Protocol

Study ID: 213357

Official Title of Study: COHORT A: PARP INHIBITOR-NAÏVE PLATINUM-RESISTANT OVARIAN CANCER TREATMENT COHORT WITH TSR-042, BEVACIZUMAB, AND NIRAPARIB

Approval Date of Document: 20-MAR-2018

SUPPLEMENT A

3000-02-005

COHORT A: PARP INHIBITOR-NAÏVE PLATINUM-RESISTANT OVARIAN CANCER TREATMENT COHORT WITH TSR-042, BEVACIZUMAB, AND NIRAPARIB

Sponsor:	TESARO 1000 Winter Street, Suite 3300 Waltham, MA 02451 +1 339 970 0900
Medical Monitor:	PPD MD
Clinical Research Organization:	Not applicable
IND No.:	100,996
EudraCT No.:	To be determined
NCT No.	To be determined
Development Phase:	2
Date of Original Protocol:	20 March 2018

SPONSOR SIGNATURE PAGE

Declaration of Sponsor or Responsible Medical Officer

Title (Study Number): Phase 2 Multicohort Study to Evaluate the Safety and Efficacy of Novel Treatment Combinations in Patients with Recurrent Ovarian Cancer (PR-3000-02-005)

Cohort A: PARP Inhibitor-Naïve Platinum-Resistant Ovarian Cancer Treatment Cohort with TSR-042, Bevacizumab, and Niraparib

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

PPD

Katarina Luptakova, MD
Medical Director, TESARO

PPD

Date

INVESTIGATOR'S AGREEMENT

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

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

PROCEDURES IN CASE OF EMERGENCY

Procedures in case of emergency are outlined in the master protocol.

2. SYNOPSIS

<table>
<tr><td colspan="2">Name of Sponsor/Company: TESARO</td></tr>
<tr><td colspan="2">Name of Investigational Product: TSR-042, bevacizumab, and niraparib</td></tr>
<tr><td colspan="2">Name of Active Ingredient: TSR-042, bevacizumab, and niraparib</td></tr>
<tr><td colspan="2">Title of Study: Phase 2 Multicohort Study to Evaluate the Safety and Efficacy of Novel Treatment Combinations in Patients with Recurrent Ovarian Cancer
Cohort A: PARP Inhibitor-Naïve Platinum-Resistant Ovarian Cancer Treatment Cohort with TSR-042, Bevacizumab, and Niraparib</td></tr>
<tr><td colspan="2">Study center(s): To be determined</td></tr>
<tr><td colspan="2">Principal Investigator: To be determined
Investigators: To be determined</td></tr>
<tr><td>Studied period (years):
Estimated date first patient enrolled: Q3 2018
Estimated date last patient completed: Q2 2020</td><td>Phase of development: 2</td></tr>
<tr><td colspan="2">Objectives:
Primary:
• To evaluate the efficacy of the combination of TSR-042, bevacizumab, and niraparib, as assessed by confirmed objective response rate (ORR), in patients with advanced, relapsed, high-grade ovarian, fallopian tube, or primary peritoneal cancer who have received 1 to 2 prior lines of anticancer therapy, are poly(adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitor-naïve, and have platinum-resistant but not refractory disease.
Secondary:
• To evaluate the following measures of clinical benefit for TSR-042, bevacizumab, and niraparib in patients with advanced, relapsed, high-grade ovarian, fallopian tube, or primary peritoneal cancer who have received 1 to 2 prior lines of anticancer therapy, are PARP inhibitor-naïve, and have platinum-resistant but not refractory disease:
o Progression-free survival (PFS)
o Overall survival (OS)
o Duration of response (DOR)
o Disease control rate (DCR)
• To evaluate safety and tolerability in patients treated with TSR-042, bevacizumab, and niraparib.
Exploratory:
• To identify potential biomarkers including breast cancer susceptibility gene (BRCA) status, homologous recombination repair (HRR) gene status, homologous recombination deficiency (HRD) score, programmed death-ligand 1 (PD-L1) expression, and other disease-related or treatment-related biomarkers that would associate with tumor responses to the combination of niraparib, TSR-042, and bevacizumab based on the molecular profile of tumor tissue, blood, and optional ascitic fluid samples.
• To evaluate the evolution of the molecular profile of the tumor and tumor microenvironment in response to treatment.</td></tr>
</table>

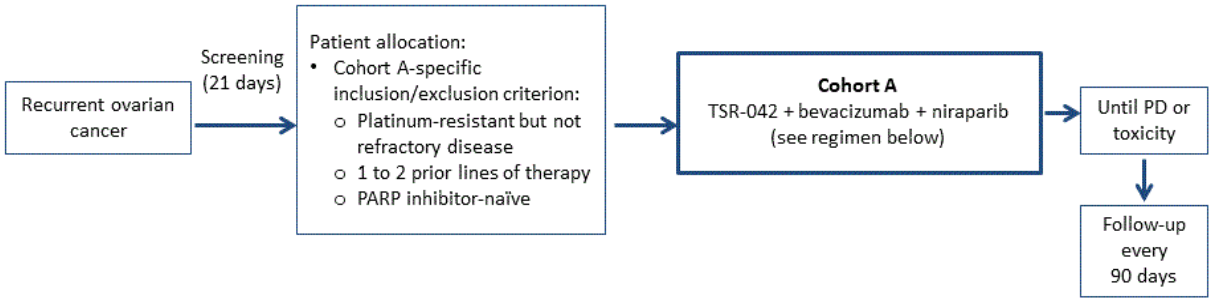
Methodology:

The overall study design is described in the master protocol.

In this cohort, all patients will receive treatment with TSR-042, bevacizumab, and niraparib (collectively referred to as "study treatment") beginning on Cycle 1 Day 1 using the regimen detailed in the figure below.

The safety, tolerability, and maximum tolerated dose of combination treatment with TSR-042, bevacizumab, and niraparib is currently being assessed in ongoing Study 3000-01-002 (NCT03307785). If results from that study are not available at the initiation of treatment for this cohort, an interim safety analysis, which will be detailed in the statistical analysis plan, will be performed after a total of 12 patients are enrolled between Cohorts A and B and have completed 2 cycles of therapy. If results from Study 3000-01-002 are available and support the feasibility of the outlined starting dose regimens, the safety interim analysis will not be performed.

Cohort A Study Schema



TSR-042 500 mg on Day 1 Q3W for 4 cycles, followed by 1,000 mg every other cycle (Q6W) beginning on Cycle 5 Day 1 until PD or toxicity
Bevacizumab 15 mg/kg on Day 1 of every 21-day cycle (Q3W) for up to 15 months
Niraparib Starting doses are as follows: - 300 mg in patients with screening actual body weight ≥77 kg AND screening platelet count ≥150,000/µL - 200 mg in patients with screening actual body weight <77 kg OR screening platelet count <150,000/µL administered on Days 1 to 21 Q3W until PD or toxicity

Abbreviations: PD = progressive disease; Q3W = every 3 weeks; Q6W = every 6 weeks.

Number of patients (planned):

A total of 40 patients are planned for enrollment in Cohort A.

Diagnosis and main criteria for inclusion:

The overall list of eligibility criteria for entry into this study is provided in the master protocol. The following are additional cohort-specific eligibility criteria for this cohort. Patients must meet all criteria in both the master protocol and this cohort-specific supplement in order to be eligible for enrollment in this cohort.

Patients will be eligible for entry in this cohort if all of the criteria for inclusion in the master protocol are met, as well as the following cohort-specific criteria:

A1. Patients must be resistant to the most recent platinum-based therapy, defined for the purpose of this protocol as progression within 6 months from completion of a minimum of 4 cycles of platinum-containing therapy. This should be calculated from the date of the last administered dose of platinum therapy to the date of the radiographic imaging showing disease progression. Patients with primary platinum-refractory disease as defined by those who progressed during or within 4 weeks of completion of first platinum-based chemotherapy are not eligible.

A2. Patient must not have received any prior therapy for ovarian cancer with a PARP inhibitor

A3. Patient has had 1 to 2 prior lines of anticancer therapy for ovarian cancer (The definition of prior lines of therapy is provided in section 8.1, inclusions 3 of the master protocol).

A4. Patient is able to take oral medications.

Main criteria for exclusion:

Patients will not be eligible for entry in this cohort if any of the criteria for exclusion in the master protocol are met, or any of the following cohort-specific criteria:

A1. Patient has known hypersensitivity to TSR-042, bevacizumab, niraparib, their components, or their excipients

A2. Patient has a known history of myelodysplastic syndrome or acute myeloid leukemia.

A3. Patient has active autoimmune disease that has required systemic treatment in the past 2 years (ie, with use of disease-modifying agents, corticosteroids, or immunosuppressive drugs). Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment

A4. Patient received prior treatment with an anti-programmed death-1 or anti-PD-L1 agent

A5. Patient has received prior treatment with anti-angiogenic therapy with the exception of bevacizumab. (Patients who received prior bevacizumab are eligible only if they did not discontinue bevacizumab due to toxicity, as established by the Investigator.)

A6. Patient has bowel obstruction, had bowel obstruction within the past 3 months, or is otherwise judged by the Investigator to be at high risk for bowel obstruction related to the underlying disease. Patient has any history of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscesses. Evidence of recto-sigmoid involvement by pelvic examination or significant bowel involvement on computed tomography scan

A7. Patient has proteinuria as demonstrated by urine protein:creatinine ratio ≥1.0 at screening or urine dipstick for proteinuria ≥2 (Patients discovered to have ≥2 proteinuria on dipstick at baseline should undergo 24-hour urine collection and must demonstrate <2 g of protein in 24 hours to be eligible.)

