected nonserious AEs and SAEs are also known as AESI and must be recorded as such on the eCRF and reported within 24 hours to the Sponsor as soon as the Investigator becomes aware of them, as noted for SAEs in Section 7.1.6.1.

In conjunction with the survival assessment, AESI (regardless of causality) and study-drug related SAEs will be collected until study closeout (Table 12, Section 7.1.4 and Section 8.2.6). AESIs for niraparib and pembrolizumab, are outlined in Section 7.1.7.1 and Section 7.1.7.2, respectively.

To date, no AESIs have been identified for TSR-042 (dostarlimab).

7.1.7.1. Niraparib

Patients are to be monitored from the day of informed consent as noted below:

- MDS and AML (through study closeout)

- Secondary primary cancers (new malignancies other than MDS/AML).

7.1.7.2. Pembrolizumab

Patients are to be monitored from the day of informed consent through study closeout for elevated AST or ALT value that is ≥ 3 × ULN concurrent with an elevated total bilirubin value that is ≥ 2 × ULN and, at the same time, an alkaline phosphatase value that is < 2 × ULN, as determined by protocol-specified laboratory testing or unscheduled laboratory testing.

Note: These criteria are based upon Hy's law and available regulatory guidance documents.[66] The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The study site guidance for assessment and follow-up of these criteria can be found in the Investigator Trial File Binder (or equivalent).

7.1.8. Hypertension, Including Hypertensive Crisis

Hypertension, including hypertensive crisis, has been reported with the use of niraparib. Preexisting 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.

BP 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.

7.1.9. 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 MRI. 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.

7.1.10. Allergic Reaction

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

7.1.11. Lifestyle Considerations

Cases of photosensitivity have been reported for patients on niraparib treatment. Participants must be informed on measures to decrease exposure to ultraviolet light, such as minimizing time in direct sunlight unless wearing hats and long-sleeves and application of sun protection creams.

7.1.12. Protocol-defined Overdose

A niraparib overdose is defined as 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.

An overdose of pembrolizumab is defined, for this study, as a dose ≥ 1,000 mg (5 times the dose). No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, the patient should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

For fixed doses, an overdose of TSR-042 (dostarlimab) is defined as any dose that is ≥ 20% than 1000 mg Q6W.

7.1.12.1. Reporting of Overdoses and Special Situations

All occurrences of abuse, misuse, medication error, overdose, and accidental or occupational exposure with 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.

7.1.13. Pregnancy Reporting and Follow-up

Pregnancies occurring in patients enrolled in a study or in a female partner of a male patient must be reported and followed to outcome. If a female patient inadvertently becomes pregnant while on study treatment, the patient will immediately be removed from the study. Any pregnancies of female study patients and partners of male study patient that occur within 180 days following the last dose of study treatment must be captured in the eCRF (Table 12).

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

The site will follow-up with the patient at least monthly and document the patient's status until the pregnancy has been completed or terminated. The Investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor. The Pregnancy Outcome report form should be completed and submitted to the Sponsor within 24 hours after the Investigator becomes aware of the pregnancy outcome. If an SAE occurred, then the SAE Report Form must be completed and submitted as well.

In the event the pregnancy outcome occurs following the end of the study and database lock, the Investigator will report the pregnancy outcome to the Sponsor (or designee) within 24 hours after the outcome of the pregnancy is known to the Investigator in accordance with the procedure for reporting SAEs (Section 7.1.6.1).

Pregnancy alone is not regarded as an AE unless there is a possibility that the study drug may have interfered with the effectiveness of a contraceptive medication. Elective abortions without

complications should not be considered AEs unless they were therapeutic abortions, but should be reported to the Sponsor. Hospitalization for normal delivery of a healthy newborn should not be considered an SAE. Pregnancy is not considered an SAE unless there is an associated serious outcome. Spontaneous abortions should always be reported as SAEs.

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

The Pregnancy Notification form, the Pregnancy Outcome form, and any related SAE Report Forms must be reported to the Sponsor as outlined for SAEs in Section 7.1.6.

7.1.14. Clinical Laboratory Assessments

The following laboratory variables will be determined in accordance with the schedule of events (Table 13 and Table 14). These tests will be performed by the local laboratory at the clinical site.

- **CBC:**
  - Hemoglobin
  - Mean corpuscular volume
  - White blood cell count
  - Platelets
  - Differential white cell count
- **Serum chemistry:**
  - Sodium
  - Potassium
  - Chloride
  - Creatinine
  - Urea or blood urea nitrogen
  - Glucose
  - Calcium
  - Phosphate
  - Magnesium
  - Total bilirubin
  - Alkaline phosphatase
  - Aspartate aminotransferase
  - Alanine aminotransferase
  - Total protein
  - Albumin
  - Amylase
  - Lactate dehydrogenase
- **Urinalysis:**
  - Specific gravity
  - Protein

  - Leukocyte esterase
  - Nitrite
  - Blood
  - Glucose
  - Ketones
  - Bilirubin

- **Thyroid-stimulating hormone** (TSH), **triiodothyronine** (T3), or **free triiodothyronine** (FT3), **and free thyroxine** (FT4) (*Applies only to Cohorts 1, 1A, 2, and 2A*)
- **Serum pregnancy testing** (a urine pregnancy test may be performed if the serum pregnancy result is not available before dosing)

Any laboratory values assessed as clinically significant should be recorded as an AE. If SAE criteria are met or the laboratory abnormality is an AESI (Section 7.1.7), the event should be recorded and reported according to the SAE reporting process (Section 7.1.6).

Hematological testing may occur more frequently than is specified in Table 13 and Table 14 when additional testing is medically indicated per Investigator judgment or if the event meets the criteria for niraparib dose modification (Section 6.3.1). Additional tests may be performed at a laboratory facility other than the study site, but test results must be reported to the study site, the study site must keep a copy of test results with the patient's study file, and the results must be entered into the eCRF.

It is strongly recommended that any suspected MDS/AML case reported while a patient is receiving treatment or followed for post-treatment assessments be referred to a local hematologist, who must perform bone marrow aspirate and biopsy testing. A whole blood sample will also be collected for cytogenetic analysis (mutations of select myeloid-associated genes). Testing completed as part of standard of care is sufficient as long as the methods are acceptable to the Sponsor's Medical Monitor or designee. The study site must receive a copy of the hematologist's report of aspirate/biopsy findings, which must include a classification according to World Health Organization (WHO)[67] 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. The hematologist's report should also be reported with the MDS/AML SAE Report Form and specialized questionnaire within 24 hours of becoming aware per Section 7.1.6.

Further details on sample collection and analysis can be found in the Laboratory Manual.

7.1.15. Physical Examination and Vital Signs

Physical examinations, including height (screening only), weight, and vital signs (blood pressure [BP], pulse, and temperature), will be performed in accordance with the schedule of events (Table 13 and Table 14).

Any physical examination or vital signs assessed as clinically significant should be recorded as an AE or SAE. If SAE criteria are met or the abnormality is an AESI (Section 7.1.7), the event should be recorded and reported according to the SAE reporting process (Section 7.1.6).

7.1.16. Eastern Cooperative Oncology Group Performance Status

Performance status will be assessed using the ECOG scale (see Appendix B) in accordance with the schedule of events (Table 13 and Table 14). The same observer should assess performance status each time.

7.1.17. Additional Safety Assessments

All patients will undergo ECGs in accordance with the schedule of events (Table 13 and Table 14). Patients will be supine and rested for approximately 2 minutes before ECGs are recorded.

Any ECG findings assessed as clinically significant should be recorded as an AE. If SAE criteria are met the event should be recorded and reported according to the SAE reporting process (Section 7.1.6).

7.2. Demographics and Baseline Characteristics

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

7.2.1. Patient Eligibility

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

7.2.2. Patient Demography

Patient demography consists of age at screening, race, ethnicity, smoking status (nonsmoker, former smoker, and current smoker), and sex.

7.2.3. Disease History

For disease history the following will be documented:

- Date of first diagnosis of lung cancer
- Histology at diagnosis and most recent biopsy if additional biopsy performed
- Date of first diagnosis of advanced (unresectable) or recurrent or metastatic disease
- Stage at enrollment
- EGFR mutation, BRAF mutation, KRAS mutation, ALK translocation, and ROS-1 translocation, if known
- Information on prior neoadjuvant/adjuvant treatment, if applicable:
  - Date of start of treatment
  - Agents used in treatment
  - Date of last dose of treatment

- Information on first anticancer treatment, if applicable:
  - Date of start of first treatment
  - Agents used in first treatment
  - Date of last dose of first treatment
- Information on second and subsequent anticancer treatments, if applicable:
  - Dates of start of all subsequent treatments
  - Agents in all subsequent treatments
  - Dates of last dose of all subsequent treatments
- Best response and toxicities (including hematologic events) for each prior anticancer treatment
- Date of recurrence for each prior anticancer treatment

7.2.4. Medical and Surgical History

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

7.2.5. Previous and Concomitant Medications and Procedures

Previous and concomitant medication will be documented as described in Section 6.7. Medications will be coded using the most up-to-date version of the WHO Anatomical Therapeutic Chemical classification.

