NIRAPARIB; TSR-042; TSR-022
3000-01-002

Phase 1b Dose-Finding Study of Niraparib, TSR-022, Bevacizumab, and Platinum-Based Doublet Chemotherapy in Combination With TSR-042 in Patients With Advanced or Metastatic Cancer

Sponsor:	TESARO 1000 Winter Street Suite 3300 Waltham, MA 02451 USA PPD
Medical Monitor:	PPD, MD Senior Medical Director PPD
Clinical Research Organization:	Not applicable
Sponsor Protocol No.	3000-01-002
IND No.:	126472
Study Drug Names:	Niraparib, TSR-042, TSR-022, carboplatin-paclitaxel, carboplatin-pemetrexed, carboplatin–nab-paclitaxel, and bevacizumab
Development Phase:	1b
Date of Original Protocol:	07 July 2017
Date of Amendment 1:	15 November 2017
Date of Amendment 2:	15 August 2018
Version of Protocol	3.0

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

Confidentiality Statement

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SPONSOR SIGNATURE PAGE

Declaration of Sponsor or Responsible Medical Officer

Phase 1b Dose-Finding Study of Niraparib, TSR-022, Bevacizumab, and Platinum-Based Doublet Chemotherapy in Combination With TSR-042 in Patients With Advanced or Metastatic Cancer

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

PPD

August 15th, 2018

PPD, MD

Date

Senior Medical Director

INVESTIGATOR'S AGREEMENT

Declaration of the Principal Investigator

Phase 1b Dose-Finding Study of Niraparib, TSR-022, Bevacizumab, and Platinum-Based Doublet Chemotherapy in Combination With TSR-042 in Patients With Advanced or Metastatic Cancer

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

Principal Investigator

Name:	**Date**
Title:	
Institution:	

1. SYNOPSIS

Name of Sponsor/Company: TESARO	
Name of Investigational Products: Niraparib, TSR-042, TSR-022, carboplatin-paclitaxel, carboplatin-pemetrexed, carboplatin–nab-paclitaxel, bevacizumab	
Name of Active Ingredients: Niraparib, TSR-042, TSR-022, carboplatin-paclitaxel, carboplatin-pemetrexed, carboplatin–nab-paclitaxel, bevacizumab	
Title: Phase 1b Dose-Finding Study of Niraparib, TSR-022, Bevacizumab, and Platinum-Based Doublet Chemotherapy in Combination With TSR-042 in Patients With Advanced or Metastatic Cancer	
Study Center(s): Up to 31 sites in the United States	
Principal Investigator: To be determined **Investigators:** To be determined	
Studied Period (Years): Estimated date of first patient enrolled: Q4 2017 Estimated date of last patient enrolled: Q2 or Q3 2019	**Phase of Development:** Phase 1b

Objectives:

Primary Objectives

The primary objectives for Part A of this study are as follows:

- To evaluate dose-limiting toxicities (DLTs) of TSR-042 and niraparib combination treatment during the first cycle of treatment in patients with advanced or metastatic cancer and to establish a recommended Phase 2 dose (RP2D)
- To evaluate the safety and tolerability of TSR-042 and niraparib combination treatment

The primary objectives for Part B of this study are as follows:

- To evaluate DLTs of TSR-042 and carboplatin-paclitaxel combination treatment during the first cycle of treatment in patients with advanced or metastatic cancer and to confirm an RP2D
- To evaluate the safety and tolerability of TSR-042 and carboplatin-paclitaxel combination treatment

The primary objectives for Part C of this study are as follows:

- To evaluate DLTs of TSR-042, niraparib and bevacizumab combination treatment during the first cycle of treatment in patients with advanced or metastatic cancer and to establish an RP2D
- To evaluate the safety and tolerability of TSR-042, niraparib and bevacizumab combination treatment

The primary objectives for Part D of this study are as follows:

- To evaluate DLTs of TSR-042, carboplatin-paclitaxel and bevacizumab combination treatment during the first cycle of treatment in patients in whom carboplatin-paclitaxel and bevacizumab combination treatment is a reasonable therapy, and to confirm an RP2D
- To evaluate the safety and tolerability of TSR-042, carboplatin-paclitaxel and bevacizumab combination treatment

The primary objectives for Part E of this study are as follows:

- To evaluate DLTs of TSR-042 and carboplatin-pemetrexed combination treatment during the first cycle of treatment, as first-line treatment in patients with advanced or metastatic non-squamous non-small cell lung cancer (NSCLC), and to confirm an RP2D
- To evaluate the safety and tolerability of TSR-042 and carboplatin-pemetrexed combination treatment

The primary objectives for Part F of this study are as follows:

- To evaluate DLTs of TSR-042, TSR-022, and carboplatin-pemetrexed combination treatment during the first cycle of treatment, as first-line treatment in patients with advanced or metastatic non-squamous NSCLC, and to confirm an RP2D
- To evaluate the safety and tolerability of TSR-042, TSR-022, and carboplatin-pemetrexed combination treatment

The primary objectives for Part G of this study are as follows:

- To evaluate DLTs of TSR-042 and carboplatin–nab-paclitaxel combination treatment during the first cycle of treatment, as first-line treatment in patients with advanced or metastatic NSCLC, and to confirm an RP2D
- To evaluate the safety and tolerability of TSR-042 and carboplatin–nab-paclitaxel combination treatment

The primary objectives for Part H of this study are as follows:

- To evaluate DLTs of TSR-042, TSR-022, and carboplatin–nab-paclitaxel combination treatment during the first cycle of treatment, as first-line treatment in patients with advanced or metastatic NSCLC, and to confirm an RP2D
- To evaluate the safety and tolerability of TSR-042, TSR-022, and carboplatin–nab-paclitaxel combination treatment

The primary objectives for Part I of this study are as follows:

- To evaluate DLTs of TSR-042, TSR-022, and carboplatin-paclitaxel combination treatment during the first cycle of treatment, as first-line treatment in patients with advanced or metastatic NSCLC, and to confirm an RP2D
- To evaluate the safety and tolerability of TSR-042, TSR-022, and carboplatin-paclitaxel combination treatment

Secondary Objectives

The secondary objectives for Part A of the study are as follows:

- To evaluate measures of clinical benefit as assessed by the Investigators, including objective response rate (ORR), duration of response (DOR), disease control rate (DCR), and progression-free survival (PFS) by Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1)
- To evaluate the pharmacokinetics (PK) of niraparib, its major metabolite M1, and TSR-042 during TSR-042 and niraparib combination treatment
- To evaluate anti-drug antibodies (ADAs) of TSR-042 during TSR-042 and niraparib combination treatment

The secondary objectives for Part B of the study are as follows:

- To evaluate measures of clinical benefit as assessed by the Investigators, including ORR, DOR, DCR, and PFS by RECIST v1.1
- To evaluate the PK of TSR-042 during TSR-042 and carboplatin-paclitaxel combination treatment
- To evaluate ADAs of TSR-042 during TSR-042 and carboplatin-paclitaxel combination treatment

The secondary objectives for Part C of the study are as follows:

- To evaluate measures of clinical benefit as assessed by the Investigators, including ORR, DOR, DCR, and PFS by RECIST v1.1
- To evaluate the PK of niraparib, its major metabolite M1, and TSR-042 during TSR-042, niraparib and bevacizumab combination treatment
- To evaluate ADAs of TSR-042 during TSR-042, niraparib and bevacizumab combination treatment

The secondary objectives for Part D of the study are as follows:

- To evaluate measures of clinical benefit as assessed by the Investigators, including ORR, DOR, DCR, and PFS by RECIST v1.1
- To evaluate the PK of TSR-042 during TSR-042, carboplatin-paclitaxel and bevacizumab combination treatment
- To evaluate ADAs of TSR-042 during TSR-042, carboplatin-paclitaxel and bevacizumab combination treatment

The secondary objectives for Part E of the study are as follows:

- To evaluate measures of clinical benefit as assessed by the Investigators, including ORR, DOR, DCR, and PFS by RECIST v1.1
- To evaluate the PK of TSR-042 during TSR-042 and carboplatin-pemetrexed combination treatment

- To evaluate ADAs of TSR-042 during TSR-042 and carboplatin-pemetrexed combination treatment

The secondary objectives for Part F of the study are as follows:

- To evaluate measures of clinical benefit as assessed by the Investigators, including ORR, DOR, DCR, and PFS by RECIST v1.1
- To evaluate the PK of TSR-042 and TSR-022 during TSR-042, TSR-022, and carboplatin-pemetrexed combination treatment
- To evaluate ADAs of TSR-042 and TSR-022 during TSR-042, TSR-022, and carboplatin-pemetrexed combination treatment

The secondary objectives for Part G of the study are as follows:

- To evaluate measures of clinical benefit as assessed by the Investigators, including ORR, DOR, DCR, and PFS by RECIST v1.1
- To evaluate the PK of TSR-042 during TSR-042 and carboplatin–nab-paclitaxel combination treatment
- To evaluate ADAs of TSR-042 during TSR-042 and carboplatin–nab-paclitaxel combination treatment

The secondary objectives for Part H of the study are as follows:

- To evaluate measures of clinical benefit as assessed by the Investigators, including ORR, DOR, DCR, and PFS by RECIST v1.1
- To evaluate the PK of TSR-042 and TSR-022 during TSR-042, TSR-022, and carboplatin–nab-paclitaxel combination treatment
- To evaluate ADAs of TSR-042 and TSR-022 during TSR-042, TSR-022, and carboplatin–nab-paclitaxel combination treatment

The secondary objectives for Part I of the study are as follows:

- To evaluate measures of clinical benefit as assessed by the Investigators, including ORR, DOR, DCR, and PFS by RECIST v1.1
- To evaluate the PK of TSR-042 and TSR-022 during TSR-042, TSR-022, and carboplatin-paclitaxel combination treatment
- To evaluate ADAs of TSR-042 and TSR-022 during TSR-042, TSR-022, and carboplatin-paclitaxel combination treatment

Exploratory Objectives

The exploratory objectives for Part A of the study are as follows:

- To explore biomarkers that may be predictive of benefit from TSR-042 and niraparib combination treatment based on the pretreatment biomarker profile
- To explore changes in biomarkers (e.g., immune cells and immune proteins) in the blood following TSR-042 and niraparib combination treatment and correlate with clinical benefit

The exploratory objectives for Part B of the study are as follows:

- To explore biomarkers that may be predictive of benefit from TSR-042 and carboplatin-paclitaxel combination treatment based on the pretreatment biomarker profile
- To explore changes in biomarkers (e.g., immune cells and immune proteins) in the blood following TSR-042 and carboplatin-paclitaxel combination treatment and correlate with clinical benefit

The exploratory objectives for Part C of the study are as follows:

- To explore biomarkers that may be predictive of benefit from TSR-042, niraparib and bevacizumab combination treatment based on the pretreatment biomarker profile
- To explore changes in biomarkers (e.g., immune cells and immune proteins) in the blood following TSR-042, niraparib and bevacizumab combination treatment and correlate with clinical benefit

The exploratory objectives for Part D of the study are as follows:

- To explore biomarkers that may be predictive of benefit from TSR-042, carboplatin-paclitaxel and bevacizumab combination treatment based on the pretreatment biomarker profile
- To explore changes in biomarkers (e.g., immune cells and immune proteins) in the blood following TSR-042, carboplatin-paclitaxel and bevacizumab combination treatment and correlate with clinical benefit

The exploratory objectives for Part E of the study are as follows:

- To explore biomarkers that may be predictive of benefit from TSR-042 and carboplatin-pemetrexed combination treatment based on the pretreatment biomarker profile
- To explore changes in biomarkers (e.g., immune cells and immune proteins) in the blood following TSR-042 and carboplatin-pemetrexed combination treatment and correlate with clinical benefit

The exploratory objectives for Part F of the study are as follows:

- To explore biomarkers that may be predictive of benefit from TSR-042, TSR-022, and carboplatin-pemetrexed combination treatment based on the pretreatment biomarker profile
- To explore changes in biomarkers (e.g., immune cells and immune proteins) in the blood following TSR-042, TSR-022, and carboplatin-pemetrexed treatment and correlate with clinical benefit

The exploratory objectives for Part G of the study are as follows:

- To explore biomarkers that may be predictive of benefit from TSR-042 and carboplatin–nab-paclitaxel combination treatment based on the pretreatment biomarker profile
- To explore changes in biomarkers (e.g., immune cells and immune proteins) in the blood following TSR-042 and carboplatin–nab-paclitaxel combination treatment and correlate with clinical benefit

The exploratory objectives for Part H of the study are as follows:

- To explore biomarkers that may be predictive of benefit from TSR-042, TSR-022, and carboplatin–nab-paclitaxel combination treatment based on the pretreatment biomarker profile
- To explore changes in biomarkers (e.g., immune cells and immune proteins) in the blood following TSR-042, TSR-022, and carboplatin–nab-paclitaxel treatment and correlate with clinical benefit

The exploratory objectives for Part I of the study are as follows:

- To explore biomarkers that may be predictive of benefit from TSR-042, TSR-022, and carboplatin-paclitaxel combination treatment based on the pretreatment biomarker profile
- To explore changes in biomarkers (e.g., immune cells and immune proteins) in the blood following TSR-042, TSR-022, and carboplatin-paclitaxel treatment and correlate with clinical benefit

Methodology:

Overall Study Design

This is a multicenter, open-label, 9-part Phase 1b study evaluating the safety and preliminary efficacy of niraparib or niraparib/bevacizumab in combination with TSR-042 treatment and confirming the safety and tolerability of carboplatin-paclitaxel, carboplatin-paclitaxel/bevacizumab, carboplatin-pemetrexed, TSR-022/carboplatin-pemetrexed, carboplatin–nab-paclitaxel, TSR-022/carboplatin–nab-paclitaxel, and TSR-022/carboplatin-paclitaxel in combination with TSR-042 treatment in patients with advanced or metastatic cancer. Specifically, patients eligible for this study are as follows:

- Part A (dose finding—TSR-042 and niraparib combination treatment): all comers, defined as patients with previously treated advanced or metastatic cancer
- Part B (safety and tolerability evaluation—TSR-042 and carboplatin-paclitaxel combination treatment): patients with advanced or metastatic cancer for which treatment with carboplatin and paclitaxel is indicated (e.g., including, but not limited to, non-small cell lung cancer [NSCLC], ovarian cancer, and cervical cancer)
- Part C (dose finding—TSR-042, niraparib and bevacizumab combination treatment): all comers, defined as patients with previously treated advanced or metastatic cancer
- Part D (safety and tolerability evaluation—TSR-042, carboplatin-paclitaxel and bevacizumab combination treatment): in patients in whom carboplatin-paclitaxel and bevacizumab is considered a reasonable therapy
- Part E (safety and tolerability evaluation—TSR-042 and carboplatin-pemetrexed combination treatment): as first-line treatment in patients with advanced or metastatic non-squamous NSCLC
- Part F (safety and tolerability evaluation—TSR-042, TSR-022, and carboplatin-pemetrexed combination treatment): as first-line treatment in patients with advanced or metastatic non-squamous NSCLC

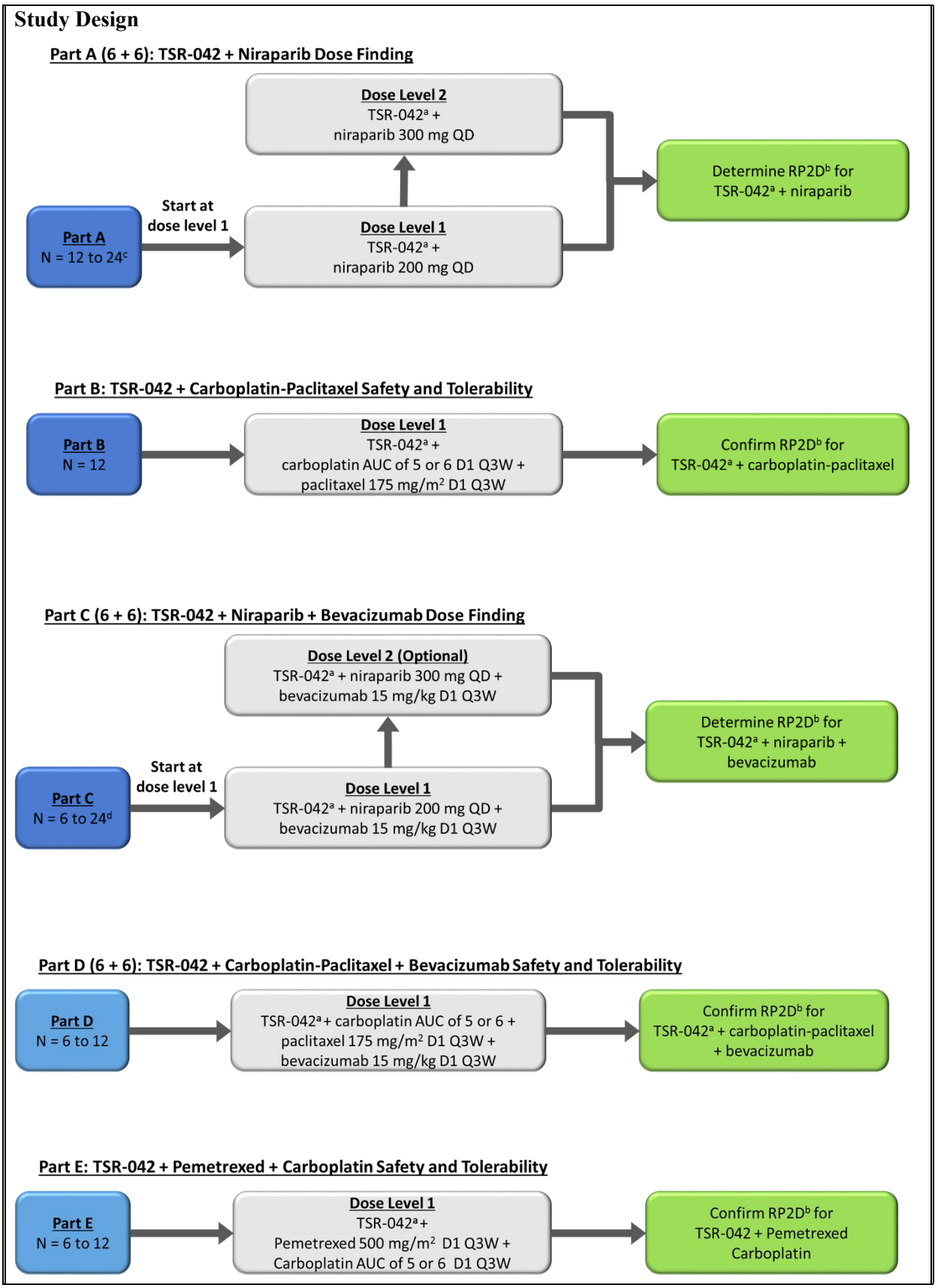
- Part G (safety and tolerability evaluation—TSR-042 and carboplatin–nab-paclitaxel combination treatment): as first-line treatment in patients with advanced or metastatic NSCLC
- Part H (safety and tolerability evaluation—TSR-042, TSR-022, and carboplatin–nab-paclitaxel combination treatment): as first-line treatment in patients with advanced or metastatic NSCLC
- Part I (safety and tolerability evaluation—TSR-042, TSR-022, and carboplatin-paclitaxel combination treatment): as first-line treatment in patients with advanced or metastatic NSCLC

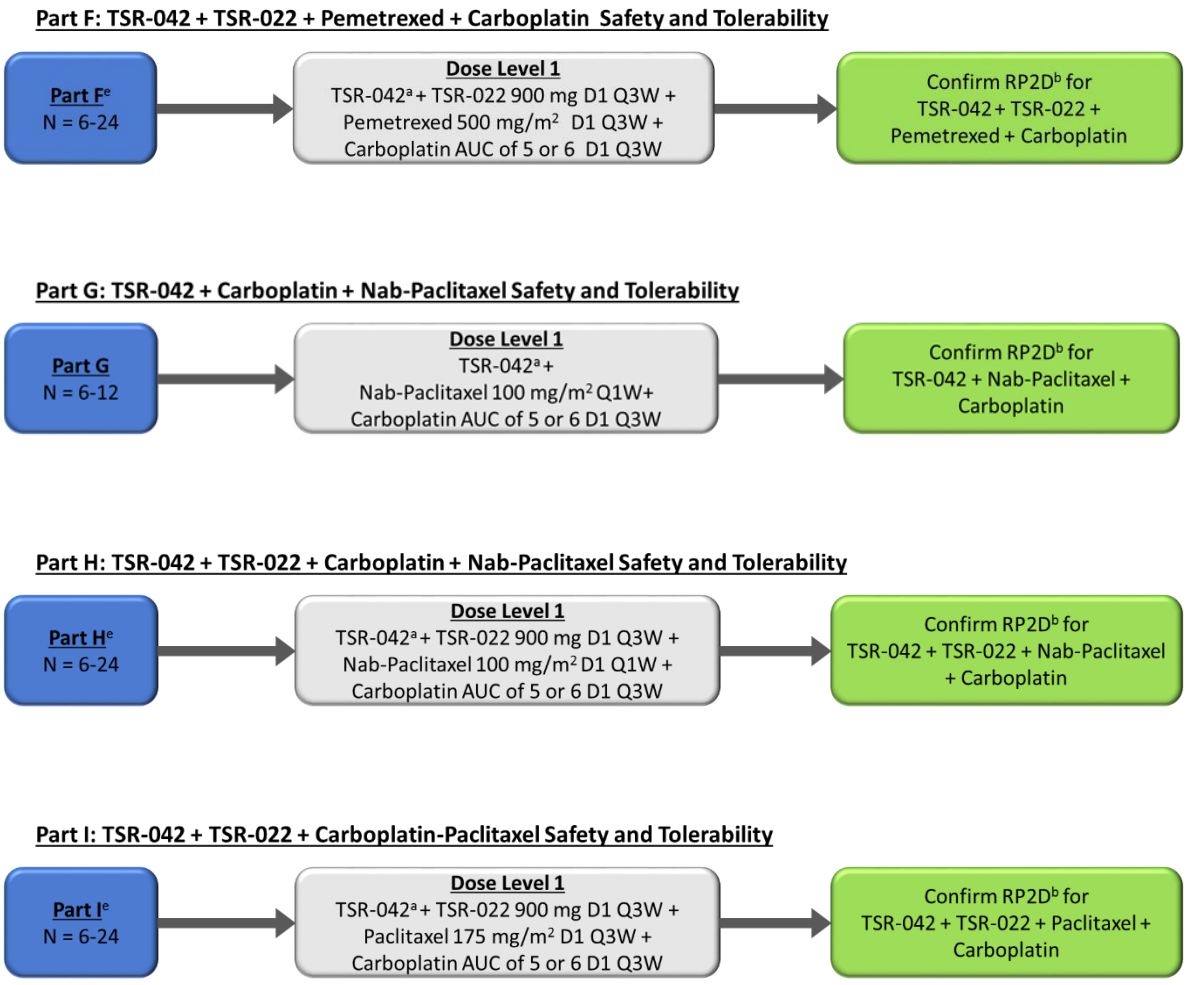
The study will include 9 parts: Parts A, B, C, D, E, F, G, H, and I. Part A will be a dose-finding evaluation conducted in all comers (12 to 24 patients) to determine the RP2D of niraparib in combination with TSR-042. Part B will evaluate the safety and tolerability of TSR-042 and carboplatin-paclitaxel combination treatment in approximately 12 patients with advanced or metastatic cancer for which carboplatin-paclitaxel is indicated. Part C will be a dose-finding evaluation conducted in all comers (6 to 24 patients) to determine the RP2D of niraparib and bevacizumab in combination with TSR-042. Part D will evaluate the safety and tolerability of TSR-042, carboplatin-paclitaxel and bevacizumab combination treatment in 6 to 12 patients in whom carboplatin-paclitaxel and bevacizumab combination treatment is considered a reasonable therapy. Part E will evaluate the safety and tolerability of TSR-042 and carboplatin-pemetrexed combination treatment as first-line treatment in 6 to 12 patients with advanced or metastatic non-squamous NSCLC. Part F will evaluate the safety and tolerability of TSR-042, TSR-022, and carboplatin-pemetrexed combination treatment as first-line treatment in 6 to 24 patients with advanced or metastatic non-squamous NSCLC. Part G will evaluate the safety and tolerability of TSR-042 and carboplatin–nab-paclitaxel combination treatment as first-line treatment in 6 to 12 patients with advanced or metastatic NSCLC. Part H will evaluate the safety and tolerability of TSR-042, TSR-022, and carboplatin–nab-paclitaxel combination treatment as first-line treatment in 6 to 24 patients with advanced or metastatic NSCLC. Part I will evaluate the safety and tolerability of TSR-042, TSR-022, and carboplatin-paclitaxel combination treatment as first-line treatment in 6 to 24 patients with advanced or metastatic NSCLC.