A8. Patient is at increased bleeding risk due to concurrent conditions (eg, major injuries or surgery within the past 28 days prior to start of study treatment, history of hemorrhagic stroke, transient ischemic attack, subarachnoid hemorrhage, or clinically significant hemorrhage within the past 3 months)

A9. Patient has a history of recent major thromboembolic event defined as follows:

a. Pulmonary embolism diagnosed within 3 months of enrollment

b. Lower extremity deep venous thrombosis diagnosed within 3 months of enrollment

Note: Patients with a history of thromboembolic disease on stable therapeutic anticoagulation for more than 3 months prior to enrollment are eligible for this study.

Investigational product, dosage, and mode of administration:

On days on which more than one study treatment is administered, TSR-042 will be administered first, followed by bevacizumab, and then niraparib, as applicable.

TSR-042:

TSR-042 will be administered via a 30-minute intravenous (IV) infusion on Day 1 every 3 weeks (Q3W) at 500 mg for 4 cycles followed by 1,000 mg every other cycle (every 6 weeks) beginning on Cycle 5 Day 1. The Pharmacy Manual contains descriptions of the packaging of TSR-042 and instructions for the preparation and administration of TSR-042.

Bevacizumab:

Bevacizumab 15 mg/kg will be administered via IV infusion on Day 1 of every 21-day cycle Q3W for up to 15 months. The Pharmacy Manual contains descriptions of the packaging of bevacizumab and instructions for the preparation and administration of bevacizumab.

Niraparib:

Niraparib will be supplied as 100-mg capsules and will be administered orally once daily continuously throughout each 21-day cycle at the assigned dose. The starting dose will be 300 mg in patients with a screening actual body weight ≥77 kg AND screening platelet count ≥150,000/μL, and 200 mg in patients with a screening actual body weight <77 kg OR screening platelet count <150,000/μL. On or after Cycle 3 Day 1, patients receiving the 200-mg niraparib starting dose may have their niraparib dose increased to 300 mg daily after discussion with medical monitor or designee if hemoglobin is ≥9 g/dL, platelets are ≥100,000/μL, and neutrophils are ≥1500/μL for all laboratory evaluations performed during the first 2 cycles. Patients will be instructed to take niraparib at the same time each day. Bedtime administration may be a potential method for managing nausea. Patients must swallow and not chew all capsules. The consumption of water and food is permissible. Niraparib will be dispensed to patients on Day 1 of every cycle (every 21 days) until the patient discontinues study treatment. The Pharmacy Manual contains descriptions of the packaging of niraparib and instructions for the preparation and administration of niraparib.

Duration of treatment:

Treatment with TSR-042 and niraparib will continue until disease progression or toxicity. Treatment with bevacizumab will continue for a maximum of 15 months in the absence of disease progression or toxicity. Unless otherwise indicated, treatment with each combination agent will continue independent of dose adjustments, interruptions, or discontinuation of treatment for other combination agents.

Reference therapy, dosage and mode of administration:

Not applicable.

Criteria for evaluation:

Efficacy:

Efficacy endpoints are described in the master protocol.

Safety:

Safety endpoints are described in the master protocol.

Biomarkers:

Tumor tissue, blood, and optional ascitic fluid samples will be assessed to identify potential biomarkers including *BRCA* status, HRR gene status, HRD score, PD-L1 expression, and other disease-related or treatment-related biomarkers that would associate with tumor responses to the combination of TSR-042, bevacizumab, and niraparib. Additionally, samples will be assessed to evaluate the evolution of the molecular profile of the tumor and tumor microenvironment in response to treatment.

Statistical methods:

Sample size calculation was performed using SAS® version 9.4 with the EXACT method. A sample size of approximately 40 patients is estimated for this cohort to provide assessment of clinical activity of the treatment based on ORR. The null hypothesis that the true response rate is ≤25% (H0: $p \leq 0.25$) will be tested against a 1-sided alternative of ≥45% (Ha: $p \geq 0.45$). If there are 15 or more responses observed among 40 treated patients, it will be concluded that the lower bound of 80% confidence interval excludes H_0 and the null hypothesis will be rejected. With 40 patients treated, the cohort has 87% power to rule out a ≤25% ORR (null hypothesis) when the true ORR is 45% at the 10% type I error rate (1-sided).

Enrollment will be stratified based on histology (epithelial vs carcinosarcoma). Enrollment of patients with carcinosarcoma will be limited to comprise approximately 10% of the cohort (ie, approximately 4 patients).

Statistical methods are further described in the master protocol.

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

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

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

Table 1: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
ADP	adenosine diphosphate
AE	adverse event
AESI	adverse event of special interest
ASCO	American Society of Clinical Oncology
BIW	twice weekly
BRCA	breast cancer susceptibility gene
CBC	complete blood count
CI	confidence interval
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
eCRF	electronic case report form
EOT	End of Treatment
EU	European Union
GCSF	granulocyte colony-stimulating factor
HR	hazard ratio
HRD	homologous recombination deficiency
HRR	homologous recombination repair
Ig	immunoglobulin
IL-2	interleukin-2
irAEI	immune-related adverse event of interest
IV	intravenous
mPD-1	mouse programmed death-1
MRI	magnetic resonance imaging
ORR	objective response rate
PARP	poly(ADP-ribose) polymerase
PD	progressive disease
PD-1	programmed death-1
PD-L1	programmed death-ligand 1

Abbreviation or Specialist Term	Explanation
PD-L2	programmed death-ligand 2
PFS	progression-free survival
PK	pharmacokinetic(s)
PO	orally
PROC	platinum-resistant ovarian cancer
Q2W	every 2 weeks
Q3W	every 3 weeks
Q6W	every 6 weeks
QD	once daily
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
TEAE	treatment-emergent adverse event
TIL	tumor-infiltrating lymphocyte
TNBC	triple-negative breast cancer
US	United States

5. INTRODUCTION

The objective of this study is to evaluate the efficacy and safety of novel combinations of niraparib and agents with strong scientific rationale for synergistic activity in patients with recurrent ovarian cancer. An introduction to the overall study is provided in the master protocol.

Most patients with ovarian cancer present with advanced disease at diagnosis, and the majority of these patients will relapse after initial treatment. Recurrence within 6 months of platinum-based chemotherapy is defined as platinum-resistant disease, which confers a significantly worse prognosis, with median overall survival (OS) reported in clinical studies ranging from less than a year to 19 months.[1, 2, 3, 4] Current treatment options for patients with recurrent platinum-resistant ovarian cancer (PROC) provide only modest benefit. The National Comprehensive Cancer Network guidelines recommend nonplatinum-based regimens such as docetaxel, oral etopside, gemcitabine, paclitaxel with or without pazopanib, liposomal doxorubicin with or without bevacizumab, paclitaxel/bevacizumab, or topotecan with and without bevacizumab.[5] For patients who have a breast cancer susceptibility gene (BRCA) mutation, the guidelines recommend olaparib and rucaparib.[5] Use of a single chemotherapeutic agent will yield a reported objective response rate (ORR) in the range of 10% to 30%, with relatively short-lived responses of less than 8 months.[6, 7, 8, 9, 10, 11, 12] The anti-angiogenesis agent bevacizumab has a modest single-agent activity with an ORR of 15% and a median progression-free survival (PFS) of 4.4 months reported for patients with PROC.[13] A more recent randomized Phase 2 study evaluated paclitaxel with or without the anti-angiogenic agent pazopanib in patients with PROC who had received 1 to 2 prior lines of therapy, yielding ORRs of 56% and 25% and median PFSs of 6.4 and 3.5 months, respectively.[4] Chemotherapy with or without bevacizumab was evaluated in a Phase 3 study that demonstrated a median PFS of 3.4 months with chemotherapy alone versus 6.7 months with combination of chemotherapy with bevacizumab, ORR (by Response Evaluation Criteria in Solid Tumors [RECIST]) was 11.8% versus 27.3%, respectively.[3] A post-hoc analysis of this study suggested somewhat better outcomes in the paclitaxel and bevacizumab-treated patients (ORR of 53% and median PFS of 10.4 months).[14] Based on these results, bevacizumab in combination with paclitaxel, pegylated liposomal doxorubicin, or topotecan was approved for the treatment of platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer.[15]

The objective of this cohort (Cohort A) is to evaluate the efficacy and safety of the novel combination of TSR-042, bevacizumab, and niraparib in patients with recurrent PROC not previously exposed to treatment with poly(adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitors who had 1 to 2 prior lines of therapy.

5.1. Background

5.1.1. Background of TSR-042

TSR-042 is an immunoglobulin (Ig)G4-κ humanized monoclonal antibody that binds with high affinity to programmed death-1 (PD-1), resulting in inhibition of binding to programmed death-ligand 1 (PD-L1) and programmed death-ligand 2 (PD-L2). This antibody was generated based on a proprietary platform that utilizes affinity maturation to select highly-specific antibodies with desired functional characteristics. The functional antagonist activity of TSR-042 was confirmed in a mixed lymphocyte reaction assay, demonstrating enhanced interleukin-2

(IL-2) production upon addition of TSR-042. Furthermore, TSR-042 has an acceptable safety profile based on toxicology studies in cynomolgus monkeys. Additional information on the nonclinical and clinical experience with TSR-042 can be found in the TSR-042 Investigator's Brochure.

5.1.1.1. Nonclinical Experience

TSR-042 binds with high affinity to human and cynomolgus monkey PD-1. TSR-042 blocks binding of soluble ligands to human PD-1 expressed on the surface of Chinese hamster ovary cells, with a 50% maximum inhibitory concentration of approximately 1 nM. TSR-042 enhances T cell activation, as measured by the production of IL-2 from activated CD4+ T cells, with a 50% maximum effective concentration of approximately 1 nM. Full PD-1 receptor occupancy achieved by TSR-042 in human and cynomolgus monkey T cells from peripheral blood mononuclear cells was determined to occur at concentrations of approximately 1 μg/mL.