All concomitant procedures (including transfusions) will be recorded from the time of the first dose of any study drug through the Safety Follow-up Visit (30 + 7 days after the last dose of study drug).

7.3. Clinical Activity Endpoints

7.3.1. Evaluation of Tumor Response

7.3.1.1. Overview

The efficacy of single agent niraparib as well as the combination treatment of niraparib and a PD-1 inhibitor will be evaluated by assessment of tumor response to treatment according to RECIST v1.1[68] per Investigator assessment (Appendix C).

Response to treatment will be based on Investigator evaluation of radiographic images. All radiographic images/scans at the time points specified in Table 13 and Table 14 as well as any unscheduled images/scans should be archived by the study sites for potential future evaluation.

Tumor imaging (chest, abdomen, and other sites as clinically indicated) should be performed by CT (preferred). MRI should only be used when CT is contraindicated and preferably for imaging

of the brain, but the same imaging technique should be used in a patient throughout the study. CT scan is the more commonly used modality and is preferred for the majority of patients. An MRI can be utilized if clinically appropriate. Positron emission tomography (PET)/CT may be used according to RECIST guidelines (Appendix C) and as clinically indicated.

7.3.1.2. Timing of Radiographic Evaluations

All patients will undergo serial radiographic evaluation to assess tumor response. Initial tumor imaging at screening must be performed within 21 days prior to the date of the first dose of study treatment. Scans performed prior to the signing of the ICF as part of routine clinical management are acceptable for use as initial tumor imaging if they are of diagnostic quality and performed within 28 days prior to first dose date.

For patients in Cohorts 1, 1A, 2, and 2A, the first on-study imaging tumor assessment should be performed 9 weeks (63 ± 7 days) after the first dose of study treatment. Subsequent tumor imaging will be performed every 9 weeks (63 ± 7 days) until Week 72, or more frequently if clinically indicated. After Week 72, patients should have imaging performed every 12 weeks (84 ± 7 days) until progression (Section 8).

For sqNSCLC patients in Cohort 3, the first on-study imaging tumor assessment should be performed 6 weeks (42 ± 7 days) after the first dose of study treatment. Subsequent tumor imaging will be performed every 6 weeks (42 ± 7 days) until Week 24 (6 months), or more frequently if clinically indicated. After Week 24, patients should have imaging performed every 9 weeks (63 ± 7 days) until Week 52 (12 months) and then every 12 weeks (84 ± 7 days) until progression (Section 8).

Imaging should not be delayed for delays in cycle starts or extension of combination treatment cycle intervals.

Per RECIST v1.1 (see Appendix C), CR or PR should be confirmed by a repeat tumor imaging assessment. The tumor imaging for confirmation of response must be performed at the earliest 28 days after the first indication of response but no later than 35 days after the response. The subsequent scan after the confirmatory scan should be obtained per original schedule (9 weeks ± 7 days from confirmatory scan for Cohorts 1, 1A, 2, and 2A, and 6 weeks ± 7 days from confirmatory scan for Cohort 3).

Continue to perform imaging until whichever of the following occurs:

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

For Cohorts 1, 1A, 2, and 2A: In patients who have initial evidence of radiological PD, it is at the discretion of the treating physician whether to continue a patient on study treatment. This clinical judgment decision should be based on the patient's overall clinical condition, including performance status, clinical symptoms, and laboratory data. Patients may receive study treatment if they are clinically stable as defined by the following criteria:

- Absence of symptoms and signs indicating clinically significant progression of disease (including worsening of laboratory values)

- No decline in ECOG performance status
- Absence of rapid progression of disease
- Progressive tumor at critical anatomical sites (eg, cord compression) requiring urgent alternative medical intervention

When feasible, patients should not be discontinued until progression is confirmed by repeat imaging. In addition, patients may continue to receive study treatment even after confirmed radiologic progression if all the above conditions continue to be met *and* the Investigator deems that the patient is deriving clinical benefit. This allowance to continue treatment despite radiologic progression takes into account the observation that some patients can have a transient tumor flare in the first few months after the start of immunotherapy but with subsequent disease response. Patients who are deemed clinically unstable are not required to have repeat imaging for confirmation of PD.

For Cohort 3 (single agent niraparib), patients with radiologic evidence of PD should be discontinued from treatment.

Patients who discontinue study treatment for reasons other than PD will continue post-treatment imaging studies for disease status follow-up at the same frequency as already followed, eg, every 6, 9 or 12 weeks ± 7 days depending on the length of treatment with the study combination drugs, until disease progression, start of a nonstudy anticancer treatment, withdrawal of consent to study participation, becoming lost to follow-up, death, or end of the study.

All radiographic images/scans should be archived for potential future evaluation.

7.3.1.3. Assessment of Response by RECIST

RECIST v1.1 will be used by the Investigator as the primary measure for assessment of tumor response, date of disease progression, and as a basis for all protocol guidelines related to disease status. Details on RECIST v1.1, including evaluation of target and nontarget lesions and definitions of response are provided in Appendix C.

7.3.2. Efficacy Endpoints

7.3.2.1. Objective Response Rate

The primary efficacy endpoint is ORR, defined as the proportion of patients with a confirmed best overall response of CR or PR in the analysis population. Tumor assessments after the initiation of further anticancer therapy are excluded for the assessment of best overall response.

7.3.2.2. Duration of Response

DOR will be evaluated as a secondary endpoint and is defined as the time from first documented CR or PR until the subsequently documented disease progression or death, whichever occurs earlier.

7.3.2.3. Disease Control Rate

DCR will be evaluated as a secondary endpoint and is defined as the proportion of patients with a best overall response of CR, PR or SD.

7.3.2.4. Progression-Free Survival

PFS will be assessed as a secondary endpoint and is defined as the time from the date of first dose to the date of disease progression or death due to any cause, whichever occurs earlier.

7.4. Pharmacokinetic Assessment

Pharmacokinetic samples will be collected from patients in all cohorts. An overview of blood sampling times for PK analysis is presented in Table 15 and Table 16.

7.4.1. Niraparib Concentrations

Blood samples for PK assessment of niraparib will be collected in Cycle 1/Day 1, Cycle 2/Day 1, Cycle 4/Day 1, and Cycle 8/Day 1 (or EOT if patient discontinues before Cycle 8) in all patients in Cohorts 1, 2, and 3. Blood samples for PK assessment of niraparib will be collected in Cycle 1/Day 1, Cycle 2/Day 1, Cycle 4/Day 1, and Cycle 9/Day 1 (or EOT if patient discontinues before Cycle 9) in all patients in Cohorts 1A and 2A.

The samples will be collected at predose (within 30 minutes prior to dosing of niraparib) and 4 hours ± 15 minutes post dosing of niraparib in all cohorts (Table 15).

In a subset of patients, who consent to additional PK blood draws, (N = 8) in each cohort, blood samples for PK assessment of niraparib will be collected on Cycle 1/Day 1 and Cycle 4/Day 1 at predose (within 30 minutes prior to dosing of niraparib) at 0.5 hour ± 5 minutes, 1 hour ± 10 minutes, 2 hours ± 15 minutes, 4 hours ± 15 minutes, 8 hours ± 1 hour, and 24 hours ± 3 hours postdosing of niraparib. For all these time points the exact collection time needs to be recorded (Table 16). Niraparib will be analyzed in plasma using liquid chromatography with mass spectroscopic detection. The timing of each required sample collection for niraparib for PK blood draws will be recorded.

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

7.4.2. Pembrolizumab Concentrations

Blood samples for PK assessment of pembrolizumab will be collected on Cycle 1/Day 1, Cycle 2/Day 1, Cycle 4/Day 1, and Cycle 8/Day 1 (or EOT if patient discontinues before Cycle 8) in all patients in Cohorts 1 and 2. The samples will be collected at predose (within 30 minutes prior to dosing of pembrolizumab) and 30 minutes (- 5, + 20 minutes) from the beginning of infusion (immediately following the end of infusion) (Table 15).

Blood samples for pembrolizumab will only be analyzed to understand an AE in an individual patient. The samples will be collected according to the specified schedule, stored, and analyzed as needed.

For pembrolizumab, serum PK samples in an individual patient may be analyzed using enzyme-linked immunosorbent assay (ELISA) if required for understanding of AEs. The timing of each required sample collection for pembrolizumab for PK blood draws will be recorded.