Enrollment of patients into Parts A, B, D, E, G, and I will occur concurrently. Part C will be initiated after dose level 1 (niraparib 200 mg) in Part A is determined to be safe. Part F will be initiated after TSR-042 and carboplatin-pemetrexed combination treatment in Part E is determined to be safe. Part H will be initiated after TSR-042 and carboplatin–nab-paclitaxel combination treatment in Part G is determined to be safe.

The study will be conducted in conformance with the protocol, Good Clinical Practice (GCP), and applicable regulatory requirements. The study design is provided below.

Study Design





Abbreviations: AE = adverse event; AUC = area under the plasma or serum concentration-time curve; D1 = Day 1; D21 = Day 21; DLT = dose-limiting toxicity; N = xx; PK = pharmacokinetics; Q1W = every week; Q3W = every 3 weeks; Q6W = every 6 weeks; QD = once daily; RP2D = recommended Phase 2 dose.

[a] In addition to receiving niraparib (Part A), carboplatin-paclitaxel (Part B), niraparib and bevacizumab (Part C), carboplatin-paclitaxel and bevacizumab (Part D), carboplatin-pemetrexed (Part E), TSR-022 and carboplatin-pemetrexed (Part F), carboplatin–nab-paclitaxel (Part G), TSR-022 and carboplatin–nab-paclitaxel (Part H), and TSR-022 and carboplatin-paclitaxel (Part I) at the specified regimen, all patients will be administered TSR-042 at 500 mg on Day 1 of every cycle (Q3W) for 4 cycles. Beginning on Day 1 of Cycle 5, TSR-042 will be administered to patients in Parts A, B, C, and D at 1,000 mg on Day 1 of every other cycle (Q6W) until the patient discontinues study treatment. Patients in Parts E, F, G, H, and I will continue to receive TSR-042 500 mg on Day 1 of every cycle (Q3W) throughout the study.

[b] The RP2D for TSR-042 and niraparib combination treatment (Part A); TSR-042 and carboplatin-paclitaxel combination treatment (Part B); TSR-042, niraparib, and bevacizumab combination treatment (Part C); TSR-042, carboplatin-paclitaxel, and bevacizumab combination treatment (Part D); TSR-042 and carboplatin-pemetrexed (Part E); TSR-042, TSR-022, and carboplatin-pemetrexed (Part F); TSR-042 and carboplatin–nab-paclitaxel (Part G); TSR-042, TSR-022, and carboplatin–nab-paclitaxel (Part H); and TSR-042, TSR-022, and carboplatin-paclitaxel (Part I), will be determined or confirmed based on an evaluation of multiple endpoints, which may include the DLT rate in first and subsequent cycles of combination treatment, the rate of dose modifications for non-DLT AEs, the ability to manage toxicities, PK, niraparib dose intensity, and signs of clinical efficacy.

[c] 12 to 24 patients will be enrolled in Part A to determine the RP2D for TSR-042 and niraparib combination treatment.
[d] Initially, dose level 1 in Part C will enroll 6 to 12 patients to determine the RP2D for TSR-042, niraparib, and bevacizumab combination treatment. Dose level 2 is optional.
[e] 900 mg of TSR-022 is the highest dose tested in dose escalation in combination with TSR-042 that provides maximal pharmacodynamic effect; this dose may be lowered to dose level -1 (300 mg) if needed. Based on available safety information, the Sponsor may decide to test additional dose levels.

General Study Conduct

Part A: Dose Finding for TSR-042 and Niraparib Combination Treatment

Determination of the RP2D for TSR-042 and niraparib combination treatment will be conducted using the dose levels described in the table below:

Dose Regimen for TSR-042 and Niraparib Combination Treatment

Dose Level	Niraparib	TSR-042 Dose
1	200 mg administered on Days 1 to 21 repeated Q3W	500 mg on Day 1 of every cycle (Q3W) for 4 cycles, followed by 1,000 mg on Day 1 of every other cycle (Q6W) beginning on Day 1/Cycle 5
2	300 mg administered on Days 1 to 21 repeated Q3W	

Abbreviations: Q3W = every 3 weeks; Q6W = every 6 weeks.

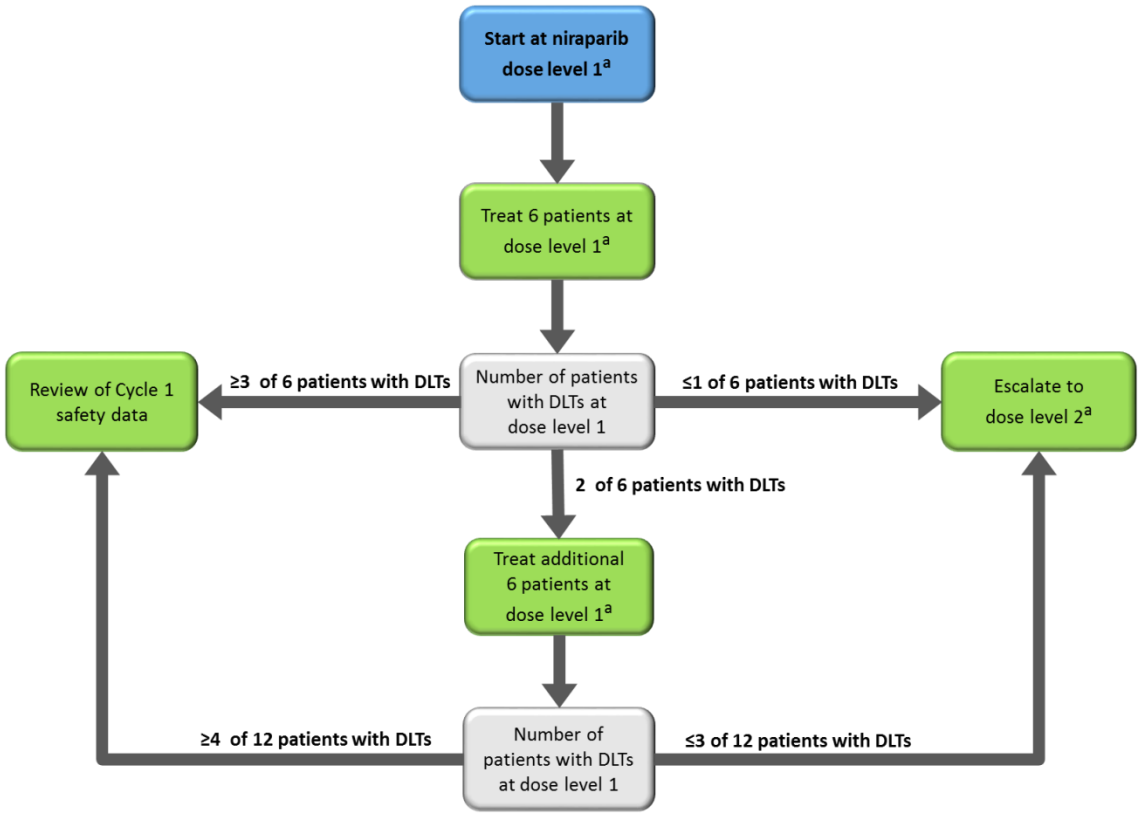
At dose level 1, a cohort of 6 patients will be enrolled initially. After all patients in dose level 1 who are evaluable for safety have completed Cycle 1 of combination treatment, if ≤1 patient experiences a DLT (see DLT Assessment below), dose level 1 will be considered safe. If 2 of 6 patients experience DLTs, 6 additional patients will be enrolled at dose level 1. If 12 patients are enrolled at dose level 1 and ≤3 of 12 patients experience DLTs, dose level 1 will be considered safe. The combination therapy will be considered unsafe if ≥3 of 6 or ≥4 of 12 patients experience DLTs during Cycle 1 (see Part A dose-finding scheme below). However, when determining the RP2D, the Sponsor will review and consider safety data from all patients treated with the combination therapy. Note: Part A has been completed as of Amendment 2.

Once dose level 1 (200 mg) is determined to be safe, the decision to open the next higher dose level (dose level 2) will be made based on evaluation of safety data from dose level 1. Dose level 2 (300 mg) will be opened only if less than one-third of evaluable patients (i.e., ≤1 of 6 patients or ≤3 of 12 patients) at dose level 1 experience a DLT during Cycle 1. Patients at dose level 2 will be enrolled using the same 6 + 6 scheme used at dose level 1. For patients in Part A, the dose of niraparib may be increased after Cycle 2 to a higher dose level that has been found to be safe during the dose-escalation phase following discussion with the Sponsor. No further dose escalation will be evaluated if dose level 2 is reached.

The RP2D for TSR-042 and niraparib combination treatment will be a dose with DLTs observed in less than one-third of evaluable patients (i.e., ≤1 of 6 patients or ≤3 of 12 patients) during Cycle 1 of combination treatment and will be determined following discussion and agreement between the Investigators and Sponsor based on evaluation of multiple endpoints, which may include the DLT rate in first and subsequent cycles of combination treatment, the rate of dose modifications for non-DLT adverse events (AEs), the ability to manage toxicities, PK, niraparib dose intensity, and signs of clinical efficacy. The goal will be to identify the dose and regimen of niraparib with the greatest dose intensity that can be safely combined with the recommended dose and regimen of TSR-042.

The Part A dose-finding scheme is summarized below.

Part A Dose-Finding Scheme for TSR-042 and Niraparib Combination Treatment



Abbreviations: DLT = dose-limiting toxicity; Q3W = every 3 weeks; Q6W = every 6 weeks.

[a] Niraparib will be administered at the specified dose level as described in the table above (Dose Regimen for TSR-042 and Niraparib Combination Treatment). In addition to receiving niraparib at the specified regimen, all patients will be administered TSR-042 at 500 mg on Day 1 of every cycle (Q3W) for 4 cycles. Beginning on Day 1 of Cycle 5, TSR-042 will be administered at 1,000 mg on Day 1 of every other cycle (Q6W).

Treatment with niraparib must be interrupted for any treatment-related nonhematologic Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or 4 AE. Once resolved to Grade ≤1, the patient may restart treatment with niraparib with a dose level reduction unless prophylaxis is considered feasible. If the event recurs at a similar or worse grade, treatment should be interrupted again and, upon resolution, a further dose reduction must be made to a lower dose level, if available, or niraparib dosing should be discontinued. For hematologic toxicities, dose interruption and modification for niraparib will be based on blood counts. Dose interruption is required for platelet count < 100,000/µL, neutrophil count < 1,000/µL, and hemoglobin ≤ 8 g/dL. Blood counts will be monitored weekly until recovery, after which, patients may restart treatment with niraparib at the same dose (first occurrence of thrombocytopenia with platelet count 75,000 to <100,000/µL only) or with a dose level reduction (subsequent occurrence of thrombocytopenia and any occurrence of platelet count < 75,000/µL, neutropenia, or anemia). Upon restarting niraparib, blood counts will continue to be monitored once weekly until the AE resolved to the specified blood count levels. To ensure the safety of the new dose, weekly blood draws for complete blood count (CBC) will be required for an additional 4 weeks after the AE has resolved, after which monitoring every 4 weeks may resume. Permanent discontinuation of niraparib is required for any confirmed diagnosis of myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML).

For both nonhematologic and hematologic toxicities, if the toxicity requiring dose interruption has not resolved to the specified level during a maximum 4-week (≤28-day) dose interruption period, the

patient has already undergone a maximum of 2 dose reductions (to a minimum dose of 100 mg once daily [QD], or both), the patient must permanently discontinue treatment with niraparib. Once the dose of niraparib has been reduced, any re-escalation must be discussed with the Sponsor.