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

In a 4-week repeat-dose toxicology study in cynomolgus monkeys, administration of TSR-042 at doses of 0, 10, 30, or 100 mg/kg was well tolerated and did not result in any treatment-emergent adverse events (TEAEs) on clinical signs, body weight, food consumption, electrocardiograms, ophthalmology, safety pharmacology parameters, clinical pathology, gross pathology, organ weight, or histopathology. The no-observed-adverse-effects level was ≥100 mg/kg in this study.

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

5.1.1.2. Clinical Experience

TSR-042 has been evaluated as monotherapy in one Phase 1 study to date. Study 4010-01-001 (NCT02715284) is an ongoing first-in-human Phase 1 study of TSR-042 to evaluate the safety and tolerability, PK, pharmacodynamics, and clinical activity of TSR-042 in patients with advanced solid tumors. The study is being conducted in 2 parts:

- Part 1 (dose escalation) of the study used a modified 3 + 3 design to evaluate 3 ascending weight-based doses of TSR-042 as follows: 1, 3, and 10 mg/kg administered every 2 weeks (Q2W) via IV infusion.

- Part 2 of the study is being conducted in 2 subparts (Part 2A and Part 2B) to explore the safety and clinical activity of TSR-042 administered as a fixed dose (ie, not weight based).
  - In Part 2A, following the completion of Part 1, the safety and tolerability of TSR-042 was evaluated at fixed doses of 500 mg every 3 weeks (Q3W) and 1,000 mg every 6 weeks (Q6W) using a modified 6 + 6 design.
  - In Part 2B, the clinical activity, tolerability, and safety of TSR-042 at the recommended Phase 2 dose will be evaluated in patients with specific tumor types.

As of 21 January 2018, 135 subjects with heavily pretreated advanced solid tumors have been treated with TSR-042 in Study 4010-01-001: 21 subjects in Part 1 and 114 subjects in Part 2A and 2B. 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.

TSR-042 is also being studied in combination with other treatments, including TSR-022, an anti-TIM3 antibody (4020-01-001) and TSR-033, an anti-LAG3 antibody (4040-01-001). As of January 2018, 28 subjects received TSR-042 in combination with TSR-022 in Study 4020-01-001.

5.1.2. Background of Bevacizumab

Bevacizumab is an antiangiogenic recombinant humanized monoclonal Ig G1 antibody against the vascular endothelial growth factor protein. Bevacizumab (Avastin; Genentech/Roche United States [US]) has been approved in the US and European Union (EU) for the treatment of multiple tumor types in combination with certain other treatments. In the EU, bevacizumab is approved for the front-line treatment of adult patients with advanced (International Federation of Gynecology and Obstetrics Stages IIIB, IIIC, and IV) ovarian cancer. In the US, bevacizumab is approved for the treatment of patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer that is either platinum-resistant (in combination with paclitaxel, pegylated liposomal doxorubicin, or topotecan) or platinum-sensitive (in combination with carboplatin and paclitaxel or in carboplatin and gemcitabine, followed by Avastin as a single agent).

Bevacizumab has been evaluated in multiple clinical studies, including in 361 patients with recurrent PROC as part of a Phase 3 study (AURELIA).[3, 14] Patients receiving bevacizumab administered concurrently with single-agent chemotherapy (N=179) showed statistically significant improvement in PFS compared to chemotherapy alone (6.7 months vs 3.4 months; hazard ratio [HR], 0.48; $p < 0.001$) and statistically significant improvement in objective response rate (ORR) compared to chemotherapy alone (30.9% vs 12.6%; 95% confidence

interval [CI], 9.6-27.0; $p < 0.001$, by RECIST and/or Gynecology Cancer Intergroup cancer antigen 125 criteria).

Statistically significant improvement with bevacizumab was observed regardless of chemotherapy regimen (paclitaxel: 10.4 months vs 3.9 months; HR, 0.46; 95% CI, 0.30-0.71; pegylated liposomal doxorubicin: 5.4 months vs 3.5 months; HR, 0.57; 95% CI, 0.39-0.83; and topotecan: 5.8 months vs 2.1 months; HR, 0.32; 95% CI, 0.21-0.49).

Safety observations in this study were consistent with the safety profile of bevacizumab. Grade ≥2 hypertension and proteinuria were observed more frequently with bevacizumab than with chemotherapy alone. No new safety signals were observed.

5.1.3. Background of Niraparib

Overall clinical experience with niraparib is summarized in the master protocol.

5.1.4. Background of Combination of TSR-042 and Niraparib

5.1.4.1. Nonclinical Experience

The efficacy and tolerability of niraparib in combination with anti-PD-1 therapy was evaluated in several nonclinical models. The combination was well tolerated in all of these studies. The combination was first tested in a homologous recombination-deficient ovarian cancer mouse model derived from breast cancer susceptibility gene (*BRCA*) null genetic background[16], as PARP inhibition was previously shown to increase immune cell infiltration in *BRCA*-deficient models.[17] In a study of an ovarian carcinoma mouse model[18], niraparib (50 mg/kg orally [PO] once daily [QD]) and anti-mouse programmed death-1 (mPD-1; 5 mg/kg intraperitoneally twice weekly [BIW]) were administered to mice either alone or in combination for 16 days. The combination was tolerated with no treatment-related death. Almost all the tumors achieved complete regression upon treatment with niraparib, anti-mPD-1, and the combination. Complete regression was first observed on treatment Day 16 in 2 of 6, 1 of 6, and 4 of 6 mice from the niraparib, anti-mPD-1, and combination groups, respectively. These results suggest that the therapeutic approach of combining niraparib with a PD-1 inhibitor such as TSR-042 may provide additional benefit for patients with homologous recombination-deficient tumors.

Niraparib and anti-PD-1 combination treatment has also been evaluated in several syngeneic models representing breast cancer 1 and breast cancer 2 (*BRCA1/2*) wild-type tumors, 1 of which was the breast cancer mouse model LPA1-T22. In study of a syngeneic transplant breast cancer model, niraparib (50 mg/kg PO QD) and anti-PD-1 antibody (10 mg/kg IV BIW) were administered to mice either alone or in combination for 15 days. While these tumors were moderately responsive to niraparib or anti-PD-1 antibody alone, with average tumor growth inhibition of approximately 50% for niraparib and 30% for PD-1 antibody, synergistic anti-tumor activity with near-complete tumor growth inhibition (>95%) was achieved with the combination.[19] 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-1 alone (30.5%).[20] Together, these data support the therapeutic approach of combining niraparib with an anti-PD-1 agent.

5.1.4.2. Clinical Experience

Combination treatment with TSR-042 and niraparib is currently being assessed in ongoing Study 3000-01-002 (NCT03307785); no clinical data are currently available for TSR-042 and niraparib combination treatment.

Niraparib is also being evaluated in combination with another anti-PD-1 agent, pembrolizumab, in patients with triple-negative breast cancer (TNBC) or recurrent PROC as part of a Phase 1/2 study (TOPACIO/KEYNOTE-162).[21]

In Phase 1 of the study, 5 patients with TNBC and 9 patients with recurrent PROC received 200 mg pembrolizumab via IV infusion on Day 1 of each 21-day cycle and 200 mg (Dose Level 1) or 300 mg (Dose Level 2) niraparib per day orally. DLTs included neutropenia, anemia, and thrombocytopenia in 1 patient at Dose Level 1 and thrombocytopenia in 2 patients at Dose Level 2. The recommended Phase 2 dose regimen was determined to be 200 mg niraparib per day orally (increasing to 300 mg after Cycle 2 in patients with no significant hematologic toxicities) in combination with 200 mg pembrolizumab via IV infusion on Day 1 of each 21-day cycle. Tumor responses included partial response or complete response in 5 of the 9 patients with recurrent PROC; the remaining 4 patients had stable disease.

In Phase 2 of the study as of August 2017, no new safety signals have been observed. In 36 patients with recurrent PROC, the most frequently reported Grade ≥3 TEAEs were anemia (16.7%), fatigue and platelet count decreased (5.6% each), and thrombocytopenia (2.8%).

5.1.5. Background of Combination of Bevacizumab and Niraparib

The combination of a PARP inhibitor and an angiogenesis inhibitor has the potential for improved PFS benefits in patients with or without homologous recombination deficiency (HRD).

Tumor cells with a deficiency in homologous recombination are exquisitely sensitive to PARP inhibitors due to synthetic lethality. It has been observed that, for tumors without genetic or epigenetic defects in homologous recombination pathway genes, a functional state of HRD may be induced by hypoxia through transcriptional downregulation of homologous recombination-related genes, including *RAD51* and *BRCA1*. In addition, cyclic (acute) hypoxia and reoxygenation can induce both single-strand and double-strand deoxyribonucleic acid (DNA) breaks within tumor cells due to increased levels of reactive oxygen species.[22, 23] These 2 mechanisms working together lead to heightened sensitivity to PARP inhibitors when cells are under hypoxic stress exerted by angiogenesis inhibitors. It has been observed that PARP inhibitors selectively induce apoptosis in hypoxic tumor regions in vivo, supporting the idea of contextual synthetic lethality between hypoxia-induced functional HRD and PARP inhibition. In the clinical setting, preliminary evidence of clinical efficacy has been observed in patients with platinum-sensitive ovarian cancer treated with either niraparib combined with bevacizumab (ENGOT-OV24/AVANOVA trial[24]) or olaparib combined with cediranib (Phase 2), irrespective of their *BRCA* mutation or HRD status.[25] These data provide a strong rationale for combining a PARP inhibitor with an angiogenesis inhibitor.