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

7.4.3. TSR-042 (Dostarlimab) Concentrations

Blood samples for PK assessment of TSR-042 (dostarlimab) will be collected on Cycle 1/Day 1, Cycle 2/Day 1, Cycle 4/Day 1, and Cycle 9/Day 1 (or EOT if patient discontinues before Cycle 9) in all patients in Cohorts 1A and 2A. The samples will be collected at predose (within 30 minutes prior to dosing of TSR-042 (dostarlimab)) and 30 minutes (- 5, + 20 minutes) from the beginning of infusion (immediately following the end of infusion) (Table 15).

For TSR-042 (dostarlimab), serum PK samples in an individual patient will be analyzed using ELISA. The timing of each required sample collection for TSR-042 (dostarlimab) for PK blood draws will be recorded.

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

7.4.4. Determination of Pharmacokinetic Parameters

7.4.4.1. Niraparib

In the subset of patients with intense PK sampling (N=8 per cohort), noncompartmental methods will be used to evaluate the PK characteristics of niraparib and, as appropriate. Pharmacokinetic parameters to be determined may include area under the concentration × time curve (AUC), AUC at steady state (AUC_{ss}), minimum concentration (C_{min}), maximum concentration (C_{max}), clearance after oral administration (CL/F), volume of distribution after oral administration (V_z/F), C_{min} at steady state ($C_{min,ss}$), and C_{max} at steady state ($C_{max,ss}$). Additional PK parameters may be estimated if deemed appropriate.

In patients where no intense sampling was performed, model predicted AUCs will be derived. Parameters of interest may include AUC, C_{min}, C_{max}, CL/F, V_z/F, AUC_{ss}, $C_{min,ss}$, and $C_{max,ss}$.

Plasma concentrations and PK parameter estimates will be presented using descriptive statistics by cohort.

7.4.4.2. Pembrolizumab

If samples are analyzed for pembrolizumab concentrations to understand an AE, the plasma concentrations will be summarized by cohort.

Model predicted AUCs may be derived. Parameters of interest may include AUC, C_{min}, C_{max}, CL, V_{ss} AUC_{ss}, $C_{min,ss}$, and $C_{max,ss}$.

7.4.4.3. TSR-042 (Dostarlimab)

The plasma concentrations for TSR-042 (dostarlimab) will be summarized by cohort. Model predicted AUCs may be derived. Parameters of interest may include AUC, C_{min}, C_{max}, CL, V_{ss}, AUC_{ss}, $C_{min,ss}$, and $C_{max,ss}$.

7.5. Biomarkers

7.5.1. Biomarker Sample Collection

The following patient samples are required for biomarker assessment:

1. Archival FFPE tumor tissue block, which may have been collected at any time prior to Screening, should be submitted to confirm histological morphology, presence of tumor, and to conduct biomarker analysis. A fresh biopsy is required if archival tumor tissue is not available. Open biopsies, punch biopsies, and core biopsies (3) are acceptable. Fine needle aspirate, frozen sample, plastic embedded sample, cell block, clot, and cytological specimen (with the exception of Cohort 3) are not acceptable for analysis. (*For Cohort 3 only*: if diagnosis was made by cytology and archival tissue is not available, patient will not need to provide tumor tissue.) The archival tumor tissue sample should be submitted within 30 days of the patient's first dose. If a replacement biopsy is required in lieu of an archival FFPE sample, then the biopsy should be performed prior to dosing (before Cycle 1 Day 1).
2. Blood samples for the analysis of tumor-related circulating biomarkers such as CTC will be collected at Cycle 1/Day 1 predose. Blood samples for the analysis of ctDNA will be obtained at Screening, Cycle 2/Day 1 predose, as well as EOT.

All samples will be collected and managed centrally when possible, and distributed either directly or subsequently to designated translational research laboratories for biomarker testing. Details on blood and tissue sample collection, processing, storage, shipping, and handling instructions can be found in the Laboratory Manual.

7.5.2. Biomarker Testing on Tumor Samples

PD-L1 status will be confirmed retrospectively in a central IHC laboratory using an FDA-approved *in vitro* companion diagnostic indicated as an aid in identifying NSCLC patients for treatment with a PD-1 inhibitor to confirm results from local testing. Additional markers for infiltrating immune cells may also be performed.

DNA may be extracted from tumor and analyzed for specific genomic aberrations (eg, BRCA1/2, ATM) that impair homologous recombination repair, other mechanisms of DNA damage repair (DDR), as well as other oncogenic lesions (eg, KRAS mutation). Homologous recombination deficiency (HRD) status may also be evaluated using algorithms based on overall genomic instability. Tumor mutation burden (TMB) may also be assessed.

RNA may be extracted and analyzed for gene expression signatures associated with sensitivity/ resistance to niraparib, PD-1 inhibitors (pembrolizumab or TSR-042 (dostarlimab)), or the combination.

Results from biomarker analyses will be correlated with efficacy outcomes.

Remaining tumor tissue samples and tumor derived samples such as DNA and RNA may be stored for potential future biomarker testing, including potential bridging to candidate companion diagnostic assays.

7.5.3. Biomarker Testing on Circulating Biomarkers in Blood

ctDNA may be extracted from plasma and analyzed for specific genomic aberrations (eg, BRCA1/2, ATM) that impair HRR, other mechanisms of DNA damage repair, as well as other oncogenic lesions.

CTCs may be stained by immunofluorescence and evaluated for HRD using algorithms based on cell morphology. Alternatively, they may be stained for other protein biomarkers or used for DNA extraction and sequencing.

Results from blood based biomarker analyses will be compared with corresponding analyses on tumor samples for concordance, whenever applicable. They may also be correlated with efficacy outcomes.

Remaining blood and/or blood derived samples such as plasma, ctDNA and CTC will be stored for potential future biomarker testing, including potential bridging to candidate companion diagnostic assays.

8. STUDY CONDUCT

8.1. Schedule of Procedures

A schedule of study procedures is provided in Table 13 and Table 14.

Table 13: Schedule of Events for Cohorts 1, 1A, 2, and 2A

Cycle/Visit	**Screening**	**Cycle 1**			**Subsequent Cycles**	**EOT**	**Safety Follow-Up**	**Follow-Up Assessment**
Day of Procedure	**-21 to -1**	**1**	**8**	**15**	**Cycle n, Day 1**		**30 + 7 days post-treatment**	**(every 90 ± 14 days)**
Informed consent	X							
Inclusion/exclusion criteria review	X	X						
Demographics	X							
Medical, surgical, cancer, smoking, and medication history	X							
Archival FFPE tumor tissue	X[1]							
Blood sample for ctDNA	X				X[2]	X		
Blood sample for CTC		X						
Blood sample for PK		X[3, 4]			X[3, 4]			
Tumor assessment	X[5]	First on-study imaging assessment should be performed 9 weeks (63 ± 7 days) after first dose. Subsequent tumor imaging will be performed every 9 weeks (63 ± 7 days) until Week 72 and every 12 weeks (84 ± 7 days) thereafter[6]				If patient discontinues treatment for a reason other than progression, death, withdrawal of consent, or loss to follow-up, imaging should continue every 9 weeks (63 ± 7 days) until Week 72 and every 12 weeks (84 ± 7 days) thereafter[6]		
Clinical laboratory assessments								
CBC	X	X[7]	X	X	X	X	X	X[8]
Serum chemistry	X	X[7]		X	X	X	X	X[8]
Pregnancy test[9]	X							
Urinalysis	X							
TSH, T3 or FT3, and FT4	X[10]				X[10]	X[10]	X[10]	

Table 13: Schedule of Events for Cohorts 1, 1A, 2, and Cohort 2A (Continued)

Cycle/Visit	Screening	Cycle 1			Subsequent Cycles	EOT	Safety Follow-Up	Follow-Up Assessment
Day of Procedure	**-21 to -1**	**1**	**8**	**15**	**Cycle n, Day 1**		**30 + 7 days post-treatment**	**(every 90 ± 14 days)**
ECG	X					X		
Physical examination	X					X		
Symptom-directed physical examination		X		X	X		X	
Vital signs and weight	X	X			X	X	X	
Height	X							
ECOG performance status	X	X			X	X		
Concomitant medications/procedures[11]		Recorded from first dose of study drug through Safety Follow-up						
AE monitoring[12]	X	X	X	X	X	X	X[13]	X[13]
Pembrolizumab treatment administered[14] **(Stage 1 only)**		X			X			
TSR-042 (dostarlimab) treatment administered **(Stage 2 only)**		X			X[15]			
Niraparib treatment dispensed/collected		X			X	X		
Survival/AESI (regardless of causality) and study-drug related SAEs (Telephone assessment allowed)								X[16]

Abbreviations: AE = adverse event; AESI = Adverse Event of Special Interest, CBC = complete blood count; CTC = circulating tumor cell; ctDNA = circulating tumor DNA; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; FFPE = formalin fixed paraffin embedded; FT3 = free triiodothyronine; FT4 = free thyroxine; ICF = informed consent form; PK = pharmacokinetics; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; T3 = triiodothyronine; TSH = thyroid-stimulating hormone.