Part B: Safety and Tolerability Evaluation for TSR-042 and Carboplatin-Paclitaxel Combination Treatment

Confirmation of the RP2D for TSR-042 and carboplatin-paclitaxel combination treatment will be conducted using the dose level described in the table below:

Dose Regimen for TSR-042 and Carboplatin-Paclitaxel Combination Treatment

Dose Level	Carboplatin-Paclitaxel Dose	TSR-042 Dose
1	Carboplatin[a] AUC of 5 or 6 on Day 1 Q3W and paclitaxel 175 mg/m^2 on Day 1 Q3W administered for 4 to 6 cycles as clinically indicated	500 mg on Day 1 of every cycle (Q3W) for 4 cycles, followed by 1,000 mg on Day 1 of every other cycle (Q6W) beginning on Day 1/Cycle 5

Abbreviations: AUC = area under the plasma or serum concentration-time curve; Q3W = every 3 weeks; Q6W = every 6 weeks.

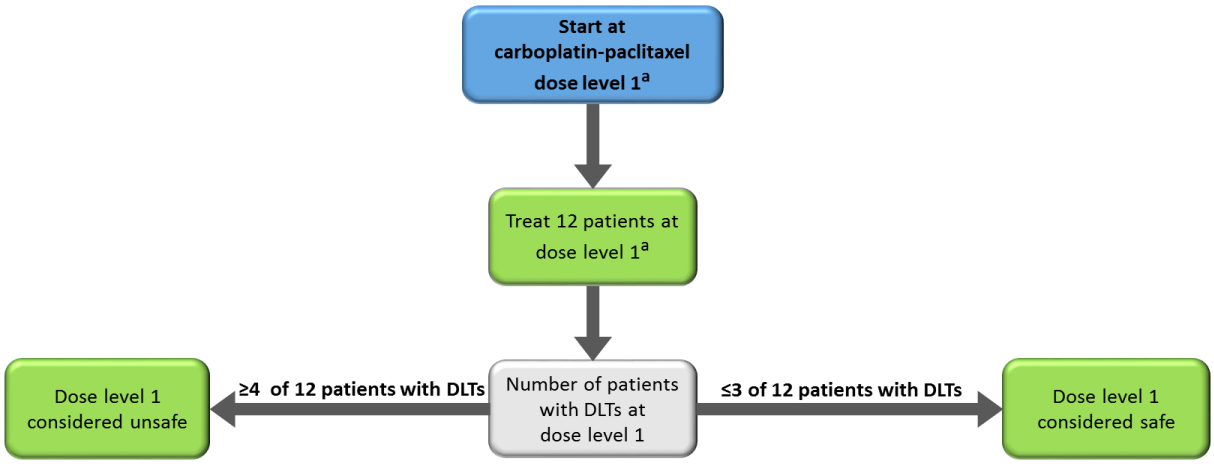
[a] The carboplatin dose will be determined by the Investigator, taking into consideration the patient's prior anticancer therapies and pre-existing medical conditions.

A cohort of approximately 12 patients will be enrolled at dose level 1 in Part B. After all patients who are evaluable for safety have completed Cycle 1 of combination treatment, if ≤3 patients experience a DLT (see DLT Assessment below), TSR-042 and carboplatin-paclitaxel combination treatment will be considered safe. The combination therapy will be considered unsafe if ≥4 of 12 patients experience DLTs during Cycle 1 (see Part B dose confirmation scheme below). However, when determining the RP2D, the Sponsor will review and consider safety data from all patients treated with the combination therapy. Note: Part B has been completed as of Amendment 2.

The RP2D for TSR-042 and carboplatin-paclitaxel combination treatment will be confirmed following discussion and agreement between the Investigators and Sponsor based on evaluation of multiple endpoints, which may include the DLT rate in first and subsequent cycles of combination treatment, the rate of dose modifications for non-DLT AEs, the ability to manage toxicities, PK, and signs of clinical efficacy.

The Part B dose confirmation scheme is summarized below.

Part B Dose Confirmation Scheme for TSR-042 and Carboplatin-Paclitaxel Combination Treatment



Abbreviations: DLT = dose-limiting toxicity; Q3W = every 3 weeks; Q6W = every 6 weeks.

[a] Carboplatin-paclitaxel will be administered at the specified dose level as described in the table above (Dose Regimen for TSR-042 and Carboplatin-Paclitaxel Combination Treatment). In addition to receiving carboplatin-paclitaxel at the specified regimen, patients will be administered TSR-042 at 500 mg on Day 1 of every cycle (Q3W) for 4 cycles. Beginning on Day 1 of Cycle 5, TSR-042 will be administered at 1,000 mg on Day 1 of every other cycle (Q6W).

Part C: Dose Finding for TSR-042, Niraparib and Bevacizumab Combination Treatment

Determination of the RP2D for TSR-042, niraparib, and bevacizumab combination treatment will be conducted using the dose levels described in the table below:

Dose Regimen for TSR-042, Niraparib, and Bevacizumab Combination Treatment

Dose Level	Niraparib Dose	TSR-042 Dose	Bevacizumab Dose
1	200 mg administered on Days 1 to 21 repeated Q3W	500 mg on Day 1 of every cycle (Q3W) for 4 cycles, followed by 1,000 mg on Day 1 of every other cycle (Q6W) beginning on Day 1/Cycle 5	15 mg/kg on Day 1 of every 21-day cycle Q3W for up to 15 months
2 (optional)	300 mg administered on Days 1 to 21 repeated Q3W		

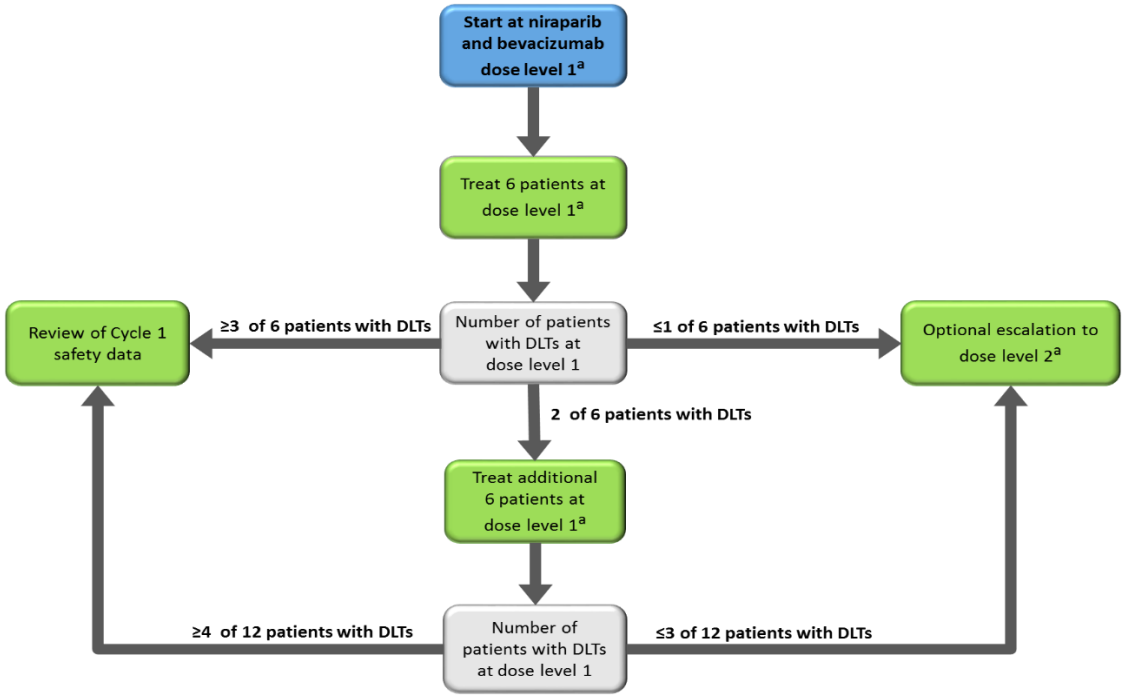
Abbreviations: Q3W = every 3 weeks; Q6W = every 6 weeks.

At dose level 1 (200 mg), a cohort of 6 patients will be enrolled initially. After all patients in dose level 1 who are evaluable for safety have completed Cycle 1 of combination treatment, if ≤1 patient experiences a DLT (see DLT Assessment below), dose level 1 will be considered safe. If 2 of 6 patients experience DLTs, 6 additional patients will be enrolled at dose level 1. If 12 patients are enrolled at dose level 1 and ≤3 of 12 patients experience DLTs, dose level 1 will be considered safe. The combination therapy will be considered unsafe if ≥3 of 6 or ≥4 of 12 patients experience DLTs during Cycle 1 (see Part C dose-finding scheme below). However, when determining the RP2D, the Sponsor will review and consider safety data from all patients treated with the combination therapy.

For patients in Part C, the dose of niraparib may be increased after Cycle 2 to a higher dose level that has been found to be safe during the dose-escalation phase following discussion with the Sponsor. No further dose escalation will be evaluated if dose level 2 is reached.

The decision to open dose level 2 (300 mg) will be made by the Sponsor based on evaluation of safety data from dose level 1. Dose level 2 will be optional and opened only if less than one-third of evaluable patients (i.e., ≤1 of 6 patients or ≤3 of 12 patients) at dose level 1 experience a DLT during Cycle 1.

Part C Dose-Finding Scheme for TSR-042, Niraparib, and Bevacizumab Combination Treatment



Abbreviations: DLT = dose-limiting toxicity; Q3W = every 3 weeks; Q6W = every 6 weeks.

[a] Niraparib and bevacizumab will be administered at the specified dose level as described in the table above (Dose Regimen for TSR-042, Niraparib, and Bevacizumab Combination Treatment). In addition to receiving niraparib at the specified regimen, all patients will be administered TSR-042 at 500 mg on Day 1 of every cycle (Q3W) for 4 cycles. Beginning on Day 1 of Cycle 5, TSR-042 will be administered at 1,000 mg on Day 1 of every other cycle (Q6W). Bevacizumab 15 mg/kg will be administered on Day 1 Q3W for up to 15 months.

Refer to the niraparib dose interruption and modification guidance described in Part A.

Part D: Safety and Tolerability Evaluation for TSR-042, Carboplatin-Paclitaxel, and Bevacizumab Combination Treatment

Confirmation of the RP2D for TSR-042, carboplatin-paclitaxel, and bevacizumab combination treatment will be conducted using the dose level described in the table below:

Dose Regimen for TSR-042, Carboplatin-Paclitaxel, and Bevacizumab Combination Treatment

Dose Level	Carboplatin-Paclitaxel Dose	TSR-042 Dose	Bevacizumab Dose
1	Carboplatin[a] AUC of 5 or 6 on Day 1 Q3W and paclitaxel 175 mg/m^2 on Day 1 Q3W administered for 4 to 6 cycles as clinically indicated	500 mg on Day 1 of every cycle (Q3W) for 4 cycles, followed by 1,000 mg on Day 1 of every other cycle (Q6W) beginning on Day 1/Cycle 5	15 mg/kg on Day 1 of every 21-day cycle Q3W for up to 15 months

Abbreviations: AUC = area under the plasma or serum concentration-time curve; Q3W = every 3 weeks; Q6W = every 6 weeks.

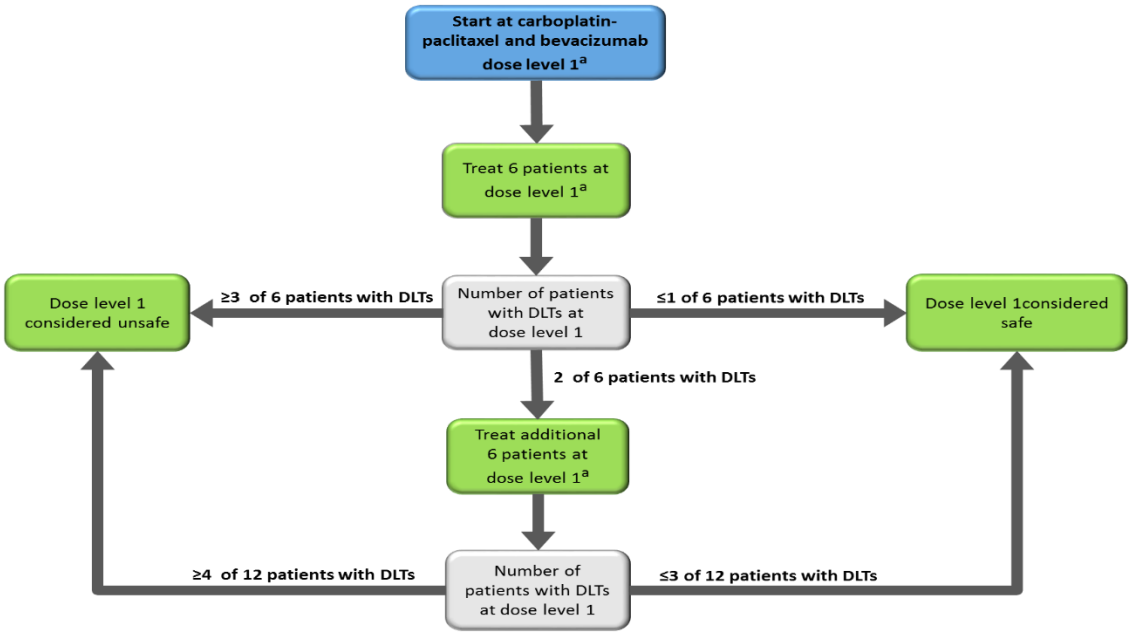
[a] The carboplatin dose will be determined by the Investigator, taking into consideration the patient's prior anticancer therapies and pre-existing medical conditions.