To validate the hypothesis that tumors without HRD can be effectively treated with the combination of niraparib and bevacizumab, the HRD status for pretreatment tumor tissue will be determined using the Myriad research HRD assay.

The combination of niraparib and bevacizumab treatment is currently being explored in patients with recurrent platinum-sensitive ovarian cancer as part of an ongoing Phase 1/2 study (AVANOVA).[24] Phase 1 of the study (dose escalation) has determined the recommended Phase 2 dose in this population to be 300 mg niraparib orally once daily and 15 mg/kg bevacizumab via IV infusion Q3W. Results to date, although limited, indicate clinical activity of the combination in this patient population.

Overall, the combination of niraparib and bevacizumab appears to be safe for administration, with a manageable safety profile. Adverse events (AEs) observed to date are consistent with those of the individual components and are readily managed through routine laboratory testing (ie, complete blood count), clinical surveillance (ie, blood pressure monitoring), and adherence to the recommended dose modifications.

5.1.6. Combination of TSR-042, Bevacizumab, and Niraparib

Combination treatment with TSR-042, bevacizumab, and niraparib is currently being assessed in ongoing Study 3000-01-002 (NCT03307785); no clinical data are currently available. However, the efficacy and safety of the combination of a PD-L1 inhibitor, a PARP inhibitor, and an anti-angiogenic agent have been studied in a Phase 1/2 study in women's cancers.[26] Data from the study indicates anticancer activity of the triplet combination, especially in ovarian cancer. At the dosing levels explored, the combination was tolerable and hematologic toxicity and cardiovascular toxicity observed in the study were consistent with PARP inhibitor-class and anti-vascular endothelial growth factor receptor treatments, respectively.

5.2. Rationale for Current Study

Over recent years, research has revealed the importance of tumor infiltrating lymphocytes in controlling the clinical progression of various cancers, and their presence in a tumor is associated with response to immune checkpoint inhibitors.[27] In ovarian cancer, intraepithelial CD8+ T cells correlated with the presence of mutation or loss of expression of *BRCA*1 through promoter methylation.[28] Ovarian cancer patients that were sensitive to agents targeting defects in DNA repair are likely to overlap with those tumors with an active yet checkpoint-blocked immune response.

The activity of PD-1/PD-L1 inhibitors observed in ovarian cancer (ORR of 11% to 12% with single agent pembrolizumab or avelumab in small studies) has been modest so far.[29, 30] However, preclinical data suggest there may be synergistic interaction between immune checkpoint inhibitors and PARP inhibitors. Nonclinical experiments in syngeneic mouse models have shown an increased response rate to the combination of anti-PD-1 and PARP inhibitors over either agent alone, providing additional support to investigate this combination in patients.[31, 32] Exposure of a tumor in vivo to PARP inhibitor results in increased cancer cell death by 2 independent mechanisms. First, through the mechanism of synthetic lethality, the PARP inhibitor can kill tumors with HRD through apoptosis. Second, the PARP inhibitor can increase the number of CD8+ T cells and natural killer cells, as well as their production of interferon-γ and tumor necrosis factor-α.[16, 33] Niraparib has also been shown to enhance immune responses in tumor microenvironment via activation of the stimulator of the interferon gene (STING) pathway, which renders tumors immunologically "hot" with an increase in infiltrating lymphocytes, resulting in an improved response to checkpoint blockade.[31]

Combination treatment with anti-PD-1 agent pembrolizumab and PARP inhibitor niraparib was evaluated in a dose escalation Phase 1b study and was shown to be tolerable with early signs of efficacy in patients with advanced solid tumors, including ovarian and breast cancers.[34] A study to determine the safety, tolerability, and recommended Phase 2 dose of PD-1 inhibitor TSR-042 in combination with niraparib (Study 3000-01-002, NCT03307785) is underway.

The combination of niraparib and bevacizumab treatment is currently being explored in patients with recurrent platinum-sensitive ovarian cancer as part of an ongoing Phase 1/2 study (AVANOVA).[24] Although limited, results to date indicate clinical activity of the combination in this patient population.

In addition to a strong scientific rationale for the combinations of PARP inhibitors with immune checkpoint inhibitors as well as antiangiogenic agents, the approach of combining all 3 mechanism of action was tested in a Phase 1/2 study of olaparib (PARP inhibitor), cediranib (anti-angiogenic agent), and durvalumab (PD-L1 inhibitor).[35] This 3-drug combination showed acceptable safety data and early encouraging anticancer effects, supporting the potential synergistic effect of the combination. Among 9 patients treated, 3 (33%) had partial response (6, 6 plus, and 7 plus months, respectively) and 4 (44%) had stable disease (3, 7 plus, 9, and 15 plus months, respectively).[36]

Cohorts A and B of the present clinical study are designed to evaluate the novel triple combination of PD-1 inhibitor TSR-042, bevacizumab, and niraparib in the PROC patient population, based on the nonoverlapping safety and metabolic profiles and nonclinical and clinical data suggesting possible synergy. The safety and tolerability of this combination are currently being evaluated in Study 3000-01-002 (NCT03307785), and the results of Study 3000-01-002 will further support the justification of the starting dose in Cohort A of the current trial.

Given recent as well as future anticipated approvals of several PARP inhibitors for treatment and maintenance in ovarian cancer, the treatment landscape in ovarian cancer will be changing significantly. The use of PARP inhibitors, initially approved for treatment in late lines of therapy, is expected to move into maintenance setting in earlier lines, especially for patients with *BRCA* mutation/HRD. However, the efficacy of re-treatment with the same mechanism of action for patients who previously progressed on PARP inhibitors is unknown. Therefore, Cohort A of the present protocol will be evaluating the efficacy of TSR-042, bevacizumab, and niraparib in patients with PROC not previously exposed to PARP inhibition, while Cohort B will evaluate if patients who previously progressed on PARP inhibitors can subsequently respond to a combination approach and be resensitized to PARP inhibitors through synergy with bevacizumab and PD-1 antibody. Given the expected treatment landscape evolution, Cohort A will focus on patients with early relapse (1 or 2 prior lines of therapy), and Cohort B will focus on the PROC patient population in later lines of therapy (2 to 3 prior lines of therapy).

6. TRIAL OBJECTIVES AND PURPOSE

The following are the cohort-specific objectives for this study, which have been further specified from the overall study objectives presented in the master protocol.

6.1. Primary Objective

- To evaluate the efficacy of the combination of TSR-042, bevacizumab, and niraparib, as assessed by confirmed ORR, in patients with advanced, relapsed, high-grade ovarian, fallopian tube, or primary peritoneal cancer who have received 1 to 2 prior lines of anticancer therapy, are PARP inhibitor-naïve, and have platinum-resistant but not refractory disease.

6.2. Secondary Objectives

- To evaluate the following measures of clinical benefit for TSR-042, bevacizumab, and niraparib in patients with advanced, relapsed, high-grade ovarian, fallopian tube, or primary peritoneal cancer who have received 1 to 2 prior lines of anticancer therapy, are PARP inhibitor-naïve, and have platinum-resistant but not refractory disease:
  - Progression-free survival (PFS)
  - Overall survival (OS)
  - Duration of response (DOR)
  - Disease control rate (DCR)
- To evaluate safety and tolerability in patients treated with TSR-042, bevacizumab, and niraparib.

6.3. Exploratory Objectives

- To identify potential biomarkers including *BRCA* status, homologous recombination repair (HRR) gene status, HRD score, PD-L1 expression, and other disease-related or treatment-related biomarkers that would associate with tumor responses to the combination of TSR-042, bevacizumab, and niraparib based on the molecular profile of tumor tissue, blood, and optional ascitic fluid samples.
- To evaluate the evolution of the molecular profile of the tumor and tumor microenvironment in response to treatment.

7. INVESTIGATIONAL PLAN

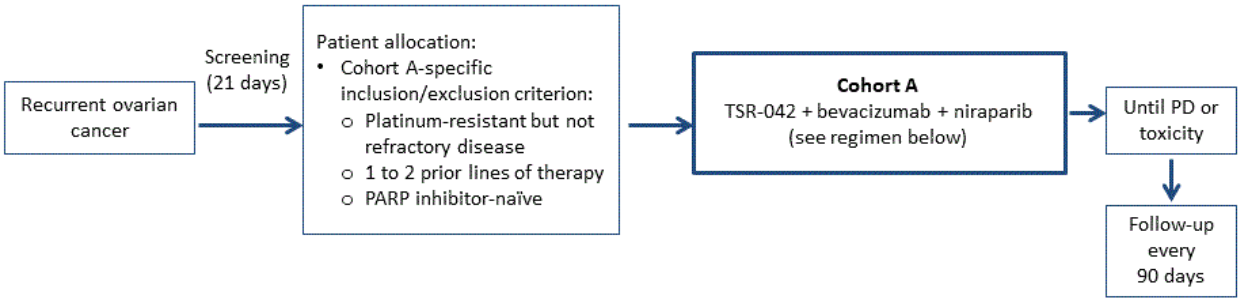
7.1. Overall Study Design

The overall study design is described in the master protocol.

In this cohort, all patients will receive treatment with TSR-042, bevacizumab, and niraparib (collectively referred to as "study treatment") beginning on Cycle 1/Day 1 using the regimen detailed in Figure 1.

As described in Section 5.1.6, combination treatment with TSR-042, bevacizumab, and niraparib is currently being assessed in ongoing Study 3000-01-002 (NCT03307785). If results from that study are not available at the initiation of treatment for this cohort, an interim safety analysis will be performed after a total of 12 patients are enrolled between Cohorts A and B and have completed 2 cycles of therapy. If results from Study 3000-01-002 are available and support the feasibility of the outlined starting dose regimens, the safety interim analysis will not be performed.