[1] An archival FFPE tumor tissue specimen, which may have been collected at any time prior to Screening, should be submitted for exploratory biomarker analysis within 30 days of the patient's first dose. If no archival FFPE tumor tissue is available, a tumor tissue biopsy should be obtained before Cycle 1/Day 1.

[2] Required for Cycle 2/Day 1 only.

[3] Blood sample for niraparib and pembrolizumab PK will be collected on Cycle 1/Day 1, Cycle 2/Day 1, Cycle 4/Day1, and Cycle 8/ Day 1 (or EOT if patient discontinues before Cycle 8) in all patients in Cohorts 1 and 2. Blood samples for PK assessment of niraparib will be collected in Cycle 1/Day 1, Cycle 2/Day

1, Cycle 4/Day 1, and Cycle 9/Day 1 (or EOT if patient discontinues before Cycle 9) in all patients in Cohorts 1A and 2A. Blood sample for TSR-042 (dostarlimab) will be collected on Cycle 1/Day 1, Cycle 2/Day 1, Cycle 4/Day1, and Cycle 9/ Day 1 (or EOT if patient discontinues before Cycle 9). See Table 15 for detailed schedule.

[4] Intensive niraparib PK sampling will be collected only for a subset of patients (N = 8/cohort) in Cycle 1 and Cycle 4. See Section 8.3 and Table 16 for detailed schedule. Patients in this subset will be instructed to hold their niraparib dose, which will be taken in clinic on specified days for PK sampling.

[5] 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 are performed within 28 days prior to first dose date

[6] For details on tumor assessment per RECIST v1.1 see Section 7.3.1, Section 8.2, and Appendix C. All radiographic images/scans at the specified time points as well as any unscheduled images/scans should be archived by the study sites for potential future evaluation.

[7] If screening assessments were performed within 72 hours of Day 1, repeat testing is not required.

[8] CBC and serum chemistry at the Follow-up Assessment should be conducted only on Day 90 post-treatment to assess for possible AESI (Section 7.1.7).

[9] Serum pregnancy test for women of childbearing potential within 72 hours of first dose of study treatment. If the serum pregnancy result is not available before dosing, a urine pregnancy test may be performed.

[10] Blood samples for TSH, T3 or FT3, and FT4 are to be collected at screening, every 6 weeks from Cycle 1/Day 1, and at EOT. Blood samples for TSH, T3 or FT3, and FT4 should be collected at 30-day post-treatment Safety Follow-up only if assessment is clinically indicated.

[11] Any new anticancer treatment started during the study should also be collected.

[12] Collection of AEs begins when the ICF is signed.

[13] AEs are required to be captured through 30 days after cessation of study treatment (Section 7.1.4). However, SAEs are required to be captured through 90 days after cessation of study treatment (or to a minimum of 30 days post-treatment if the patient starts alternate anticancer therapy) (Section 7.1.6), and any pregnancies that occur within 180 days post-treatment are to be captured. AESIs should be collected until study closeout, regardless of causality (Section 7.1.7).

[14] Pembrolizumab should be administered once every 21 days (200 mg intravenous) on Day 1 of each cycle. Pembrolizumab may be administered up to 3 days before or after the scheduled Day 1 of each cycle after Cycle 1 due to administrative reasons. On days where pembrolizumab is administered, it should be administered before niraparib.

[15] TSR-042 (dostarlimab) will be administered at a dose of 500 mg on Day 1 every 3 weeks in Cycles 1 through 4, followed by 1,000 mg every other cycle (every 6 weeks) thereafter, beginning on Cycle 5 Day 1. On days where TSR-042 (dostarlimab) is administered, it should be administered before niraparib.

[16] Patients will be followed until study closeout for survival status, AESI (regardless of causality), and study-drug related SAEs (Section 7.1.7).

Table 14: Schedule of Events for Cohort 3

Cycle/Visit:	**Screening**	**Cycle 1**			**Subsequent Cycles**	**EOT**	**Safety Follow-Up**	**Follow-Up Assessment**
Day of Procedure	**-21 to -1**	**1**	**8**	**15**	**Cycle n, Day 1**		**30 + 7 days post-treatment**	**(every 90 ± 14 days)**
Informed consent	X							
Inclusion/exclusion criteria review	X	X						
Demographics	X							
Medical, surgical, cancer, smoking, and medication history	X							
Archival tumor tissue	X[1]							
Blood sample for ctDNA	X				X[2]	X		
Blood sample for CTC		X						
Blood sample for PK		X[3, 4]			X[3, 4]			
Tumor assessment	X[5]	First on-study imaging assessment should be performed 6 weeks (42 ± 7 days) after first dose. Subsequent tumor imaging will be performed every 6 weeks (42 ± 7 days) until Week 24 (6 months). After Week 24, tumor imaging will be performed every 9 weeks (63 ± 7 days) until Week 52 (12 months) and every 12 weeks (84 ± 7 days) thereafter[6]				If patient discontinues treatment for a reason other than progression, death, withdrawal of consent, or loss to follow-up, imaging should continue every 6 weeks (42 ± 7 days) until Week 24 (6 months), then every 9 weeks (63 ± 7 days) until Week 52 (12 months) and every 12 weeks (84 ± 7 days) thereafter[6]		
Clinical laboratory assessments								
CBC[15]	X	X[7]	X	X	X	X	X	X[8]
Serum chemistry	X	X[7]		X	X	X	X	X[8]

Table 14: Schedule of Events for Cohort 3 (Continued)

Cycle/Visit:	Screening	Cycle 1			Subsequent Cycles	EOT	Safety Follow-Up	Follow-Up Assessment
Day of Procedure	**-21 to -1**	**1**	**8**	**15**	**Cycle n, Day 1**		**30 + 7 days post-treatment**	**(every 90 ± 14 days)**
Pregnancy test[9]	X							
Urinalysis	X							
ECG	X					X		
Physical examination	X					X		
Symptom-directed physical examination		X		X	X		X	
Vital signs and weight[14]	X	X	X	X	X (weekly for 5 weeks)	X	X	
Height	X							
ECOG performance status	X	X			X	X		
Concomitant medications/procedures[10]		Recorded from first dose of study drug through Safety Follow-up						
AE monitoring[11]	X	X	X	X	X	X	X[12]	X[12]
Niraparib treatment dispensed/collected		X			X	X		
Survival/AESI (regardless of causality) and study-drug related SAEs (telephone assessment allowed)								X[13]

Abbreviations: AE = adverse event; AESI = Adverse Event of Special Interest; CBC = complete blood count; CTC = circulating tumor cell; DNA = deoxyribonucleic acid; ctDNA = circulating tumor DNA; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; FFPE = formalin fixed paraffin embedded; ICF = informed consent form; PK = pharmacokinetics; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event

[1] An archival FFPE tumor tissue specimen, which may have been collected at any time prior to Screening, should be submitted for exploratory biomarker analysis within 30 days of the patient's first dose. If diagnosis was made by cytology and archival FFPE tissue is not available, patient will not need to provide tumor tissue.

[2] Required for Cycle 2/Day 1 only.

[3] Blood sample for niraparib PK will be collected on Cycle 1/Day 1, Cycle 2/Day 1, Cycle 4/Day 1, and Cycle 8/Day 1 (or EOT if patient discontinues before Cycle 8). See Table 15 for detailed schedule.

[4] Intensive niraparib PK sampling will be collected only for a subset of patients (N = 8/cohort) on Cycle 1 and Cycle 4. See Section 8.3 and Table 16 for detailed schedule. Patients in this subset will be instructed to hold their niraparib dose, which will be taken in clinic on specified days for PK sampling.

[5] 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 are performed within 28 days prior to first dose date.

[6] For details on tumor assessment per RECIST v1.1 see Section 7.3.1, Section 8.2 and Appendix C. All radiographic images/scans at the specified time point as well as any unscheduled images/scans should be archived by the study sites for potential future evaluation.

[7] If screening assessments were performed within 72 hours of Day 1, repeat testing is not required.

[8] CBC and serum chemistry at the Follow-up Assessment should be conducted only on Day 90 post-treatment to assess for possible AESI (Section 7.1.7)

[9] Serum pregnancy test for women of childbearing potential within 72 hours of first dose of study treatment. If the serum pregnancy result is not available before dosing, a urine pregnancy test may be performed.

[10] Any new anticancer treatment started during the study should also be collected.

[11] Collection of AEs begins when the ICF is signed.