At dose level 1, a cohort of 6 patients will be enrolled initially. After all patients in dose level 1 who are evaluable for safety have completed Cycle 1 of combination treatment, if ≤1 patient experiences a DLT (see DLT Assessment below), dose level 1 will be considered safe. If 2 of 6 patients experience DLTs, 6 additional patients will be enrolled at dose level 1. If ≤3 of 12 patients experience DLTs at dose level 1, the combination will be considered safe. The combination therapy will be considered unsafe if ≥3 of 6 or ≥4 of 12 patients experience DLTs during Cycle 1 (see Part D dose confirmation scheme below). However, when determining the RP2D, the Sponsor will review and consider safety data from all patients treated with the combination therapy. Note: Part D has been completed as of Amendment 2.

The RP2D for TSR-042, carboplatin-paclitaxel, and bevacizumab combination treatment will be confirmed following discussion and agreement between the Investigators and Sponsor based on evaluation of multiple endpoints, which may include the DLT rate in first and subsequent cycles of combination treatment, the rate of dose modifications for non-DLT AEs, the ability to manage toxicities, PK, and signs of clinical efficacy.

The Part D dose confirmation scheme is summarized below.

Part D Dose Confirmation Scheme for TSR-042, Carboplatin-Paclitaxel, and Bevacizumab Combination Treatment



Abbreviations: DLT = dose-limiting toxicity; Q3W = every 3 weeks; Q6W = every 6 weeks.

[a] Carboplatin-paclitaxel and bevacizumab will be administered at the specified dose level as described in the table above (Dose Regimen for TSR-042, Carboplatin-Paclitaxel, and Bevacizumab Combination Treatment). In addition to receiving carboplatin-paclitaxel and bevacizumab at the specified regimen, patients will be administered TSR-042 at 500 mg on Day 1 of every cycle (Q3W) for 4 cycles. Beginning on Day 1 of Cycle 5, TSR-042 will be administered at 1,000 mg on Day 1 of every other cycle (Q6W). Bevacizumab 15 mg/kg will be administered on Day 1 of every 21-day cycle (Q3W) for up to 15 months.

Part E: Safety and Tolerability Evaluation for TSR-042 and Carboplatin-Pemetrexed Combination Treatment

Confirmation of the RP2D for TSR-042 and carboplatin-pemetrexed combination treatment will be conducted using the dose level described in the table below:

Dose Regimen for TSR-042 and Carboplatin-Pemetrexed Combination Treatment

Dose Level	TSR-042 Dose	Pemetrexed Dose	Carboplatin Dose[a]
1	500 mg on Day 1 of every cycle Q3W	500 mg/m^2 on Day 1 Q3W (with vitamin supplementation)	AUC of 5 or 6 on Day 1 Q3W administered for 4 to 6 cycles as clinically indicated

Abbreviations: AUC = area under the plasma or serum concentration-time curve; Q3W = every 3 weeks.

[a] The carboplatin dose will be determined by the Investigator, taking into consideration the patient's prior anticancer therapies and pre-existing medical conditions.

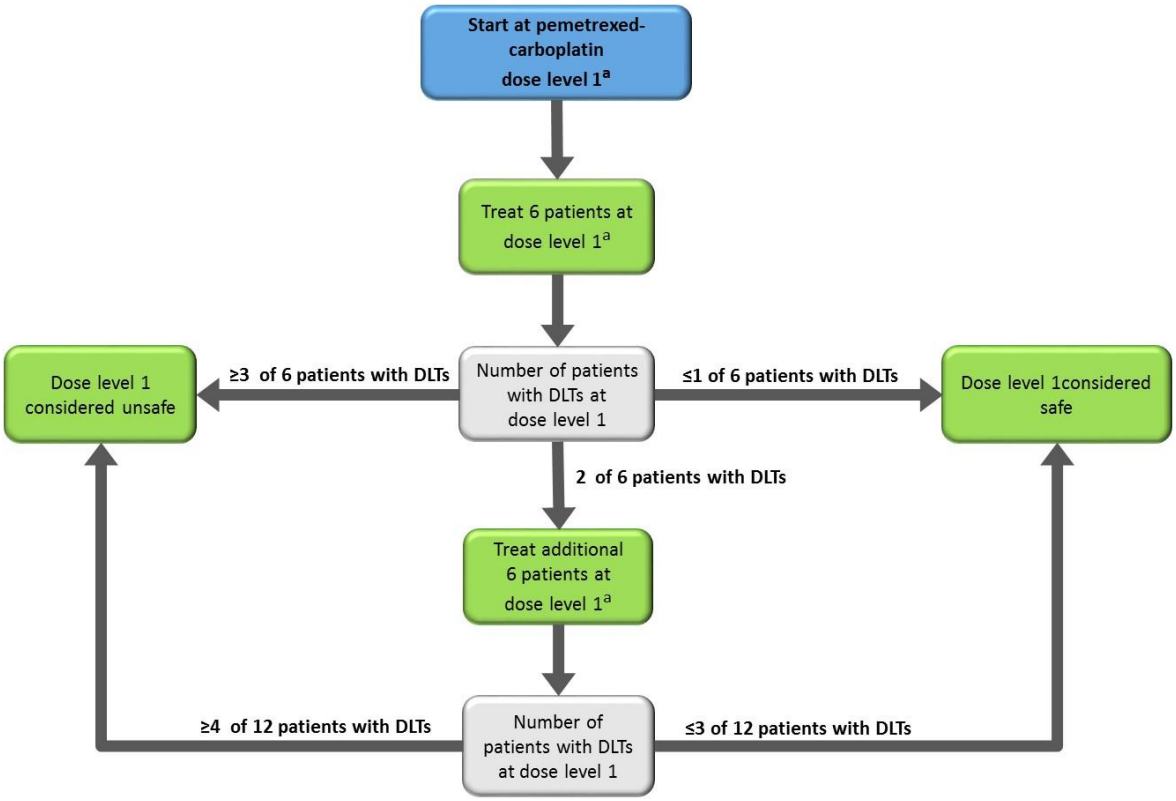
At dose level 1, a cohort of 6 patients will be enrolled initially. After all patients in dose level 1 who are evaluable for safety have completed Cycle 1 of combination treatment, if ≤ 1 patient experiences a DLT (see DLT Assessment below), dose level 1 will be considered safe. If 2 of 6 patients experience DLTs, 6 additional patients will be enrolled at dose level 1. If ≤ 3 of 12 patients experience DLTs at dose level 1, the combination will be considered safe. The combination therapy will be considered unsafe if ≥3 of 6 or ≥4 of 12 patients experience DLTs during Cycle 1 (see Part E dose confirmation

scheme below). However, when determining the RP2D, the Sponsor will review and consider safety data from all patients treated with the combination therapy.

The RP2D for TSR-042 and carboplatin-pemetrexed combination treatment will be confirmed following discussion and agreement between the Investigators and Sponsor based on evaluation of multiple endpoints, which may include the DLT rate in first and subsequent cycles of combination treatment, the rate of dose modifications for non-DLT AEs, the ability to manage toxicities, PK, and signs of clinical efficacy.

The Part E dose confirmation scheme is summarized below.

Part E Dose Confirmation Scheme for TSR-042 and Carboplatin-Pemetrexed Combination Treatment



Abbreviations: DLT = dose-limiting toxicity.

[a] Carboplatin-pemetrexed will be administered at the specified dose level as described in the table above (Dose Regimen for TSR-042 and carboplatin-pemetrexed combination treatment). In addition to receiving carboplatin-pemetrexed at the specified regimen, patients will be administered TSR-042 at 500 mg on Day 1 of every cycle Q3W.

Part F: Safety and Tolerability Evaluation for TSR-042, TSR-022, and Carboplatin-Pemetrexed Combination Treatment

Part F will begin after combination therapy in Part E has been determined as safe. Confirmation of the RP2D for TSR-042, TSR-022, and carboplatin-pemetrexed combination treatment will be conducted using the dose levels described in the table below:

Dose Regimen for TSR-042, TSR-022, and Carboplatin-Pemetrexed Combination Treatment

Dose Level	TSR-042 Dose	TSR-022 Dose	Pemetrexed Dose	Carboplatin Dose[a]
1	500 mg on Day 1 of every cycle Q3W	900 mg on Day 1 Q3W[b]	500 mg/m^2 on Day 1 Q3W (with vitamin supplementation)	AUC of 5 or 6 on Day 1 Q3W administered for 4 to 6 cycles as clinically indicated
-1	500 mg on Day 1 of every cycle Q3W	300 mg on Day 1 Q3W[b]	500 mg/m^2 Day 1 Q3W (with vitamin supplementation)	AUC of 5 or 6 on Day 1 Q3W administered for 4 to 6 cycles as clinically indicated

Abbreviations: AUC = area under the plasma or serum concentration-time curve; Q3W = every 3 weeks.

[a] The carboplatin dose will be determined by the Investigator, taking into consideration the patient's prior anticancer therapies and pre-existing medical conditions.

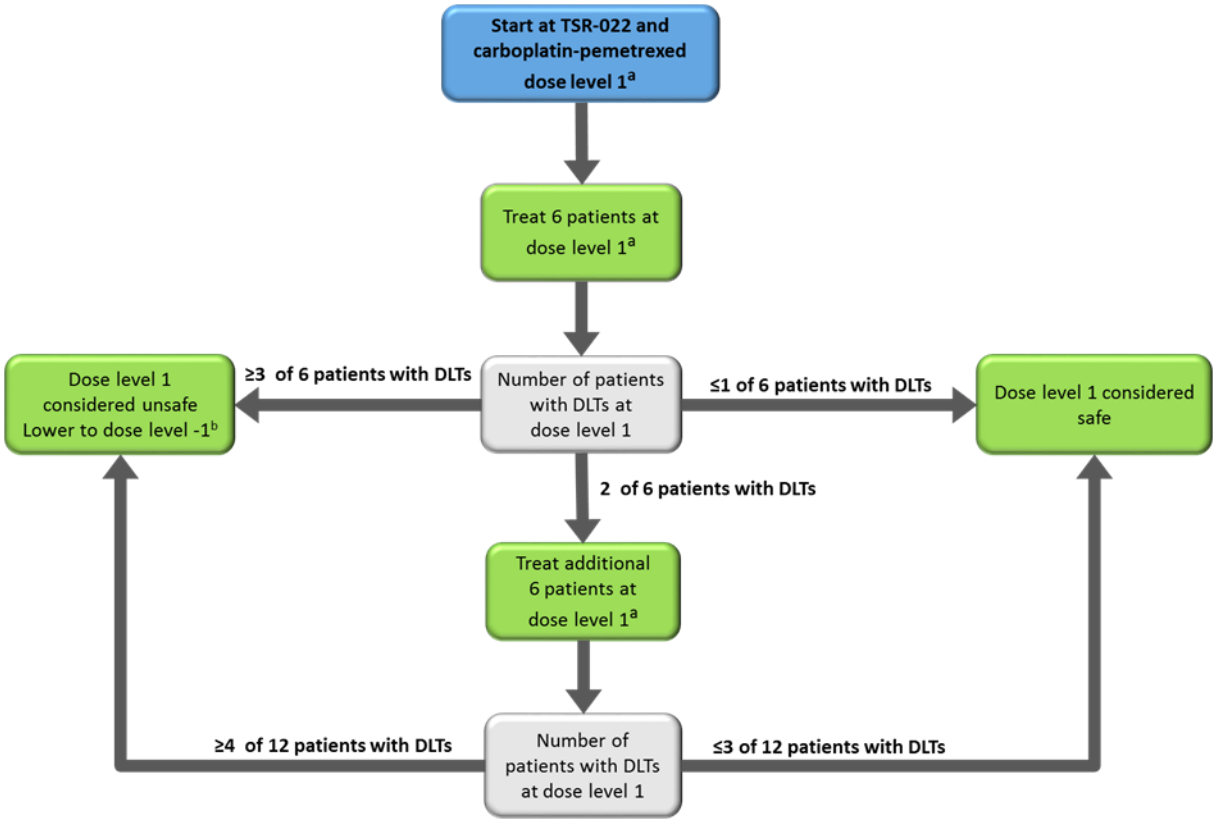
[b] 900 mg of TSR-022 is the highest dose tested in dose escalation in combination with TSR-042 that provides maximal pharmacodynamic effect; this dose may be lowered to dose level -1 if needed. Based on available safety information, the Sponsor may decide to test additional dose levels of TSR-022.