Figure 1: Cohort A Study Schema



TSR-042 500 mg on Day 1 Q3W for 4 cycles, followed by 1,000 mg every other cycle (Q6W) beginning on Cycle 5 Day 1 until PD or toxicity
Bevacizumab 15 mg/kg on Day 1 of every 21-day cycle (Q3W) for up to 15 months
Niraparib Starting doses are as follows: - 300 mg in patients with screening actual body weight ≥77 kg AND screening platelet count ≥150,000/µL - 200 mg in patients with screening actual body weight <77 kg OR screening platelet count <150,000/µL administered on Days 1 to 21 Q3W until PD or toxicity

Abbreviations: PD = progressive disease; Q3W = every 3 weeks; Q6W = every 6 weeks.

7.2. Number of Subjects

A total of 40 patients are planned for enrollment in Cohort A.

7.3. Treatment Assignment

All patients enrolled in this cohort will receive TSR-042, bevacizumab, and niraparib as indicated in Figure 1.

7.4. Dose Adjustment Criteria

7.4.1. Safety Criteria for Adjustment or Stopping Doses

Dosing regimens for TSR-042, bevacizumab, and niraparib are described in Section 7.1. The rationale for the starting doses of TSR-042 and niraparib is provided in Section 5.1.4.2; the rationale for weight- and platelet-based dosing for niraparib is provided in Section 5.1.2.2 of the master protocol. Unless otherwise indicated, treatment with each combination agent will continue independent of dose adjustments, interruptions, or discontinuation of treatment for other combination agents.

7.4.1.1. TSR-042

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

In general, TSR-042 must be withheld for drug-related Grade 3 toxicities, as well as for certain immune-related adverse events of interest (irAEIs), but may be resumed upon recovery to Grade ≤1; TSR-042 will be permanently discontinued for any drug-related Grade 4 AE. TSR-042 must be permanently discontinued for certain irAEIs as described in Table 2.

The specific immune-related AEs typically observed with anti-PD-1 antibodies will be managed according to the guidelines summarized below.[5]

The reason for interruption or discontinuation of TSR-042 should be recorded in the electronic case report form (eCRF).

Immune-related Adverse Events of Interest and Guidelines for Management

Given the mechanism of action of TSR-042, it is anticipated that activation of cellular immune system can be manifested as immune-related AEs. Based on available safety data from checkpoint inhibitors, TEAEs with the specific grades listed below were selected as irAEIs. The list of irAEIs may be updated upon emerging data.

Refer to Table 2 for details on the management of TSR-042 dose delays and discontinuation for specific irAEIs. Detailed guidance for the administration of rescue medications and supportive care is available in Section 9.2.3. For all irAEIs listed in Table 2, TSR-042 should be withheld until the patient is clinically and metabolically stable and AEs have resolved to Grade ≤1. If systemic steroids are used as a part of irAEI management, the total dose of daily steroids should be equal to or less than prednisone 10 mg at the time of resuming TSR-042.

All treatment delays (including any missed doses) and discontinuations, and the reason for delays or discontinuation of TSR-042, should be recorded in the eCRF.

Of note, if the attribution of an AE is not clear between TSR-042 and niraparib (examples might include diarrhea or aspartate aminotransferase or alanine aminotransferase elevation), both agents may be withheld and a discussion with the Sponsor's Medical Monitor is recommended.

Table 2: Guidelines for Treatment of Immune-related Adverse Events of Interest

Toxicity	Withhold Treatment for AE Grade	Restarting Treatment/Discontinuation
Diarrhea/colitis	2 to 3	Restart dosing when toxicity resolves to Grade 0 to 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)	Restart dosing when toxicity resolves to Grade 0 to 1 (see exception below).[a]
	3 or 4 (AST or ALT >5× ULN or total bilirubin >3× ULN)	Permanently discontinue (see exception below).[a]
T1DM or hyperglycemia	3 or 4 hyperglycemia or T1DM (associated with metabolic acidosis or ketonuria)	Restart dosing in appropriately managed, clinically and metabolically stable patients, insulin replacement therapy is required.
Immune-related encephalitis	Any grade	Permanently discontinue.
Hypophysitis	2 to 4	For Grade 2 to 3 AEs, hold 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.
Hyperthyroidism	3	Restart dosing when toxicity resolves to Grade 0 to 1.
	4	Permanently discontinue.
Infusion-related reaction	2[b]	Restart dosing when toxicity resolves to Grade 0 to 1.
	3 or 4	Permanently discontinue.
Pneumonitis	2	Restart dosing when toxicity resolves to Grade 0 to 1. If Grade 2 recurs, permanently discontinue.
	3 or 4	Permanently discontinue.
Rash	3	Restart dosing when toxicity resolves to Grade 0 to 1.
	4	Permanently discontinue.

Toxicity	Withhold Treatment for AE Grade	Restarting Treatment/Discontinuation
Renal failure or nephritis	2	Restart dosing when toxicity resolves to Grade 0 to 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; 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; refer to Section 9.2.3 for further management details.

7.4.1.2. Bevacizumab

The Investigator is advised to consult the current bevacizumab label. Dose reductions of bevacizumab are not permitted in this study.[15, 37]

Interrupt bevacizumab treatment for the following AEs: proteinuria, medically significant hypertension that cannot be adequately controlled with antihypertensive therapy, hypertension in the presence of posterior reversible encephalopathy syndrome, development of hypertensive crisis or hypertensive encephalopathy, or nephrotic syndrome. In case of uncontrolled hypertension, niraparib should also be held in addition to bevacizumab.

Resume bevacizumab treatment only when 1) hypertension is controlled by hypertensive regimen, or 2) urine protein is <2 g per 24 hours urine collection.[15] Niraparib should be resumed with bevacizumab when hypertension is controlled by hypertensive regimen. If hypersensitivity or infusion reactions occur during bevacizumab infusion, the infusion should be discontinued. Except in cases where permanent discontinuation of bevacizumab is indicated, resumption of the standard dose of bevacizumab upon resolution of other adverse reactions is at the discretion of the Investigator.

Bevacizumab treatment should be withheld 4 weeks prior to elective surgery. In patients who experience wound healing complications during the study, treatment with bevacizumab should be withheld until the wound is fully healed.

7.4.1.3. Niraparib

Niraparib Dose Interruption and Modification

Treatment must be interrupted for any nonhematologic Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or 4 AE that the Investigator considers to be related to administration of niraparib (Table 3). If the nonhematologic toxicity is appropriately resolved to baseline or Grade ≤1 within 4 weeks (28 days) of the dose interruption period, the patient may restart treatment with niraparib but with a dose level reduction if prophylaxis is not considered feasible (see Table 4). If the event recurs at a similar or worse grade, treatment should be

interrupted again and, upon resolution, a further dose reduction must be made. No more than 2 dose reductions will be permitted (ie, to a minimum dose of 100 mg QD).

If the toxicity requiring dose interruption has not resolved completely or to CTCAE Grade 1 during the maximum 4-week (28-day) dose interruption period, or the patient has already undergone a maximum of 2 dose reductions (to a minimum dose of 100 mg QD), the patient must permanently discontinue treatment with niraparib.

Of note, if the attribution of an AE is not clear between TSR-042 and niraparib (examples might include diarrhea or aspartate aminotransferase or alanine aminotransferase elevation), both agents may be withheld and a discussion with the Sponsor's Medical Monitor is recommended.

The dose interruption and modification criteria for niraparib for hematologic parameters will be based on blood counts and are outlined in Table 5. If the hematologic toxicity has not recovered to the specified levels within 4 weeks (28 days) of the dose interruption period, or the patient has already undergone a maximum of 2 dose reductions (to a minimum dose of 100 mg QD), the patient must permanently discontinue treatment with niraparib.

Table 3: Niraparib Dose Modifications for Nonhematologic Adverse Reactions

Abnormality	Intervention
Nonhematologic CTCAE Grade ≥3 adverse reaction where prophylaxis is not considered feasible or adverse reaction persists despite treatment	Withhold niraparib for a maximum of 28 days or until resolution of adverse reaction. Resume niraparib at a reduced dose per Table 4. Up to 2 dose reductions are permitted for the starting dose of 300 mg; only 1 dose reduction is permitted for the starting dose of 200 mg.
CTCAE Grade ≥3 treatment-related adverse reaction lasting more than 28 days while patient is administered niraparib 100 mg/day	Discontinue niraparib.

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events.

Table 4: Niraparib Dose Reductions for Nonhematologic Toxicity

	Body weight <77 kg OR screening platelet count <150,000/µL	Body weight ≥77 kg AND screening platelet count ≥150,000/µL
Starting dose	200 mg/day (two 100 mg capsules)	300 mg/day (three 100 mg capsules)
First dose reduction	100 mg/day (one 100 mg capsule)	200 mg/day (two 100 mg capsules)
Second dose reduction	Discontinue medication.	100 mg/day[a] (one 100 mg capsule)

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

[a] If further dose reduction below 100 mg/day is required, discontinue niraparib.