[12] AEs are required to be captured through 30 days after cessation of study treatment (Section 7.1.4). However, SAEs are required to be captured through 90 days after cessation of study treatment (or to a minimum of 30 days post-treatment if the patient starts alternate anticancer therapy) (Section 7.1.6), and any pregnancies that occur within 180 days post-treatment are to be captured. AESIs should be collected until study closeout, regardless of causality (Section 7.1.6).

[13] Patients will be followed until study closeout for survival status, AESI (regardless of causality), and study-drug related SAEs (Section 7.1.7).

[14] Vital signs include blood pressure (BP), pulse, heart rate, and temperature. BP and heart rate should be monitored at least weekly for the first 2 months of niraparib treatment, then monthly for the first year, and periodically thereafter.

[15] Weekly CBC is to be obtained for the first 4 weeks from the start of niraparib treatment, followed by assessment at least every 4 weeks for the first year. If niraparib requires a dosing hold or dose reduction, weekly CBC is to be performed for the 4 weeks following restart of niraparib. If patients have not recovered within 28 days or have persistent cytopenia following dose modification, further investigations including bone marrow analysis and blood sample for cytogenetics must be done in addition to monthly monitoring, and consideration given as to whether to discontinue niraparib treatment.

Table 15: Pharmacokinetic Sampling: All Cohorts

Day 1 in Cycles 1, 2, 4, and 8 or 9[1]			
Time Point	**Cohort 1/1A**	**Cohort 2/2A**	**Cohort 3**
Pre-pembrolizumab dose (within 30 min)	X	X	
Post-pembrolizumab dose (30 min [- 5, + 20 min])[2]	X[3]	X[3]	
Pre-TSR-042 (dostarlimab) dose (within 30 min)	X	X	
Post-TSR-042 (dostarlimab) dose (30 min [- 5, + 20 min])[2]	X[3]	X[3]	
Pre-niraparib dose (within 30 min)	X[3, 4]	X[3, 4]	X
Post-niraparib dose (4 h ± 15 min)	X	X	X

Abbreviations: h = hours; min = minutes.

[1] Cycle 8 for niraparib and pembrolizumab (Cycle 9 for niraparib and TSR-042 (dostarlimab)) or EOT if patient discontinues before Cycle 8 (Cycle 9 for niraparib and TSR-042 (dostarlimab))

[2] **From beginning of infusion**

[3] Post-pembrolizumab/TSR-042 (dostarlimab) dose and pre-niraparib dose can be the same blood draw.

[4] Niraparib will be administered upon completion of pembrolizumab or TSR-042 (dostarlimab) infusion (only Cohorts 1, 1A, 2, and 2A).

Table 16: Intensive Niraparib Pharmacokinetic Sampling: Subset of Patients in <u>All Cohorts</u>

	Cycle 1		Cycle 4	
Day of Procedure	**1**	**2**	**1**	**2**
Pre-niraparib dose[1]				
within 30 min	X		X	
Post-niraparib dose				
0.5 h (± 5 min)	X		X	
1 h (± 10 min)	X		X	
2 h (± 15 min)	X		X	
4 h (± 15 min)	X		X	
8 h (± 1h)	X		X	
24 h (± 3 h)		X		X

Abbreviations: h = hours; min = minutes; PD-1 = programmed cell death-1.
[1] Niraparib should be administered upon completion of PD-1 inhibitor infusion (applies only for Cohorts 1, 1A, 2, and 2A).

8.2. Procedures by Visit

Treatment cycles are 21 days long, with visits on Day 1, Day 8 and Day 15 of Cycle 1. Visits are on Day 1 of each subsequent cycle and continue every 21 ± 3 days until study treatment discontinuation.

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

Standard of care tests/procedures, including clinical laboratory assessments, ECG, physical examination, vital signs, height, and weight performed prior to the patient signing the ICF can be used as part of the screening assessments as long as the tests/procedures meet the protocol-required timelines (ie, within 21 days of first dose with the exception of the pregnancy test, which must be conducted within 72 hours of first dose and the scans, which can be performed within 28 days prior to Cycle 1/Day 1) and any relevant guidelines (eg, diagnostic quality for scans).

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.

8.2.1.1. Screening: Cohorts 1, 1A, 2, and 2A (Table 13)

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

- Obtain written informed consent
  - The study ICF will be signed before any study procedures are performed.
- Inclusion/exclusion criteria review
- Demographics
- Medical, surgical, cancer, smoking, and medication history
- Archival FFPE tumor tissue for confirmation of PD-L1 status and biomarker testing
  - For patients who do not have archival tissue, or adequate sample amount, tissue from a fresh biopsy must be obtained prior to study treatment initiation (first dose). Refer to the Laboratory Manual for details on sample collection, processing, shipping, storage, and handling.
- Blood sample collection for ctDNA
- Tumor assessment (CT/MRI) for determination of measurable disease (RECIST v1.1)
  - Chest, abdomen, and other sites as clinically indicated CT (preferred method) or MRI (if clinically indicated). PET/CT may be used according to RECIST v1.1 guidelines and as clinically indicated.
  - 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 are performed within 28 days prior to first dose date.

- Clinical laboratory assessments:
  - CBC
  - Serum chemistry
  - Serum pregnancy test for women of childbearing potential within 72 hours of first dose of study treatment

    Note: If the serum pregnancy result is not available before dosing, a urine pregnancy test may be performed.
  - Urinalysis
  - TSH, T3 or FT3, and FT4
- ECG
- Physical examination
- Vital signs (BP, pulse, and temperature) and weight
- Height
- ECOG performance status
- AE monitoring

8.2.1.2. Screening: Cohort 3 (Table 14)

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

- Obtain written informed consent
  - The study ICF will be signed before any study procedures are performed.
- Inclusion/exclusion criteria review
- Demographics
- Medical, surgical, cancer, smoking, and medication history
- Archival FFPE tumor tissue for biomarker testing
  - Tissue specimen may have been collected at any time prior to Screening
  - If diagnosis was made by cytology and archival tissue is not available, patient will not need to provide tumor tissue
- Blood sample collection for ctDNA.
- Tumor assessment (CT/MRI) for determination of measurable disease (RECIST v1.1)
  - Chest, abdomen, and other sites as clinically indicated CT (preferred method) or MRI (if clinically indicated). PET/CT may be used according to RECIST v1.1 guidelines and as clinically indicated.

  - 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 are performed within 28 days prior to first dose date.

- Clinical laboratory assessments:
  - CBC
  - Serum chemistry
  - Serum pregnancy test for women of childbearing potential within 72 hours of first dose of study treatment

    Note: If the serum pregnancy result is not available before dosing, a urine pregnancy test may be performed.
  - Urinalysis
- ECG
- Physical examination
- Vital signs (BP, pulse, and temperature) and weight
- Height
- ECOG performance status
- AE monitoring

8.2.2. Cycle 1

8.2.2.1. Cycle 1/Day 1: Cohorts 1, 1A, 2, and 2A (Table 13)

At Cycle 1/Day 1 the following procedures/tests will be performed:

- Inclusion/exclusion criteria review
- Blood samples for pembrolizumab or TSR-042 (dostarlimab) PK assessment
  - Blood samples will be obtained predose (within 30 minutes) and 30 minutes (- 5, + 20 minutes) from the beginning of infusion (immediately following the end of infusion) (Table 15).
- Blood samples for niraparib PK assessment after completion of pembrolizumab or TSR-042 (dostarlimab) infusion
  - Blood samples will be obtained pre-niraparib dose (within 30 minutes) and 4 hours (±15 minutes) postdose (Table 15)
- Blood sample collection for CTC
- Clinical laboratory assessments (if screening assessments were performed within 72 hours of Day 1, repeat testing is not required):
  - CBC

  - Serum chemistry
- Symptom-directed physical examination
- Vital signs (BP, pulse, and temperature) and weight
- ECOG performance status
- Concomitant medications and procedures will be recorded from first dose of the study drug through the Safety Follow-up Visit
  - Any new anticancer treatment started during the study should also be collected
- AE monitoring
- PD-1 inhibitor (pembrolizumab for Cohorts 1 and 2 and TSR-042 (dostarlimab) for Cohorts 1A and 2A) study treatment administered after other visit procedures are completed
- Niraparib first dose administered in clinic after completion of PD-1 inhibitor infusion

8.2.2.2. Cycle 1/Day 1: Cohort 3 (Table 14)

At Cycle 1 1/Day the following procedures/tests will be performed:

- Inclusion/exclusion criteria review
- Blood samples for niraparib PK assessment
  - Blood samples will be obtained predose (within 30 minutes) and 4 hours (±15 minutes) postdose
- Blood sample collection for CTC
- Clinical laboratory assessments (if screening assessments were performed within 72 hours of Day 1, repeat testing is not required):
  - CBC
  - Serum chemistry
- Symptom-directed physical examination
- Vital signs (BP, pulse, and temperature) and weight
- ECOG performance status
- Concomitant medications and procedures will be recorded from first dose of the study drug through Safety Follow-up
  - Any new anticancer treatment started during the study should also be collected
- AE monitoring
- Niraparib first dose administered in clinic

8.2.2.3. Cycle 1/Day 8: All Cohorts (Table 13 and Table 14)

At Cycle 1/Day 8 the following procedures/tests will be performed:

- Laboratory assessment:
  - CBC
- Concomitant medications and procedures
  - Any new anticancer treatment started during the study should also be collected
- AE monitoring

8.2.2.4. Cycle 1/Day 15: Cohorts 1, 1A, 2, and 2A (Table 13)

At Cycle 1/Day 15 the following procedures/tests will be performed:

- Clinical laboratory assessments:
  - CBC
  - Serum chemistry
- Symptom-directed physical examination
- Concomitant medications and procedures
  - Any new anticancer treatment started during the study should also be collected
- AE monitoring

8.2.2.5. Cycle 1/Day 15: Cohort 3 (Table 14)

At Cycle 1/Day 15 the following procedures/tests will be performed:

- Clinical laboratory assessments:
  - CBC
  - Serum chemistry
- Symptom-directed physical examination
- Concomitant medications and procedures
  - Any new anticancer treatment started during the study should also be collected
- AE monitoring

8.2.3. Subsequent Cycles

8.2.3.1. Cohorts 1, 1A, 2, and 2A (Table 13)

8.2.3.1.1. Day 1 (Table 13)

- Blood sample collection predose for ctDNA **only on Cycle 2/Day 1**

- Blood samples for pembrolizumab PK assessment **on Cycles 2, 4, and 8 only and for TSR-042 (dostarlimab) on Cycles 2, 4, and 9 only**
  - Blood samples will be obtained predose (within 30 minutes) and 30 minutes (- 5, + 20 minutes) from the beginning of the pembrolizumab/TSR-042 (dostarlimab) infusion (immediately following the end of the infusion) (Table 15).
- Blood samples for niraparib PK assessment after completion of PD-1 inhibitor infusion **on Cycles 2, 4 and 8 only** in all patients in Cohorts 1 and 2, and **on Cycles 2, 4, and 9 only** in all patients in Cohorts 1A and 2A
  - Blood samples will be obtained pre-niraparib dose (within 30 minutes) and 4 hours (±15 minutes) postdose (Table 15).
- Clinical laboratory assessments: may be done within 24 hours prior to the visit
  - CBC
  - Serum chemistry
  - TSH, T3 or FT3, and FT4 (should be done every 6 weeks from Cycle 1/Day 1)
- Symptom-directed physical examination
- Vital signs (BP, pulse, and temperature) and weight
- ECOG performance status
- Concomitant medications and procedures
  - Any new anticancer treatment started during the study should also be collected
- AE monitoring
- For Cohorts 1 and 2: Pembrolizumab study treatment administered after other visit procedures are completed. (Pembrolizumab may be administered up to 3 days before or after the scheduled Day 1 of each cycle after Cycle 1 due to administrative reasons).
- For Cohorts 1A and 2A: TSR-042 (dostarlimab) study treatment administered after other visit procedures are completed. (TSR-042 (dostarlimab) will be administered at a dose of 500 mg on Day 1 Q3W for 4 cycles, followed by 1,000 mg on Day 1 of every other cycle (Q6W) beginning on Cycle 5 Day 1.)
- Niraparib dose administered in clinic after completion of PD-1 inhibitor infusion

8.2.3.1.2. Tumor Assessment (RECIST v1.1) (Table 13)

- Conduct radiographic evaluations of chest, abdomen, and other sites as clinically indicated
- The first on-study imaging assessment should be performed at 9 weeks (63 ± 7 days) from the date of first dose of study treatment.

- In the case of PD, a confirmatory image will be required 4 weeks later (eg, 13 weeks [91 ±7 days]) (Section 7.3.1.2).
- Patients with CR or PR must have the response confirmed by a repeat tumor imaging assessment performed at the earliest 28 days after the first indication of response but no later than 35 days after the response. The subsequent scan after the confirmatory scan should be obtained per original schedule (9 weeks ± 7 days from confirmatory scan).
- Subsequent tumor imaging will be performed every 9 weeks (63 ± 7 days) until Week 72, or more frequently if clinically indicated.
- After Week 72 (18 months of radiographic assessments), patients should have imaging performed every 12 weeks (84 ± 7 days) until progression.
- Delays in cycle starts or extension of combination treatment cycle intervals should not modify imaging schedule.
- The same modality (ie, CT or MRI) should be used for a given patient throughout the study. PET/CT may be used according to RECIST v1.1 guidelines and as clinically indicated.

8.2.3.2. Cohort 3 (Table 14)

8.2.3.2.1. Day 1 (Table 14)

- Blood sample collection predose for ctDNA **only on Cycle 2/Day 1**
- Blood samples for niraparib PK assessment **on Cycles 2, 4, and 8 only**
  - Blood samples will be obtained pre-niraparib dose (within 30 minutes) and 4 hours (±15 minutes) postdose (Table 15)
- Clinical laboratory assessments: may be done within 24 hours prior to the visit
  - CBC
  - Serum chemistry
- Symptom-directed physical examination
- Vital signs (BP, pulse, and temperature) and weight
- ECOG performance status
- Concomitant medications and procedures
  - Any new anticancer treatment started during the study should also be collected
- AE monitoring
- Niraparib dose administered in clinic

8.2.3.2.2. Tumor Assessment (RECIST v1.1) (Table 14)

- Conduct radiographic evaluations of chest, abdomen, and other sites as clinically indicated
- The first on-study imaging assessment should be performed at 6 weeks (42 ± 7 days) from the date of first dose of study treatment.
- In the case of PD, a confirmatory image will be required 4 weeks later (eg, 10 weeks [70 ±7 days]) (Section 7.3.1.2).
- Patients with CR or PR must have the response confirmed by a repeat tumor imaging assessment performed at the earliest 28 days after the first indication of response but no later than 35 days after the response. The subsequent scan after the confirmatory scan should be obtained per original schedule (6 weeks ± 7 days from confirmatory scan).
- Subsequent tumor imaging will be performed every 6 weeks (42 ± 7 days) until Week 24, or more frequently if clinically indicated.
- After Week 24 (6 months of radiographic assessments), patients should have imaging performed every 9 weeks (63 ± 7 days) until Week 52 (12 months).
- After the first year, tumor imaging will be performed every 12 weeks (84 ± 7 days) until progression.
- Delays in cycle starts or extension of combination treatment cycle intervals should not modify imaging schedule.
- The same modality (ie, CT or MRI) should be used for a given patient throughout the study. PET/CT may be used according to RECIST v1.1 guidelines and as clinically indicated.

8.2.4. End of Treatment (Within 7 Days of Last Dose)

8.2.4.1. End of Treatment: Cohorts 1, 1A, 2, and 2A (Table 13)

- Blood sample collection for ctDNA
- Tumor assessment (RECIST v1.1)
  - A final set of radiographic images is required at the time of disease progression, if not done within the last 4 weeks.
  - If a patient discontinues treatment for a reason other than progression, death, withdrawal of consent, or loss to follow-up, radiographic scans/images should continue every 9 weeks (63 ± 7 days) until Week 72 (18 months) and every 12 weeks (84 ±7 days) thereafter.
- Clinical laboratory assessments:
  - CBC
  - Serum chemistry

  - TSH, T3 or FT3, and FT4
- ECG
- Physical examination
- Vital signs (BP, pulse, and temperature) and weight
- ECOG performance status
- Concomitant medications and procedures
  - Any new anticancer treatment started during the study should also be collected
- AE monitoring
- Niraparib study treatment collected

8.2.4.2. End of Treatment: **Cohort 3** (Table 14)

- Blood sample collection for ctDNA
- Tumor assessment (RECIST v1.1)
  - A final set of radiographic images is required at the time of disease progression, if not done within the last 4 weeks.
  - If a patient discontinues treatment for a reason other than progression or death, withdrawal of consent, or loss to follow-up radiographic scans/images should continue every 6 weeks (42 ±7 days) until Week 24 (6 months), then every 9 weeks (63 ± 7 days) until Week 52 (12 months), and every 12 weeks (84 ±7 days) thereafter.
- Clinical laboratory assessments:
  - CBC
  - Serum chemistry
- ECG
- Physical examination
- Vital signs (BP, pulse, and temperature) and weight
- ECOG performance status
- Concomitant medications and procedures
  - Any new anticancer treatment started during the study should also be collected
- AE monitoring
- Niraparib study treatment collected