At dose level 1, a cohort of 6 patients will be enrolled initially. After all patients in dose level 1 who are evaluable for safety have completed Cycle 1 of combination treatment, if ≤ 1 patient experiences a DLT (see DLT Assessment below), dose level 1 will be considered safe. If 2 of 6 patients experience DLTs, 6 additional patients will be enrolled at dose level 1. If ≤ 3 of 12 patients experience DLTs, dose level 1 will be considered safe. If ≥ 4 of 12 patients experience DLTs at dose level 1, dose level -1 will enroll 6 patients. After all patients in dose level -1 who are evaluable for safety have completed Cycle 1 of combination treatment, if ≤ 1 patient experiences a DLT, dose level -1 will be considered safe. If 2 of 6 patients experience DLTs, 6 additional patients will be enrolled at dose level -1. If ≤ 3 of 12 patients experience DLTs, dose level -1 will be considered safe. The combination therapy at dose level -1 will be considered unsafe if ≥3 of 6 or ≥4 of 12 patients experience DLTs during Cycle 1 (see Part F dose confirmation scheme below). However, when determining the RP2D, the Sponsor will review and consider safety data from all patients treated with the combination therapy.

The RP2D for TSR-042, TSR-022, and carboplatin-pemetrexed combination treatment will be confirmed following discussion and agreement between the Investigators and Sponsor based on evaluation of multiple endpoints, which may include the DLT rate in first and subsequent cycles of combination treatment, the rate of dose modifications for non-DLT AEs, the ability to manage toxicities, PK, and signs of clinical efficacy.

The Part F dose confirmation scheme is summarized below.

Part F Dose Confirmation Scheme for TSR-042, TSR-022, and Carboplatin-Pemetrexed Combination Treatment



Abbreviations: DLT = dose-limiting toxicity.

[a] Carboplatin-pemetrexed will be administered at the specified dose level as described in the table above (Dose Regimen for TSR-042, TSR-022, and carboplatin-pemetrexed combination treatment). In addition to receiving carboplatin-pemetrexed at the specified regimen, patients will be administered TSR-042 at 500 mg on Day 1 of every cycle Q3W and TSR-022 at 900 mg on Day1 Q3W.

[b] Patients at dose level -1 will be enrolled using the same 6 + 6 scheme used at dose level 1.

Part G: Safety and Tolerability Evaluation for TSR-042 and Carboplatin–Nab-paclitaxel Combination Treatment

Confirmation of the RP2D for TSR-042 and carboplatin–nab-paclitaxel combination treatment will be conducted using the dose level described in the table below:

Dose Regimen for TSR-042 and Carboplatin–Nab-Paclitaxel Combination Treatment

Dose Level	TSR-042 Dose	Nab-Paclitaxel Dose	Carboplatin Dose[a]
1	500 mg on Day 1 of every cycle Q3W	100 mg/m^2 on Days 1, 8, and 15 (Q1W) of every 3-week cycle, administered for 4 to 6 cycles as clinically indicated	AUC of 5 or 6 on Day 1 Q3W administered for 4 to 6 cycles as clinically indicated

Abbreviations: AUC = area under the plasma or serum concentration-time curve; Q1W = every week; Q3W = every 3 weeks.

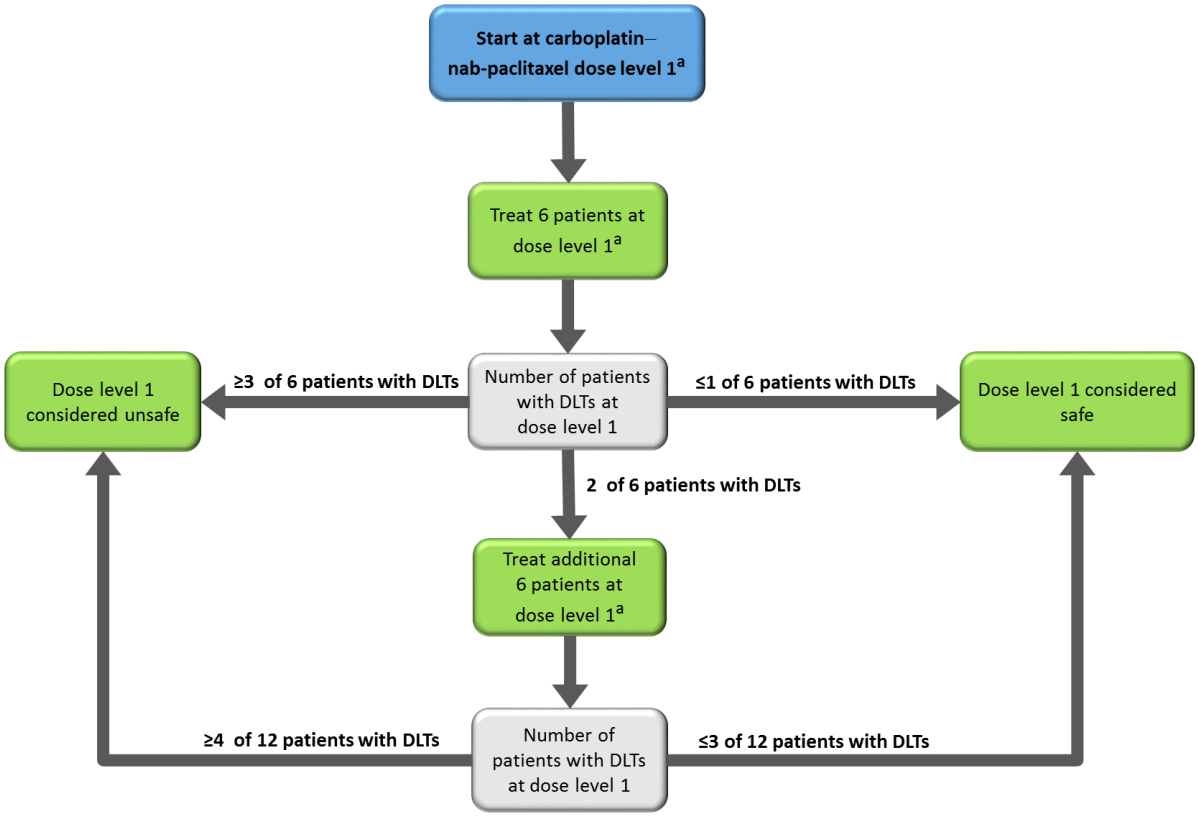
[a] The carboplatin dose will be determined by the Investigator, taking into consideration the patient's prior anticancer therapies and pre-existing medical conditions.

At dose level 1, a cohort of 6 patients will be enrolled initially. After all patients in dose level 1 who are evaluable for safety have completed Cycle 1 of combination treatment, if ≤ 1 patient experiences a DLT (see DLT Assessment below), dose level 1 will be considered safe. If 2 of 6 patients experience DLTs, 6 additional patients will be enrolled at dose level 1. If ≤ 3 of 12 patients experience DLTs, dose level 1 will be considered safe. The combination therapy will be considered unsafe if ≥3 of 6 or ≥4 of 12 patients experience DLTs during Cycle 1 (see Part G dose confirmation scheme below). However, when determining the RP2D, the Sponsor will review and consider safety data from all patients treated with the combination therapy.

The RP2D for TSR-042 and carboplatin–nab-paclitaxel combination treatment will be confirmed following discussion and agreement between the Investigators and Sponsor based on evaluation of multiple endpoints, which may include the DLT rate in first and subsequent cycles of combination treatment, the rate of dose modifications for non-DLT AEs, the ability to manage toxicities, PK, and signs of clinical efficacy.

The Part G dose confirmation scheme is summarized below.

Part G Dose Confirmation Scheme for TSR-042 and Carboplatin–Nab-Paclitaxel Combination Treatment



Abbreviations: DLT = dose-limiting toxicity.

[a] Carboplatin–nab-paclitaxel will be administered at the specified dose level as described in the table above (Dose Regimen for TSR-042 and carboplatin–nab-paclitaxel combination treatment). In addition to receiving carboplatin–nab-paclitaxel at the specified regimen, patients will be administered TSR-042 at 500 mg on Day 1 of every cycle Q3W.

Part H: Safety and Tolerability Evaluation for TSR-042, TSR-022, and Carboplatin–Nab-Paclitaxel Combination Treatment

Part H will begin after combination therapy in Part G has been determined as safe. Confirmation of the RP2D for TSR-042, TSR-022, and carboplatin–nab-paclitaxel combination treatment will be conducted using the dose levels described in the table below:

Dose Regimen for TSR-042, TSR-022, and Carboplatin–Nab-Paclitaxel Combination Treatment

Dose Level	TSR-042 Dose	TSR-022 Dose	Nab-Paclitaxel Dose	Carboplatin Dose[a]
1	500 mg on Day 1 of every cycle Q3W	900 mg on Day 1 Q3W[b]	100 mg/m^2 on Days 1, 8, and 15 (Q1W) of every 3-week cycle, administered for 4 to 6 cycles as clinically indicated	AUC of 5 or 6 on Day 1 Q3W administered for 4 to 6 cycles as clinically indicated
-1	500 mg on Day 1 of every cycle Q3W	300 mg on Day 1 Q3W[b]	100 mg/m^2 on Days 1, 8, and 15 (Q1W) of every 3-week cycle, administered for 4 to 6 cycles as clinically indicated	AUC of 5 or 6 on Day 1 Q3W administered for 4 to 6 cycles as clinically indicated

Abbreviations: AUC = area under the plasma or serum concentration-time curve; Q1W = every week; Q3W = every 3 weeks.

[a] The carboplatin dose will be determined by the Investigator, taking into consideration the patient's prior anticancer therapies and pre-existing medical conditions.