Table 5: Niraparib Dose Modifications for Hematologic Toxicity

Laboratory Abnormality	Intervention
Monitor complete blood counts weekly for the first cycle, once every treatment cycle thereafter	
Platelet count <100,000/μL	First occurrence: Withhold niraparib for a maximum of 28 days and monitor blood counts weekly until platelet counts return to ≥100,000/μL. Resume niraparib at same or reduced dose.[a] If platelet count is <75,000/μL, resume niraparib at a reduced dose
	Second occurrence: Withhold niraparib for a maximum of 28 days and monitor blood counts weekly until platelet counts return to ≥100,000/μL. Resume niraparib at a reduced dose.[a] Discontinue niraparib if the platelet count has not returned to acceptable levels within 28 days of the dose interruption period, or if the patient has already undergone dose reduction to 100 mg QD.
Neutrophil count <1,000/μL	Withhold niraparib for a maximum of 28 days and monitor blood counts until neutrophil counts return to ≥1,500/μL. Resume niraparib at a reduced dose.[a] Discontinue niraparib if neutrophil level has not returned to acceptable levels within 28 days of the dose interruption period, or if the patient has already undergone dose reduction to 100 mg QD. Note: Prophylactic cytokines (ie, granulocyte colony-stimulating factor [GCSF]) should not be administered in the first cycle of the study but may be administered in subsequent cycles according to current American Society of Clinical Oncology (ASCO) guidelines.
Hemoglobin ≤8 g/dL	Withhold niraparib for a maximum of 28 days and monitor blood counts until hemoglobin returns to ≥9 g/dL. Resume niraparib at a reduced dose.[a] Discontinue niraparib if hemoglobin has not returned to acceptable levels within 28 days of the dose interruption period, or if the patient has already undergone dose reduction to 100 mg QD.
Hematologic adverse reaction requiring transfusion	For patients with platelet count ≤10,000/μL, platelet transfusion should be considered. If there are other risk factors such as co-administration of anticoagulation or antiplatelet drugs, consider interrupting these drugs or transfusion at a higher platelet count. Red blood cell transfusion may be given at the discretion of the Investigator. Resume niraparib at a reduced dose.[a]
Confirmed diagnosis of MDS or AML	Permanently discontinue niraparib.

Abbreviation: AML = acute myeloid leukemia; MDS = myelodysplastic syndrome; QD = once daily.
[a] Niraparib dose must not be decreased below 100 mg daily. Additional details on dose reduction are described in Table 4.

If dose interruption or modification is required at any point during study treatment because of hematologic toxicity, weekly blood draws for complete blood count (CBC) will be monitored

until the AE resolves to the specified blood count levels. To ensure the safety of the new dose, weekly blood draws for CBC will be required for an additional 4 weeks after the AE has resolved, after which monitoring every treatment cycle may resume.

Any patient requiring transfusion of platelets or red blood cells (≥1 unit) must undergo a dose reduction upon recovery if study treatment is resumed.

If a diagnosis of myelodysplastic syndrome/acute myeloid leukemia is confirmed by a hematologist, the patient must permanently discontinue study treatment.

For major surgery while on study treatment, up to 4 weeks (28 days) of study treatment interruption is allowed.

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

All dose interruptions and reductions (including any missed doses), and the reasons for the reductions/interruptions, are to be recorded in the eCRF. Reasons for the discontinuation of niraparib must also be recorded in the eCRF.

7.4.2. Pharmacokinetic Criteria for Adjustment or Stopping Doses

Not applicable.

7.5. Criteria for Study Termination

Criteria for study termination are described in the master protocol.

7.6. Study Conduct

7.6.1. Schedule of Events

The schedule of study procedures is provided in Table 6.

7.6.2. Procedures by Visit

Treatment Cycles

Treatment cycles are 21 days (± 3 days) long.

Visits should occur within ± 3 days of the scheduled visit. All times should be recorded using the 24-hour clock (eg, 23:20, not 11:20 PM).

Radiographic Evaluation for Primary Outcome

All patients are required to undergo radiographic evaluation throughout the study as described in Table 6. Tumor imaging (chest, abdomen, and pelvis [plus head if clinically indicated]) should be performed by computed tomography (CT with IV contrast unless contraindication; preferred). Magnetic resonance imaging (MRI) should only be used if clinically appropriate, when CT is contraindicated, or for imaging of the head, but the same imaging technique should be used in a patient throughout the study. CT scan is the more commonly used modality and is preferred for the majority of patients. Positron emission tomography/CT may be used according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 guidelines. If the chest or head CT/MRI is

clear at screening, repeat imaging of these areas is not required in the absence of clinical indication requiring follow-up. Bone scans should be conducted per standard of care.

Serum tumor marker data (eg, cancer antigen 125) will not be used for defining objective responses or disease progression; however, serum tumor marker data can be used for clinical decisions. Response to treatment will be based on Investigator evaluation of radiographic images.

Radiographic evaluations to assess extent of disease will be conducted every 9 weeks (63 days ± 7 days) while on study treatment, independent of cycle delays or dose interruptions, or at any time when progression of disease is suspected. After 1 year of radiographic assessments, patients will have imaging performed every 12 weeks (84 ± 14 days). Radiographic evaluations will continue until progressive disease (PD), start of alternate anticancer treatment, withdrawal of consent to study participation, becoming lost to follow-up, death, or end of the study. Per RECIST v1.1, complete response or partial response should be confirmed; tumor imaging for confirmation of response may be performed at the earliest 4 weeks after the first indication of response or at the next scheduled scan (ie, 9 or 12 weeks later), whichever is clinically indicated.

There is accumulating evidence indicating clinical benefit in a subset of patients treated with immunotherapy despite initial evidence of PD.[38] Patients with PD may continue study treatment at the Investigator's discretion only after discussion with the Sponsor, until the Investigator has determined that the patient is no longer experiencing clinical benefit or until study treatment is no longer tolerated by the patient.

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 (ie, every 9 weeks [63 ± 7 days] for the first year of treatment and every 12 weeks [84 ± 14 days] thereafter) until PD, start of alternate anticancer treatment, withdrawal of consent to study participation, becoming lost to follow-up, death, or end of the study.

Biomarker Assessment

Tumor tissue, blood, and optional ascitic fluid samples will be collected as indicated in Table 6 to identify potential biomarkers.

End of Treatment Visit and Safety Follow-up Visit

All patients will undergo an End of Treatment (EOT) visit within 7 days after study treatment discontinuation. A safety follow-up visit will be conducted 30 days (± 7 days) after the last dose of study treatment. Safety follow-up visits are required only for those patients who have not started an alternate anticancer therapy. After the 30-day safety follow-up visit, all patients will enter the post-treatment follow-up period of telephone assessment for survival status and the occurrence of any treatment-related serious adverse events (SAEs) or adverse events of special interest (AESIs) every 90 (± 14 days), or as otherwise indicated in Section 12 and the master protocol, until patient discontinuation of study, withdrawal of consent, or death. Patients who discontinue the study due to treatment toxicity or intolerability and do not have PD will continue radiographic imaging until PD, start of alternate anticancer treatment, withdrawal of consent to study participation, becoming lost to follow-up, death, or end of the study.

Safety Assessments

Safety assessments conducted during this study include collection of AEs, vital sign measurements, symptom-directed physical examinations, electrocardiograms, clinical laboratory assessments, and Eastern Cooperative Oncology Group performance status.

Table 6: Schedule of Events

Cycle/Visit[a]	**Screening**	**Cycle 1**			**Cycle 2**	**Cycle 3**	**Cycle 4**	**Cycle 5**	**Cycle 6**	**Subsequent Cycles**	**EOT**	**Safety Follow-up**	**Survival Assessment**
Day **Procedure**	**-21 to -1**	**1**	**8**	**15**	**1**	**1**	**1**	**1**	**1**	**1**	**+7 days post trt**	**30 ±7 days**	**Every 90 ±14 days**
Informed consent	X												
Inclusion/Exclusion criteria	X	X											
Demographics	X												
Medical, surgical, cancer, and medication history	X												
Tumor assessment (RECIST v1.1)	X						X[b]			X[b]	X[b]		X[bc]
Tumor tissue	X[d]				X[d] (C2D1-C3D1)								
Blood sample	X[d]				X[d] (C2D1-C3D1)								
Ascitic fluid (optional)	X[e]												
Laboratory assessments	X												
CBC[f]	X	X[g]	X	X	X	X	X	X	X	X	X	X	
Serum chemistry	X	X[g]	X		X	X	X	X	X	X	X	X	
Coagulation	X	X[g]			X	X	X	X	X	X	X	X	
Pregnancy test[h]	X				X	X	X	X	X	X		X	
Urinalysis	X	X[g]			X	X	X	X	X	X	X	X	
Urine sample for protein[i]	X	X			X	X	X	X	X	X			

Cycle/Visit[a]	**Screening**	**Cycle 1**			**Cycle 2**	**Cycle 3**	**Cycle 4**	**Cycle 5**	**Cycle 6**	**Subsequent Cycles**	**EOT**	**Safety Follow-up**	**Survival Assessment**
Day **Procedure**	**-21 to -1**	**1**	**8**	**15**	**1**	**1**	**1**	**1**	**1**	**1**	**+7 days post trt**	**30 ±7 days**	**Every 90 ±14 days**
TSH, T3 or FT3, and FT4 or equivalent[j]	X					X		X		X[j]	X	X	
Serum CA-125	X	X			X	X	X	X	X	X	X	X	X[c]
ECG	X	As necessary according to standard of care											
Physical examination	X										X		
Symptom-directed physical examination	X	X			X	X	X	X	X	X		X	
Vital signs, height, and weight[k]	X	X	X	X	X	X	X	X	X	X	X		
ECOG performance status	X										X		
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	
AE monitoring[l]	X	X	X	X	X	X	X	X	X	X	X	X	X
TSR-042 study treatment administered[m]		X			X	X	X	X		X[n]			
Bevacizumab[m]		X			X	X	X	X	X	X[o]			
Niraparib study treatment dispensed/collected		X			X	X	X	X	X	X			
Survival assessment													X

Abbreviations: AE = adverse event; AESI = adverse event of special interest; C = cycle; CA-125 = cancer antigen 125; CBC = complete blood count; CT = computed tomography; D = day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = End of Treatment; FT3 = free triiodothyronine; FT4 = free thyroxin; MRI = magnetic resonance imaging; PD = disease progression; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; T3 = triiodothyronine; TSH = thyroid-stimulating hormone.