8.2.5. Safety Follow-Up Visit (30 + 7 days Post-treatment):

8.2.5.1. Cohorts 1, 1A, 2, and 2A (Table 13)

- Tumor assessment (RECIST v1.1)
  - If a patient discontinues treatment for a reason other than progression or death, withdrawal of consent, or loss to follow-up, radiographic scans/images should continue every 9 weeks (63 ± 7 days) until Week 72 (18 months) and every 12 weeks (84 ± 7 days) thereafter.
- Clinical laboratory assessments:
  - CBC
  - Serum chemistry
  - TSH, T3 or FT3, and FT4 only if clinically indicated
- Symptom-directed physical examination
- Vital signs (BP, pulse, and temperature) and weight
- Concomitant medications and procedures
  - Any new anticancer treatment started during the study should also be collected.
- AE monitoring
  - AEs are required to be captured through 30 days after cessation of study treatment (Section 7.1.4)
  - SAEs are required to be captured through 90 days after cessation of study treatment (or to a minimum of 30 days post-treatment if the patient starts alternate anticancer therapy), and any pregnancies that occur within 180 days post-treatment are to be captured (Section 7.1.6)

8.2.5.2. Cohort 3 (Table 14)

- Tumor assessment (RECIST v1.1)
  - If a patient discontinues treatment for a reason other than progression or death, withdrawal of consent, or loss to follow-up, radiographic scans/images should continue every 6 weeks (42 ± 7 days) until Week 24 (6 months), then every 9 weeks (63 ± 7 days) until Week 52 (12 months), and every 12 weeks (84 ±7 days) thereafter.
- Clinical laboratory assessments:
  - CBC
  - Serum chemistry
- Symptom-directed physical examination
- Vital signs (BP, pulse, and temperature) and weight

- Concomitant medications and procedures
  - Any new anticancer treatment started during the study should also be collected.
- AE monitoring
  - AEs are required to be captured through 30 days after cessation of study treatment (Section 7.1.4)
  - SAEs are required to be captured through 90 days after cessation of study treatment (or to a minimum of 30 days post-treatment if the patient starts alternate anticancer therapy), and any pregnancies that occur within 180 days post-treatment are to be captured (Section 7.1.6)

8.2.6. Follow-Up Assessments (Every 90 ± 14 Days):

8.2.6.1. Cohorts 1, 1A, 2, and 2A (Table 13)

- Tumor assessment (RECIST v1.1)
  - If a patient discontinues treatment for a reason other than progression or death, withdrawal of consent, or loss to follow-up, radiographic scans/images should continue every 9 weeks (63 ± 7 days) until Week 72 (18 months) and every 12 weeks (84 ± 7 days) thereafter.
- CBC and serum chemistry are to be conducted only on Day 90 post-treatment to assess for possible AESI (Section 7.1.7)
- AE monitoring
  - AEs are required to be captured through 30 days after cessation of study treatment (Section 7.1.4)
  - SAEs are required to be captured through 90 days after cessation of study treatment (or to a minimum of 30 days post-treatment if the patient starts alternate anticancer therapy), and any pregnancies that occur within 180 days post-treatment are to be captured (Section 7.1.6)
- Survival/AESI (regardless of causality) and study-drug related SAEs
  - Patients will be followed until study closeout for survival status, AESI (regardless of causality), and study-drug related SAEs (Section 7.1.7). Telephone assessment is allowed.

8.2.6.2. Cohort 3 (Table 14)

- Tumor assessment (RECIST v1.1)
  - If patient discontinues treatment for a reason other than progression, death, withdrawal of consent, or loss to follow-up, imaging should continue every 6 weeks (42 ± 7 days) until Week 24 (6 months), then every 9 weeks (63 ± 7 days) until Week 52 (12 months) and every 12 weeks (84 ± 7 days) thereafter.

- CBC and serum chemistry to be conducted only on Day 90 post-treatment to assess for possible AESI (Section 7.1.7).
- AE monitoring
  - AEs are required to be captured through 30 days after cessation of study treatment (Section 7.1.4)
  - SAEs are required to be captured through 90 days after cessation of study treatment (or to a minimum of 30 days post-treatment if the patient starts alternate anticancer therapy), and any pregnancies that occur within 180 days post-treatment are to be captured (Section 7.1.6)
- Survival/AESI (regardless of causality) and study-drug related SAEs
  - Patients will be followed until study closeout for survival status AESI (regardless of causality), and study-drug related SAEs (Section 7.1.7). Telephone assessment is allowed.

8.2.7. Unscheduled Assessments

For any patient diagnosed with MDS/AML while on study, the patient will be referred to a local hematologist, who must perform a bone marrow aspirate and biopsy and sample collection (whole blood) for cytogenetic analysis will be obtained. See Section 7.1.14 for details.

8.3. Intensive Niraparib PK evaluation: All Cohorts

Blood samples for intensive niraparib PK assessment will be obtained from 8 patients, who consent to additional PK blood draws, in each cohort in **Cycle 1 and Cycle 4** following the schedule described in Section 7.4.1 and Table 16.

9. STATISTICS

Details of the statistical analyses presented below will be provided in the 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.

9.1. Analysis Populations

The modified intent-to-treat (ITT) population includes all patients who received any study drug and did not withdraw consent prior to having at least 1 postbaseline tumor assessment. The modified ITT population will be the primary analysis population for the efficacy analyses.

The safety population includes all patients who received at least 1 dose of study medication. The safety population will be the primary analysis population for the safety analyses.

9.2. Demographics, Medical History, Baseline Characteristics

Patient disposition will be summarized, including the number of patients treated with single agent niraparib and combination of niraparib and a PD-1 inhibitor, the number of patients who discontinue and reason for discontinuation, and the number of patients included for analysis. Patient demographics will be summarized descriptively for the overall modified ITT population and by subgroup.

9.3. Sample Size Determination

The null hypothesis for this study is H_0: ORR $\leq$ Standard of Care Response Rate (RR_s) vs. the alternative hypothesis: ORR $\geq$ Target Response Rate (RR_t) for all cohorts. RR_s and RR_t for each cohort are specified in Table 17 below.

As different study drugs will be used in Stage 1 and Stage 2, the sample size for each stage was calculated separately for Cohort 1 and Cohort 2. Sample size calculation was based on the primary efficacy endpoint ORR for each cohort assuming a 1-sided alpha level of 0.10 and 80% power.

For Cohorts 1, 2, and 3, the number of patients in Stage 1 was determined based on Simon's 2-stage design. The sample size for Stage 2 (Cohorts 1A and 2A) was calculated based on a 1-stage design. Once enrollment for Stage 1 is completed, Stage 2 enrollment will start. Stage 1 data will be used to determine if further enrollment for Stage 2 is warranted. (As of Amendment 2, following a cross-program review and decision to move forward with other studies, the Sponsor decided that Cohort 3 would close to further enrollment. As of Amendment 3, Cohort 1 and Cohort 2 had completed enrollment, Cohort 1A had closed after partial enrollment and Cohort 2A was not opened for enrollment.) The total sample size for this study will range from 59 to 142.

The criteria for rejecting the alternative hypothesis and declaring the experiment treatment as not efficacious at the end of Stage 1 and Stage 2 are listed in Table 18 below. For each cohort, if the number of responders by the end of Stage 1 is the same or less as defined by the criterion, the cohort will be terminated. For a cohort that proceeds to Stage 2, if the number of responders by the end of Stage 2 is the same or less than the criterion, the alternative hypothesis will be rejected

and the experimental treatment will be considered not efficacious for the indication in the cohort, unless the clinical judgment suggests otherwise. For example, if greater than 8 patients in Cohort 1/Stage 1 respond, then enrollment in Cohort 1A/Stage 2 will continue until completion.

Table 17: Sample Size by Cohort

Cohort No.	Cohort Description	Target RR	SoC RR	Sample Size		
				1st Stage	2nd Stage	Total
1/1A	NSCLC (chemotherapy-naïve, PD-L1 TPS ≥ 50%)	65%	45%	16	36	52
2/2A	NSCLC (chemotherapy-naïve, PD-L1 TPS 1-49%)	50%	33.5%	20	47	67
3	SqNSCLC: Platinum and PD-1/PD-L1-treated	20%	9%	23	0	23

Abbreviations: NSCLC = non-small cell lung cancer; PD-1 = programmed cell death-1; PD-L1 = programmed death ligand-1; RR = response rate; SoC = standard of care; SqNSCLC = squamous non-small cell lung cancer; TPS = tumor proportion score.