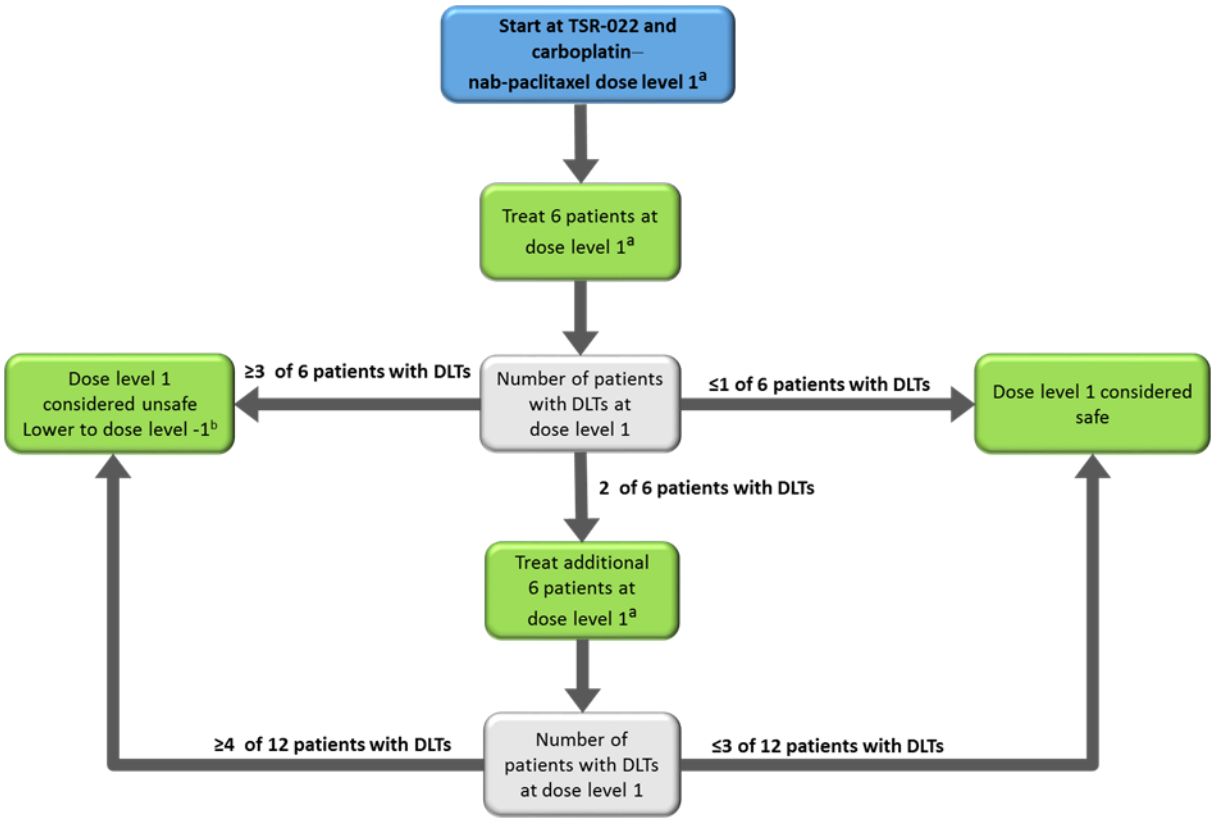
[b] 900 mg of TSR-022 is the highest dose tested in dose escalation in combination with TSR-042 that provides maximal pharmacodynamic effect; this dose may be lowered to dose level -1 if needed. Based on available safety information, the Sponsor may decide to test additional dose levels of TSR-022.

At dose level 1, a cohort of 6 patients will be enrolled initially. After all patients in dose level 1 who are evaluable for safety have completed Cycle 1 of combination treatment, if ≤ 1 patient experiences a DLT (see DLT Assessment below), dose level 1 will be considered safe. If 2 of 6 patients experience DLTs, 6 additional patients will be enrolled at dose level 1. If ≤ 3 of 12 patients experience DLTs, dose level 1 will be considered safe. If ≥ 4 of 12 patients experience DLTs at dose level 1, dose level -1 will enroll 6 patients. After all patients in dose level -1 who are evaluable for safety have completed Cycle 1 of combination treatment, if ≤ 1 patient experiences a DLT, dose level -1 will be considered safe. If 2 of 6 patients experience DLTs, 6 additional patients will be enrolled at dose level -1. If ≤ 3 of 12 patients experience DLTs, dose level -1 will be considered safe. The combination therapy at dose level -1 will be considered unsafe if ≥3 of 6 or ≥4 of 12 patients experience DLTs during Cycle 1 (see Part H dose confirmation scheme below). However, when determining the RP2D, the Sponsor will review and consider safety data from all patients treated with the combination therapy.

The RP2D for TSR-042, TSR-022, and carboplatin–nab-paclitaxel combination treatment will be confirmed following discussion and agreement between the Investigators and Sponsor based on evaluation of multiple endpoints, which may include the DLT rate in first and subsequent cycles of combination treatment, the rate of dose modifications for non-DLT AEs, the ability to manage toxicities, PK, and signs of clinical efficacy.

The Part H dose confirmation scheme is summarized below.

Part H Dose Confirmation Scheme for TSR-042, TSR-022, and Carboplatin–Nab-Paclitaxel Combination Treatment



Abbreviations: DLT = dose-limiting toxicity.

[a] Carboplatin–nab-paclitaxel will be administered at the specified dose level as described in the table above (Dose Regimen for TSR-042, TSR-022, and carboplatin–nab-paclitaxel combination treatment). In addition to receiving carboplatin–nab-paclitaxel at the specified regimen, patients will be administered TSR-042 at 500 mg on Day 1 of every cycle Q3W and TSR-022 at 900 mg on Day 1 Q3W.

[b] Patients at dose level -1 will be enrolled using the same 6 + 6 scheme used at dose level 1.

Part I: Safety and Tolerability Evaluation for TSR-042, TSR-022, and Carboplatin-Paclitaxel Combination Treatment

Confirmation of the RP2D for TSR-042, TSR-022, and carboplatin-paclitaxel combination treatment will be conducted using the dose levels described in the table below:

Dose Regimen for TSR-042, TSR-022, and Carboplatin-Paclitaxel Combination Treatment

Dose Level	TSR-042 Dose	TSR-022 Dose	Carboplatin-Paclitaxel Dose
1	500 mg on Day 1 of every cycle Q3W	900 mg on Day 1 Q3W[b]	Carboplatin[a] AUC of 5 or 6 on Day 1 Q3W and paclitaxel 175 mg/m^2 on Day 1 Q3W administered for 4 to 6 cycles as clinically indicated
-1	500 mg on Day 1 of every cycle Q3W	300 mg on Day 1 Q3W[b]	Carboplatin[a] AUC of 5 or 6 on Day 1 Q3W and paclitaxel 175 mg/m^2 on Day 1 Q3W administered for 4 to 6 cycles as clinically indicated

Abbreviations: AUC = area under the plasma or serum concentration-time curve; Q3W = every 3 weeks.

[a] The carboplatin dose will be determined by the Investigator, taking into consideration the patient's prior anticancer therapies and pre-existing medical conditions.

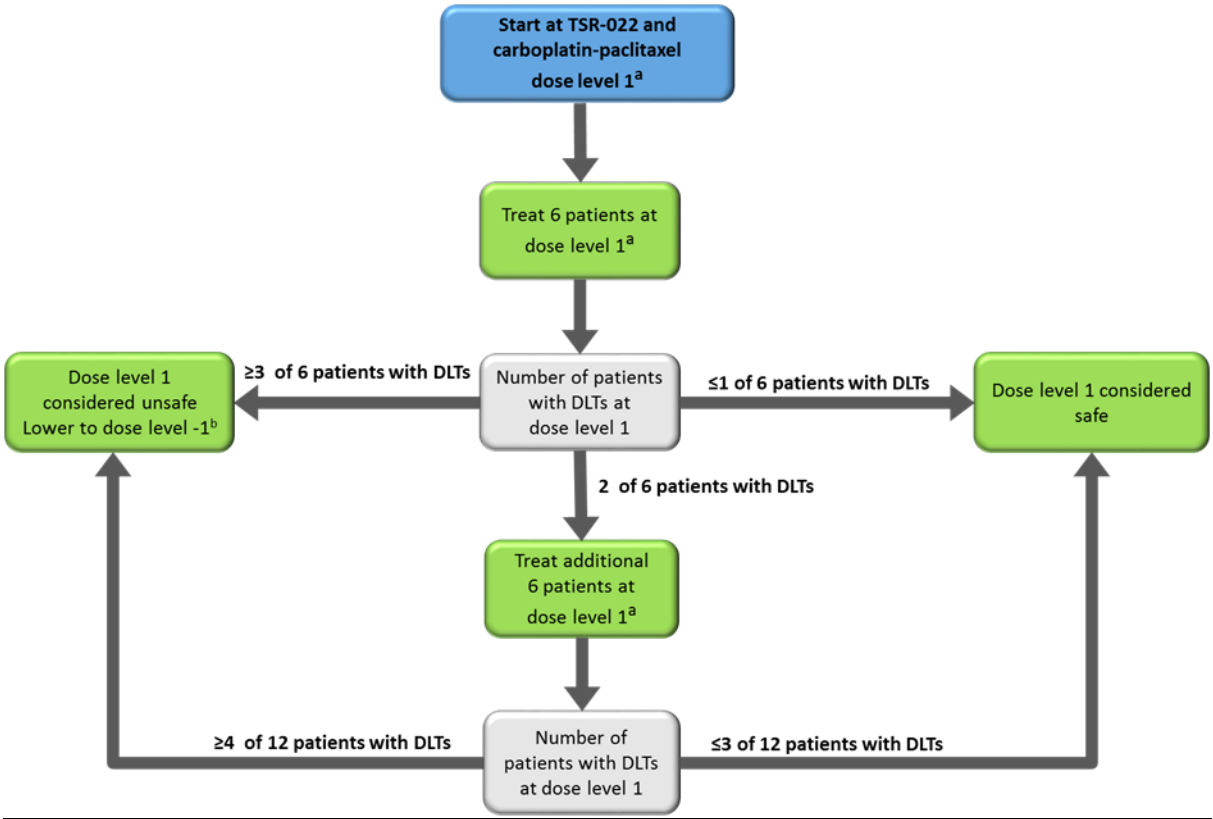
[b] 900 mg of TSR-022 is the highest dose tested in dose escalation in combination with TSR-042 that provides maximal pharmacodynamic effect; this dose may be lowered to dose level -1 if needed. Based on available safety information, the Sponsor may decide to test additional dose levels of TSR-022.

At dose level 1, a cohort of 6 patients will be enrolled initially. After all patients in dose level 1 who are evaluable for safety have completed Cycle 1 of combination treatment, if ≤ 1 patient experiences a DLT (see DLT Assessment below), dose level 1 will be considered safe. If 2 of 6 patients experience DLTs, 6 additional patients will be enrolled at dose level 1. If ≤ 3 of 12 patients experience DLTs, dose level 1 will be considered safe. If ≥ 4 of 12 patients experience DLTs in dose level 1, dose level -1 will enroll 6 patients. After all patients in dose level -1 who are evaluable for safety have completed Cycle 1 of combination treatment, if ≤ 1 patient experiences a DLT, dose level -1 will be considered safe. If 2 of 6 patients experience DLTs, 6 additional patients will be enrolled at dose level -1. If ≤ 3 of 12 patients experience DLTs, dose level -1 will be considered safe. The combination therapy at dose level -1 will be considered unsafe if ≥3 of 6 or ≥4 of 12 patients experience DLTs during Cycle 1 (see Part I dose confirmation scheme below). However, when determining the RP2D, the Sponsor will review and consider safety data from all patients treated with the combination therapy.

The RP2D for TSR-042, TSR-022, and carboplatin-paclitaxel combination treatment will be confirmed following discussion and agreement between the Investigators and Sponsor based on evaluation of multiple endpoints, which may include the DLT rate in first and subsequent cycles of combination treatment, the rate of dose modifications for non-DLT AEs, the ability to manage toxicities, PK, and signs of clinical efficacy.

The Part I dose confirmation scheme is summarized below.

Part I Dose Confirmation Scheme for TSR-042, TSR-022, and Carboplatin-Paclitaxel Combination Treatment



Abbreviations: DLT = dose-limiting toxicity.

[a] Carboplatin-paclitaxel will be administered at the specified dose level as described in the table above (Dose Regimen for TSR-042, TSR-022, and carboplatin-paclitaxel combination treatment). In addition to receiving carboplatin-paclitaxel at the specified regimen, patients will be administered TSR-042 at 500 mg on Day 1 of every cycle Q3W and TSR-022 at 900 mg on Day 1 Q3W.

[b] Patients at dose level -1 will be enrolled using the same 6 + 6 scheme used at dose level 1.

DLT Assessment

DLTs will be assessed during Cycle 1 (i.e., during the first 21 days of treatment on Day 1 to Day 21). DLT criteria are as follows:

- Any treatment-related Grade 4 nonhematologic clinical (nonlaboratory) AE
- Any treatment-related Grade 3 nonhematologic clinical (nonlaboratory) AE lasting >3 days despite optimal medical intervention
- Any treatment-related Grade 3 or 4 nonhematologic laboratory abnormality if any of the following also occur:
  - The abnormality leads to hospitalization.
  - The abnormality persists for ≥7 days from the time of AE onset and patient is symptomatic from the AE.