[a] Treatment cycles are 21 days long, with visits on Day 1 of each cycle beyond Cycle 1, unless otherwise specified. Visits for subsequent cycles continue every 21 days (±3 days) until study treatment discontinuation. Results of the laboratory evaluations (with the exception of thyroid studies) should be reviewed before study treatment administration.

[b] Radiographic evaluations (CT/MRI of chest, abdomen, and pelvis) to assess extent of disease will be conducted every 9 weeks (63 days ± 7 days) while on study treatment independent of cycle delays and/or dose interruptions, and/or at any time when progression of disease is suspected. After 1 year of radiographic assessments, patients will have imaging performed every 12 weeks (84 ± 14 days). Radiographic evaluations will continue until PD, start of alternate anticancer treatment, withdrawal of consent to study participation, becoming lost to follow-up, death, or end of the study.

[c] If a patient discontinues treatment for a reason other than progression or death, withdrawal of consent, loss to follow-up, or the end of the study, scans and cancer antigen 125 (CA 125) testing should continue at the specified intervals (ie, every 9 weeks for the first year of study and every 12 weeks thereafter until PD)

[d] All patients included in the study must provide blood and tumor samples at screening. Tumor samples provided at screening need to be obtained after most recent disease progression or freshly biopsied. All patients included in the study must provide on-treatment tumor (provided it is deemed safe and feasible by the Investigator) and blood samples. The on-treatment tumor sample must be collected between Cycle 2 Day 1 and Cycle 3 Day 1, preferably from the same lesion used for the screening assessment. The blood sample must be collected at the same time (± 3 days) as when on treatment tumor samples are collected. Time and dose of last treatment before biopsy must be collected.

[e] Ascitic fluid collection is optional but preferred when paracentesis is performed for clinical reasons between screening to EOT.

[f] If dose interruption or modification is required at any point on study because of hematologic toxicity, weekly blood draws for CBC will be monitored until the AE resolves, and to ensure safety of the new dose, weekly blood draws for CBC also will be required for an additional 4 weeks after the AE has been resolved to the specified levels, after which monitoring every treatment cycle may resume.

[g] If screening laboratory testing (CBC, serum chemistry, coagulation, urinalysis, and CA-125, and TSH, T3 or FT3, and FT4 or equivalent) is performed within 72 hours of first dose of study treatment on Day 1, repeat testing is not required.

[h] For women of childbearing potential only.

[i] Urine dipstick or urine analysis for protein determination should be performed prior to each bevacizumab administration. Patients discovered to have ≥2 proteinuria on dipstick should not be administered bevacizumab, should undergo a 24-hour urine collection, and must demonstrate <2 g of protein in 24 hours to be eligible for bevacizumab treatment to resume.

[j] If TSH, T3 or FT3, or FT4 are not available, equivalent tests should be performed. TSH testing will be done at screening, Cycle 3, and every other cycle thereafter.

[k] Vital signs include blood pressure, pulse, and temperature. Height obtained at screening only. Weight obtained at screening and Day 1 of each cycle only.

[l] AEs are required to be captured through 30 days after cessation of study treatment, 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. In conjunction with the survival assessment, AESIs (regardless of causality) and study-drug related SAEs will be collected every 90 ± 14 days after the last dose of study treatment, or as otherwise indicated in Section 12 and the master protocol.

[m] On days on which more than one study treatment is administered, TSR-042 will be administered first, followed by bevacizumab, and then niraparib, as applicable.

[n] TSR-042 will be administered at a dose of 500 mg on Day 1 every 3 weeks for 4 cycles, followed by 1000 mg every other cycle (every 6 weeks) beginning on Cycle 5 Day 1, until progression or toxicity.

[o] Bevacizumab will be administered for a maximum of 15 cycles.

8. SELECTION AND WITHDRAWAL OF SUBJECTS

The overall list of eligibility criteria for entry into this study is provided in the master protocol. The following are additional cohort-specific eligibility criteria for this cohort. Patients must meet all criteria in both the master protocol and this cohort-specific supplement in order to be eligible for enrollment in this cohort.

8.1. Subject Inclusion Criteria

A1. Patients must be resistant to the most recent platinum-based therapy, defined for the purpose of this protocol as progression within 6 months from completion of a minimum of 4 cycles of platinum-containing therapy. This should be calculated from the date of the last administered dose of platinum therapy to the date of the radiographic imaging showing disease progression. Patients with primary platinum-refractory disease as defined by those who progressed during or within 4 weeks of completion of first platinum-based chemotherapy are not eligible.

A2. Patient must not have received any prior therapy for ovarian cancer with a PARP inhibitor

A3. Patient has had 1 to 2 prior lines of anticancer therapy for ovarian cancer (The definition of prior lines of therapy is provided in Section 8.1, inclusion 3 of the Master Protocol).

A4. Patient is able to take oral medications.

8.2. Subject Exclusion Criteria

A1. Patient has known hypersensitivity to TSR-042, bevacizumab, niraparib, their components, or their excipients

A2. Patient has a known history of myelodysplastic syndrome or acute myeloid leukemia

A3. Patient has active autoimmune disease that has required systemic treatment in the past 2 years (ie, with use of disease-modifying agents, corticosteroids, or immunosuppressive drugs). Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment

A4. Patient received prior treatment with an anti-PD-1 or anti-PD-L1 agent

A5. Patient has received prior treatment with anti-angiogenic therapy with the exception of bevacizumab. (Patients who received prior bevacizumab are eligible only if they did not discontinue bevacizumab due to toxicity, as established by the Investigator.)

A6. Patient has bowel obstruction, had bowel obstruction within the past 3 months, or is otherwise judged by the Investigator to be at high risk for bowel obstruction related to the underlying disease. Patient has any history of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscesses. Evidence of recto-sigmoid involvement by pelvic examination or significant bowel involvement on computed tomography scan

A7. Patient has proteinuria as demonstrated by urine protein:creatinine ratio ≥1.0 at screening or urine dipstick for proteinuria ≥2 (Patients discovered to have ≥2 proteinuria on dipstick at baseline should undergo 24-hour urine collection and must demonstrate <2 g of protein in 24 hours to be eligible.)

A8. Patient is at increased bleeding risk due to concurrent conditions (eg, major injuries or surgery within the past 28 days prior to start of study treatment, history of hemorrhagic stroke, transient ischemic attack, subarachnoid hemorrhage, or clinically significant hemorrhage within the past 3 months)

A9. Patient has a history of recent major thromboembolic event defined as follows:

a. Pulmonary embolism diagnosed within 3 months of enrollment
b. Lower extremity deep venous thrombosis diagnosed within 3 months of enrollment

Note: Patients with a history of thromboembolic disease on stable therapeutic anticoagulation for more than 3 months prior to enrollment are eligible for this study.

8.3. Subject Withdrawal Criteria

8.3.1. Discontinuation from Treatment

Examples of reasons for discontinuing study treatment applicable across cohorts are presented in the master protocol. Details of required dose modifications related to toxicity, including interruptions, reductions, and permanent discontinuations, are provided in Section 7.4.1.

Unless otherwise indicated, treatment with each combination agent will continue independent of dose adjustments, interruptions, or discontinuation of treatment for other combination agents.

8.3.2. Discontinuation from the Study

Guidance on discontinuation of patients from the study is provided in the master protocol.

9. TREATMENT OF SUBJECTS

9.1. Description of Study Drug

The investigational products for this cohort are described in Table 7.

Table 7: Investigational Product

	Investigational Product		
Product name:	TSR-042	Bevacizumab (Avastin)	Niraparib
Dosage form:	Solution for infusion	Infusion	Capsule
Unit dose	500 mg, 50 mg/mL	15 mg/kg infusion	100 mg per capsule
Route of administration	Intravenous	Intravenous	Oral
Physical description	Solution for intravenous infusion in single-use vial	Clear to slightly opalescent, colorless to pale brown, sterile solution for intravenous infusion	Capsules in high-density polyethylene bottles
Manufacturer	WuXi AppTec	Genentech, Inc.	QSP (Charles River Laboratories Contract Manufacturing)

9.2. Concomitant Medications

Details on the definition and recording of concomitant medications are provided in the master protocol.

9.2.1. Prohibited Medications

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

Medications prohibited in the overall study are provided in the master protocol. The following additional therapies are prohibited during the screening and treatment phase for this cohort.

- Investigational agents other than TSR-042, bevacizumab, and niraparib
- 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.

- Prophylactic cytokines (ie, granulocyte colony-stimulating factor [GCSF]) should not be administered in the first cycle of the study but may be administered in subsequent cycles according to current American Society of Clinical Oncology (ASCO) guidelines.[39]

In addition, niraparib has been shown to weakly induce cytochrome P450 (CYP) 1A2 in vitro and is an insensitive substrate for P-glycoprotein. Therefore, Investigators and patients should be advised to use caution with drugs that are sensitive substrates of CYP1A2 with narrow therapeutic range, such as theophylline and tizanidine. The niraparib safety profile includes risk for thrombocytopenia, and bevacizumab may increase the potential for bleeding (hemorrhage); therefore, patients should be advised to use caution with anticoagulants (eg, warfarin) and antiplatelet drugs (eg, aspirin). Physicians should follow the current versions of the TSR-042 Investigator's Brochure, the Zejula® package insert[39], the Avastin® [Genentech/Roche US] package insert[40], and the niraparib Investigator's Brochure for information on the general management of the patients receiving these therapies.

9.2.2. Contraception

Contraception guidelines are provided in the master protocol.