Table 18: Criteria for Considering Treatment Efficacious by Cohort and Stage

Cohort No.	Cohort Description	Stage 1 Criteria*	Stage 2 Criteria
1/1A	NSCLC (chemotherapy-naïve, PD-L1 TPS ≥ 50%)	8	20‡
2/2A	NSCLC (chemotherapy-naïve, PD-L1 TPS 1-49%)	7	20‡
3	SqNSCLC: Platinum and PD-1 or PD-L1-treated	2	NA

Abbreviations: NA = not applicable; NSCLC = non-small cell lung cancer; PD-1 = programmed cell death-1; PD-L1 = programmed death ligand-1; SqNSCLC = squamous non-small cell lung cancer; TPS = tumor proportion score.
* Number of patients with responses (CR/PR)‡ Not including stage 1 responders.

9.4. Statistical Analysis

All cohorts in this study are independently designed based on different patient populations. Efficacy and safety analysis for each cohort will be done separately. There will be no multiplicity adjustment.

9.4.1. Efficacy Analyses

9.4.1.1. Analysis for Primary Efficacy Endpoint

The primary efficacy endpoint is ORR as assessed by Investigator using RECIST (v1.1). Number of responders, ORR, and its 80% and 95% binomial exact CI will be reported by cohort and stage.

9.4.1.2. Analysis for Secondary Efficacy Endpoints

Results for DOR, DCR, and PFS as assessed by Investigators per RECIST 1.1, will be summarized for each cohort separately. DCR will be analyzed using the same methods for ORR. Kaplan-Meier estimates including median and its 95% confidence interval will be tabulated for

time to event variables. In addition, Kaplan-Meier curves will also be presented for time to event variables.

9.4.2. Safety Analyses

All analysis for safety endpoints will be done in a descriptive nature. Summary statistics will be provided for safety endpoint TEAEs, clinical laboratory assessments (CBC, serum chemistry, and urinalysis), vital signs, ECGs, physical examinations, and use of concomitant medications.

Medical history and AEs will be coded using the most up-to-date version of the Medical Dictionary for Regulatory Activities. CTCAE v4.03 will be used to grade the severity of AEs and laboratory abnormalities. Prior/concomitant medication and anticancer treatment will be coded using the most up-to-date version of the WHO Anatomical Therapeutic Chemical classification.

AEs will include the following categories:

- TEAEs
- Drug-related TEAEs
- Treatment-emergent drug-related Grade 3, 4, and 5 AEs (presented by grade and overall)
- Treatment-emergent Grade 3, 4, and 5 AEs (presented by grade and overall)
- TEAEs resulting in study drug discontinuation
- Most commonly reported TEAEs (ie, those events reported by ≥10% of all patients)
- Treatment-emergent SAEs

Details for the safety analysis will be specified in the SAP.

9.5. Interim Analyses

No formal interim analysis will be done for this study. After the last patient in Stage 1 of each cohort is enrolled and has discontinued treatment or completed 2 postbaseline tumor assessments (approximately 3 to 5 months), whichever occurs earlier, the number of responders will be counted and compared to the criteria as specified in Table 18 in the sample size determination section. If the number of responders is equal or less than the number of responders specified in the criteria, enrollment will be discontinued and the cohort will be terminated for futility. Only cohorts with a number of responders larger than that defined by the criteria will be continued to finish the Stage 2 enrollment. In the case of responder criteria met before Stage 1 enrollment is finished, Stage 1 enrollment may be stopped and Stage 2 enrollment may begin. (As of Amendment 2, following a cross-program review and decision to move forward with other studies, the Sponsor decided that Cohort 3 would close to further enrollment. As of Amendment 3, Cohort 1 and Cohort 2 had completed enrollment, Cohort 1A had closed after partial enrollment and Cohort 2A was not opened for enrollment.)

9.6. Pharmacokinetic Analyses

Noncompartmental or modeling methods will be used to evaluate the PK characteristics of niraparib and pembrolizumab or TSR-042 (dostarlimab) as appropriate. Pharmacokinetic parameters to be determined may include AUC, AUC_{ss}, C_{min}, C_{max}, CL/F, V_z/F, $C_{min,ss}$, and $C_{max,ss}$ as described in Section 7.4.4.

Population PK modeling will be performed on the niraparib concentration-time data collected from this study to quantitatively describe the PK profile of niraparib in lung cancer patients, explore the PK variability, and identify any covariate effects such as demographic and pathophysiologic variables as well as co-medication on the PK of niraparib. In addition, the exposure-response relationship between measures of niraparib exposure and measures of efficacy, including, but not limited to, ORR, PFS, DOR, and DCR, will be explored. The relationship between niraparib exposure and key safety variables, including (but not limited to) AESI identified based on data, will be explored. In addition, tumor biomarkers (such as BRCA1/2 status, other HRR pathway mutations, HRD status, etc.) may be explored in the exposure-response analyses.

The population PK and exposure-response analyses will be developed and reported separately from the clinical study report.

9.7. Biomarker Analyses

For each patient in the study, blood and tumor tissue samples will be collected, evaluated and archived to support exploratory biomarker analysis. BRCA1/2 and other HRR pathway mutations, HRD score, TMB, immune cell infiltrates, KRAS mutation status, and other exploratory biomarkers will be correlated with response.

10. ETHICAL, LEGAL, AND ADMINISTRATIVE ASPECTS

10.1. Data Quality Assurance

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

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

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

10.2. Access to Source Data/Documents

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

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

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

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

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

10.3. Archiving Study Documents

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

10.4. Good Clinical Practice

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

10.5. Informed Consent

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

The ICF must be signed and dated; 1 copy will be given to the patient and the Investigator will retain a copy as part of the clinical study records. The Investigator will not undertake any investigation specifically required for the clinical study until written consent has been obtained. The terms of the consent and when it was obtained must also be documented.

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

10.6. Protocol Approval and Amendment

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

This protocol is to be followed exactly. To alter the protocol, amendments must be written, receive approval from the appropriate personnel, and receive IRB/IEC/Competent Authority approval prior to implementation (if appropriate). In the US, following approval, the protocol

amendment(s) will be submitted to the investigational new drug application under which the study is being conducted.

Specifically, enrollment in Stage 2 of this study (added under Amendment 2) must not begin before the clinical study site has received approval for Amendment 2 from the ethics committee of record for that site.

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

10.7. Patient Confidentiality and Data Protection

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

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

10.8. Study Monitoring

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

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

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

10.9. Audits and Inspections

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

10.10. Ethical Considerations

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

10.11. Publication Policy

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

10.12. Study Committee

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

10.13. 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.

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APPENDIX A. COCKCROFT-GAULT EQUATION

For males:

$$\text{Creatinine Clearance} = \left\{\frac{140 - \text{age [years]} \times \text{weight [kg]}}{72 \times \left(\text{serum creatine}\left[\frac{\text{mg}}{\text{dL}}\right]\right)}\right\} \textbf{ OR } \left\{\frac{140 - \text{age [years]} \times \text{weight [kg]}}{0.81 \times \left(\text{serum creatine}\left[\frac{\mu\text{mol}}{\text{L}}\right]\right)}\right\}$$

For females:

$$\text{Creatinine Clearance} = \left\{\frac{0.85\ (140 - \text{age [years]} \times \text{weight [kg]})}{72 \times \left(\text{serum creatine}\left[\frac{\text{mg}}{\text{dL}}\right]\right)}\right\} \textbf{ OR } \left\{\frac{0.85\ (140 - \text{age [years]} \times \text{weight [kg]})}{0.81 \times \left(\text{serum creatine}\left[\frac{\mu\text{mol}}{\text{L}}\right]\right)}\right\}$$

APPENDIX B. EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS

Description	Grade
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.	

Abbreviations: ECOG = Eastern Cooperative Oncology Group.
Source: [69]

APPENDIX C. RESPONSE EVALUATION CRITERIA IN SOLID TUMORS, V1.1

Response Criteria by Response Evaluation Criteria in Solid Tumors (RECIST), v1.1

Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or nontarget) 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 nontarget lesions and normalization of tumor marker level. All lymph nodes must be nonpathological 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 1 or more nontarget lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of 1 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 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 19: RECIST Response for Patients with Measurable Disease (ie, Target Disease)

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

Abbreviations: CR = complete response; PD = progressive disease; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease

* See RECIST v1.1 publication for further details on what is evidence of a new lesion.[68]

** Only for nonrandomized trials with response as primary endpoint.

*** In exceptional circumstances, unequivocal progression in nontarget 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.

APPENDIX D. ACCEPTABLE METHODS OF CONTRACEPTION

Patients of childbearing potential, who are sexually active, and their partners must agree to the use of 2 highly effective forms of contraception throughout their participation during the study treatment and for 180 days after the last dose of study treatment(s). Acceptable birth control methods include the following:

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
  - Oral route
  - Intravaginal route
  - Transdermal route
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Injectable
  - Implantable
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomized partner
- Sexual abstinence, if it is the preferred and usual lifestyle of the subject