9.2.3. Rescue Medications and Supportive Care Guidelines

Supportive care measures for AEs during treatment with niraparib should be provided as deemed necessary by the treating Investigator according to local institutional practice and/or guidance in the appropriate prescribing information.

During treatment with TSR-042, patients should receive appropriate supportive care measures for AEs as deemed necessary by the treating Investigator, including but not limited to the items outlined below. Prophylactic cytokines (eg, GCSF) should not be administered in the first cycle of the study but may be administered in subsequent cycles according to current ASCO guidelines.[39] 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.

9.2.3.1. 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.

9.2.3.2. 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.

9.2.3.3. 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.

9.2.3.4. 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.

9.2.3.5. 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.

9.2.3.6. 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.

9.2.3.7. 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.

9.2.3.8. 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 8 shows treatment guidelines for patients who experience infusion-related reactions associated with administration of TSR-042.

Table 8: TSR-042 Infusion Reaction Treatment Guidelines

CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 CCI	Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the Investigator.	None.
Grade 2 CCI	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	Patient may be premedicated 1.5 hours (± 30 min) prior to infusion of TSR-042 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
	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.	
Grade 3: CCI **Grade 4:** CCI	**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.

9.2.4. Other Study Restrictions

Other study restrictions are provided in the master protocol.

9.3. Treatment Compliance

Overall study treatment compliance information is presented in the master protocol. Study treatment (TSR-042, bevacizumab, and niraparib) will be administered by investigational site personnel at investigational sites as detailed in Section 10.5.

9.4. Randomization and Blinding

This study is not blinded. In order to minimize allocation bias, the sponsor may use randomized allocation for those patients meeting the eligibility criteria of more than 1 contemporarily enrolling treatment cohort as described in the master protocol.

10. STUDY DRUG MATERIALS AND MANAGEMENT

10.1. Study Drug

10.1.1. TSR-042

TSR-042 is an IgG4-κ humanized monoclonal antibody and will be supplied as a solution in vials containing 500 mg (50 mg/mL) TSR-042.

10.1.2. Bevacizumab

Bevacizumab (Avastin) is a clear to slightly opalescent, colorless to pale brown, sterile, pH 6.2 solution for IV infusion.[15] The excipients for bevacizumab are trehalose dihydrate, sodium phosphate, polysorbate 20, and water for injections. Bevacizumab is obtained from commercial sources according to local practice standards, and it is provided as a commercially available dosage.

10.1.3. 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.

10.2. Study Drug Packaging and Labeling

Overall study treatment packaging and labeling is described in the master protocol.

10.3. Study Drug Storage

Study treatment storage is described in the master protocol.

10.4. Study Drug Preparation

The Pharmacy Manual contains specific instructions for the preparation of each dose of the niraparib capsules and TSR-042 infusion solutions. Refer to local prescribing information for instructions for the preparation of bevacizumab.

10.5. Administration

On days on which more than 1 study treatment is administered, TSR-042 will be administered first, followed by bevacizumab, and then niraparib, as applicable.

10.5.1. TSR-042

TSR-042 will be administered via a 30-minute IV infusion on Day 1 Q3W at 500 mg for 4 cycles followed by 1,000 mg every other cycle (Q6W) beginning on Cycle 5 Day 1.

The Pharmacy Manual contains descriptions of the packaging of TSR-042 and instructions for the preparation and administration of TSR-042.

10.5.2. Bevacizumab

Bevacizumab 15 mg/kg will be administered via IV infusion on Day 1 of every 21-day cycle Q3W for up to 15 months.

Details on the administration of bevacizumab can be found in the bevacizumab prescribing information.

10.5.3. Niraparib

Niraparib will be supplied as 100-mg capsules and will be administered PO QD continuously throughout each 21-day cycle at the assigned dose. The starting dose will be

- 300 mg in patients with a screening actual body weight ≥77 kg AND screening platelet count ≥150,000/μL
- 200 mg in patients with a screening actual body weight <77 kg OR screening platelet count <150,000/μL.

On or after Cycle 3 Day 1, patients receiving the 200-mg niraparib starting dose may have their niraparib dose increased to 300 mg daily after discussion with medical monitor or designee if hemoglobin is ≥9 g/dL, platelets are ≥100,000/μL, and neutrophils are ≥1500/μL for all laboratory evaluations performed during the first 2 cycles.

Patients will be instructed to take niraparib at the same time each day. Bedtime administration may be a potential method for managing nausea. Patients must swallow and not chew all capsules. The consumption of water and food is permissible.

Niraparib will be dispensed to patients on Day 1 of every cycle (every 21 days) until the patient discontinues study treatment.

The Pharmacy Manual contains descriptions of the packaging of niraparib and instructions for the preparation and administration of niraparib.

10.6. Study Drug Accountability

Study treatment accountability is described in the master protocol.

10.7. Study Drug Handling and Disposal

Study treatment handling and disposal are described in the master protocol.

11. ASSESSMENT OF EFFICACY

11.1. Primary Endpoint: Objective Response Rate

The primary endpoint, ORR, is described in the master protocol.

11.2. Secondary Efficacy Endpoints

The secondary efficacy endpoints are described in the master protocol.

11.3. Biomarker Endpoints

Tumor tissue, blood, and optional ascitic fluid samples will be assessed to identify potential biomarkers including *BRCA* status, HRR gene status, HRD score, PD-L1 expression, and other disease-related or treatment-related biomarkers that would associate with tumor responses to the combination of TSR-042, bevacizumab, and niraparib.

Details on tumor tissue, blood, and optional ascitic fluid sample collection, processing, and management can be found in the Study Laboratory Manual. Any remaining blood and tumor tissue samples may be stored for up to 15 years for future biospecimen research, which may include biomarker testing.

Additionally, samples will be assessed to evaluate the evolution of the molecular profile of the tumor and tumor microenvironment in response to treatment.

12. ASSESSMENT OF SAFETY

12.1. Safety Parameters

Safety parameters for this study are described in the master protocol.

In addition, urine dipstick or urine analysis for protein determination will be performed at Screening and prior to each bevacizumab administration. Patients discovered to have ≥2 proteinuria on dipstick should not be administered bevacizumab, should undergo a 24-hour urine collection, and must demonstrate <2 g of protein in 24 hours to be eligible for bevacizumab treatment to resume.

12.2. Adverse Events and Special Situations

Guidance on AEs and special situations is provided in the master protocol.

With regard to AESIs, no AESIs have been reported to date for TSR-042, therefore all serious AEs assessed by the Investigator or Sponsor to be reasonably associated with the use of TSR-042 are considered to be unexpected and should be reported as described in the master protocol. For bevacizumab, the local approved product label should be consulted. The AESIs for niraparib are described in the master protocol.

13. STATISTICS

An overall description of the statistics for this study is provided in the master protocol. Additional details are provided in the Statistical Analysis Plan.

13.1. Sample Size Determination

Sample size calculation was performed using SAS® version 9.4 with the EXACT method.

A sample size of approximately 40 patients is estimated for this cohort to provide assessment of clinical activity of the treatment based on ORR. The null hypothesis that the true response rate is ≤25% (H0: $p \leq 0.25$) will be tested against a 1-sided alternative of ≥45% (Ha: $p \geq 0.45$). If there are 15 or more responses observed among 40 treated patients, it will be concluded that the lower bound of 80% confidence interval excludes H_0 and the null hypothesis will be rejected. With 40 patients treated, the cohort has 87% power to rule out a ≤25% ORR (null hypothesis) when the true ORR is 45% at the 10% type I error rate (1-sided).

Enrollment will be stratified based on histology (epithelial vs carcinosarcoma). Enrollment of patients with carcinosarcoma will be limited to comprise approximately 10% of the cohort (ie, approximately 4 patients).

13.2. Planned Analysis

The primary analysis will occur 6 months after the last patient in the cohort has started study treatment.

The final analysis will occur 1 year after the last patient in the cohort has received her last dose of study treatment.

Additionally, an interim safety analysis may be performed after the first 12 patients are enrolled between Cohorts A and B and have completed 2 cycles of therapy. If results from Study 3000-01-002 (NCT03307785) are available and support the feasibility of the starting dose regimens in the current trial, the safety interim analysis will not be performed.

13.3. Biomarker Analysis

Exploratory endpoints of this trial include identification of potential biomarkers that would associate with tumor responses and evaluation of the tumor and tumor microenvironment changes in response to treatment. An attrition rate of up to 50% is expected in obtaining a pre- and on-treatment paired samples, as it might not be safe or feasible to repeat a tumor biopsy in certain patients. Additionally, some of the obtained core biopsy samples may not be evaluable. Therefore, it is anticipated there will be approximately 20 evaluable paired specimens for this cohort.

As one of the measures of tumor microenvironment change in response to treatment, presence of tumor-infiltrating lymphocytes (TILs) will be quantified. Based on the literature report, a baseline CD8+ TIL of 15 cells/field (using a ×20 objective lens) is assumed, with a standard deviation of 15 cells/field.[41] With 20 evaluable paired specimens, there will be 90% power to detect an increase in CD8+ TILs from 15 cells/field to 25 cells/fields (relative delta = 67%

increase) at the 5% type I error rate (1 sided) under an assumption of an additive shift model with a Gaussian common density function.

The incidence/changes of biomarkers will be summarized using descriptive statistics. Correlation of clinical activity with biomarker subpopulations may be performed.

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

Direct access to source data and documents is described in the master protocol.

15. QUALITY CONTROL AND QUALITY ASSURANCE

Quality control and quality assurance is described in the master protocol.

16. ETHICS

Ethics is described in the master protocol.

17. DATA HANDLING AND RECORDKEEPING

Data handling and recordkeeping is described in the master protocol.

18. PUBLICATION POLICY

Publication policy is described in the master protocol.

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