- Any treatment-related hematologic toxicity defined as any of the following:
  - Grade 4 thrombocytopenia persists for ≥7 days from the time of AE onset or Grade 3 or 4 thrombocytopenia associated with clinically significant bleeding
  - Grade 4 neutropenia, Grade 3 or 4 neutropenia associated with infection, or Grade 3 or 4 febrile neutropenia persists for ≥7 days
  - Grade 4 anemia or Grade 3 anemia requiring blood transfusion
- Any treatment-related toxicity leading to prolonged delay (>2 weeks) in initiating Cycle 2
- Any treatment-related Grade 5 AE

A patient will be considered nonevaluable for DLTs if, for any reason other than safety, the patient is unable to complete the 21-day combination treatment DLT observation period or is unable to take >80% of the intended dose of either agent. For patients who skip niraparib doses due to hematologic AEs based on dose modification table which do not meet the DLT criteria, it is allowed to miss up to 10 days of niraparib during cycle 1 to be considered as evaluable for DLTs. Patients considered nonevaluable may be replaced after consultation between the Sponsor and Investigator.

Niraparib administration has been safely managed with dose interruptions or adjustments for AEs, including laboratory abnormalities, while maintaining activity in the single-agent setting. Therefore, niraparib dose interruption, dose reduction, or both, for an AE that does not meet a DLT definition as described above will be considered a non-DLT modification for Cohorts A and C. However, patients requiring a non-DLT dose modification that makes them unable to take >80% of the intended dose during Cycle 1 will be considered nonevaluable for DLTs and will be replaced.

Study Conduct

All patients will begin combination treatment (TSR-042 and niraparib combination treatment for patients enrolled in Part A; TSR-042 and carboplatin-paclitaxel combination treatment for patients enrolled in Part B; TSR-042, niraparib, and bevacizumab combination treatment for patients enrolled in Part C; TSR-042, carboplatin-paclitaxel, and bevacizumab combination treatment for patients enrolled in Part D; TSR-042 and carboplatin-pemetrexed combination treatment for patients enrolled in Part E; TSR-042, TSR-022, and carboplatin-pemetrexed combination treatment for patients enrolled in Part F; TSR-042 and carboplatin–nab-paclitaxel combination treatment for patients enrolled in Part G; TSR-042, TSR-022, and carboplatin–nab-paclitaxel for patients enrolled in Part H; and TSR-042, TSR-022, and carboplatin-paclitaxel for patients enrolled in Part I) on Day 1 of Cycle 1. Additional on-treatment safety assessments will be conducted on Days 8 and 15 of Cycle 1 and on Day 1 of all subsequent cycles. Safety assessments conducted throughout the treatment period include symptom-directed physical examination, vital signs, electrocardiograms (ECGs), Eastern Cooperative Oncology Group (ECOG) performance status, and clinical laboratory assessments (CBC, coagulation; serum chemistry; thyroid-stimulating hormone [TSH], triiodothyronine [T3] or free triiodothyronine [FT3], and free thyroxine [FT4] or equivalent tests if TSH, T3 or FT3, or FT4 are not available; urinalysis; appropriate testing of serum tumor markers; and pregnancy testing).

Radiographic evaluations (computed tomography [CT] or magnetic resonance imaging [MRI] of the chest, abdomen, and pelvis) and appropriate testing of serum tumor markers to assess the extent of disease will be conducted at 12 weeks after receiving the first dose of study treatment and every 12 weeks (84 ± 10 days) thereafter until progression while on study treatment, independent of cycle delays or dose interruptions, or at any time when progression of disease is suspected. CT or MRI of the head will be conducted if clinically indicated; bone scans will be conducted per standard of care. If a patient discontinues treatment for a reason other than progression, death, withdrawal of consent, or

loss to follow-up, radiographic scans and appropriate testing of serum tumor markers should continue at the specified interval.

Per RECIST v1.1, complete response (CR) or partial response (PR) should be confirmed; tumor imaging for confirmation of response may be performed at the earliest 4 weeks after the first indication of response or at the next scheduled scan (i.e., 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 progressive disease (PD). Therefore, patients with initial radiologic evidence of PD who are clinically stable may continue study treatment at the Investigator's discretion while awaiting confirmatory tumor imaging. Confirmatory imaging of PD is recommended to be performed at least 4 weeks and up to 6 weeks after initial evidence of PD. Patients with confirmed PD may continue study treatment at the Investigator's discretion 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.

Blood sampling for PK, ADA, and biomarker evaluation will be conducted for patients in all parts. For patients in Parts F, H, and I, submission of archival formalin-fixed paraffin-embedded (FFPE) tumor tissue (if available) for biomarker analysis is mandatory. An optional on-treatment biopsy after 4 to 6 weeks of treatment and an optional biopsy on progression (EOT visit) may be collected. Submission of FFPE tumor archival tissue samples is optional for Parts A, B, C, D, E, and G.

For patients in Parts A, B, C, and D, blood samples for biomarker analysis will be obtained at screening, predose on Day 1 of Cycle 1 and Cycle 2, and at the EOT or time of disease progression. For patients in Parts E, F, G, H, and I, blood samples for biomarker analysis will be obtained at screening, predose on Day 1 and Day 15 of Cycle 1, and predose on Day 1 of Cycle 2, Cycle 4, Cycle 6, and at the EOT or time of disease progression.

All patients will undergo an End of Treatment visit within 7 days after study treatment discontinuation or at the time of disease progression, whichever occurs first. Safety follow-up visits will be conducted 30 and 90 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. Thereafter, all patients will enter the posttreatment period for assessment of survival status and the occurrence of any new malignancies every 90 ± 14 days.

All AEs will be collected and recorded for each patient from the day of signing the informed consent form until 30 days after last dose of study treatment; serious adverse events (SAEs) and adverse events of special interest (AESIs) are required to be captured through 90 days after the last dose of study treatment (or to a minimum of 30 days post-treatment if the patient starts alternate anticancer therapy). Any event of MDS/AML or secondary cancer (new malignancies other than MDS/AML) must be reported to the Sponsor as soon as the Investigator becomes aware of the diagnosis, regardless of when it occurs. Any pregnancies that occur within 180 days posttreatment are to be captured. All AEs and SAEs experienced by a patient, irrespective of the suspected causality, will be monitored until the AE or SAE has resolved, abnormal laboratory values have returned to baseline or normalized, there is a satisfactory explanation for the change(s) observed, the patient is lost to follow-up, or the patient has died.

Number of Patients (Planned):

Part A: 12 to 24 patients

Part B: approximately 12 patients

Part C: 6 to 24 patients.

Part D: 6 to 12 patients

Part E: 6 to 12 patients

Part F: 6 to 24 patients

Part G: 6 to 12 patients

Part H: 6 to 24 patients

Part I: 6 to 24 patients

Main Criteria for Inclusion:

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

1. Patient is male or female and at least 18 years of age.
2. Patient has histologically or cytologically proven advanced (unresectable) or metastatic cancer as outlined below according to study part and disease type:
    a. Part A: Patients with previously treated advanced or metastatic cancer. Patient may have received no more than 4 lines of treatment for advanced or metastatic cancer. Hormonal treatment will not be considered a prior line of treatment.
    b. Part B: Patients with advanced or metastatic cancer for which treatment with carboplatin-paclitaxel is considered appropriate therapy. Patient may have received no more than 1 prior line of chemotherapy in the metastatic setting. Hormonal treatment will not be considered a prior line of treatment.
    c. Part C: Patients with previously treated advanced or metastatic cancer. Patient may have received no more than 4 lines of treatment for advanced or metastatic cancer. Hormonal treatment will not be considered a prior line of treatment.
    d. Part D: Patients in whom carboplatin-paclitaxel and bevacizumab is considered appropriate therapy. Patient may have received no more than 1 prior line of chemotherapy in the metastatic setting. Hormonal treatment will not be considered a prior line of treatment.
    e. Parts E, F, G, H, and I: Patients who have not received prior systemic therapy, including targeted therapy and biologic agents, for their advanced or metastatic (Stage ≥ IIIB or IV) NSCLC. Patients who have received neoadjuvant or adjuvant therapy are eligible as long as development of advanced or metastatic disease occurred at least 12 months after completion of neoadjuvant or adjuvant therapy.
3. Patient has an ECOG performance status of 0 to 1.
4. Patient has adequate organ function defined as follows (Note: CBC test should be obtained without transfusion or receipt of colony-stimulating factors in the 2 weeks before obtaining sample):
    a. Absolute neutrophil count ≥ 1,500/μL
    b. Platelets ≥ 100,000/μL
    c. Hemoglobin ≥ 9 g/dL or ≥ 5.6 mmol/L
    d. Serum creatinine ≤ 1.5 × upper limit of normal (ULN) or calculated creatinine clearance of ≥ 50 mL/min using Cockcroft-Gault equation for patients with creatinine levels > 1.5 × institutional ULN
    e. Total bilirubin ≤ 1.5 × ULN or direct bilirubin ≤ 1 × ULN
    f. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 × ULN unless liver metastases are present, in which case they must be ≤ 5 × ULN
    g. International normalized ratio or prothrombin time (PT) ≤ 1.5 × ULN unless the patient is receiving anticoagulant therapy as long as PT or partial thromboplastin time (PTT) is within therapeutic range of intended use of anticoagulants

h. Activated partial thromboplastin time ≤ 1.5 × ULN unless the patient is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

5. Female patient has a negative serum pregnancy test within 72 hours prior to taking study treatment if of childbearing potential and agrees to abstain from activities that could result in pregnancy from screening through 180 days after the last dose of study treatment, or is of nonchildbearing potential. Nonchildbearing potential is defined as follows (by other than medical reasons):

   a. ≥45 years of age and has not had menses for >1 year
   b. Patients who have been amenorrheic for <2 years without history of a hysterectomy and oophorectomy must have a follicle stimulating hormone value in the postmenopausal range upon screening evaluation.
   c. Post-hysterectomy, post-bilateral oophorectomy, or post-tubal ligation. Documented hysterectomy or oophorectomy must be confirmed with medical records of the actual procedure or confirmed by an ultrasound. Tubal ligation must be confirmed with medical records of the actual procedure, otherwise the patient must be willing to use effective contraception throughout the study, starting with the screening visit through 180 days after the last dose of study treatment. See the study protocol for a list of acceptable birth control methods. Information must be captured appropriately within the site's source documents. Note: Abstinence is acceptable if this is the established and preferred contraception for the patient.

6. Male patient agrees to use an adequate method of contraception (see the study protocol for a list of acceptable birth control methods) and not donate sperm starting with the first dose of study treatment through 90 days after the last dose of study treatment. Note: Abstinence is acceptable if this is the established and preferred contraception for the patient.

7. Patient has measurable lesions by RECIST v1.1.

For Parts A and C, in addition to the general inclusion criteria, patients must also meet the following additional criteria to be considered eligible to participate in this study:

8. Patient is able to take oral medications.

9. For patients to be eligible for any parts of the study using niraparib 300 mg as a starting dose, a screening actual body weight ≥ 77 kg **and** screening platelet count ≥ 150,000 u/L is necessary.

Main Criteria for Exclusion:

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

1. Patient has known active central nervous system metastases, carcinomatous meningitis, or both. Note: Patients with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging [using the identical imaging modality for each assessment, either MRI or CT scan] for at least 4 weeks prior to the first dose of study treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and have not been using steroids for at least 7 days prior to study treatment. Carcinomatous meningitis precludes a patient from study participation regardless of clinical stability.

2. Patient has a known additional malignancy that progressed or required active treatment within the last 2 years. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin that has undergone potentially curative therapy, or in situ cervical cancer.
3. Patient is considered a poor medical risk due to a serious, uncontrolled medical disorder, nonmalignant systemic disease, or active infection that requires systemic therapy. Specific examples include, but are not limited to, history of (noninfectious) pneumonitis that required steroids or current pneumonitis, uncontrolled ventricular arrhythmia, recent (within 90 days) myocardial infarction, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, or any psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the study (including obtaining informed consent).
4. Patient has a condition (such as transfusion-dependent anemia or thrombocytopenia), therapy, or laboratory abnormality that might confound the study results or interfere with the patient's participation for the full duration of the study treatment including the following:
    a. Patients who received a transfusion (platelets or red blood cells) within 6 weeks of the first dose of study treatment are not eligible.
    b. Patients who received colony-stimulating factors (e.g., granulocyte colony-stimulating factor, granulocyte macrophage colony-stimulating factor, or recombinant erythropoietin) within 4 weeks prior to the first dose of study treatment are not eligible.
5. Patient is pregnant or expecting to conceive children within the projected duration of the study, starting with the screening visit through 180 days after the last dose of study treatment.
    a. No data are available regarding the presence of niraparib or its metabolites in human milk, or on its effects on the breastfed infant or milk production. Because of the potential for serious adverse reactions in breastfed infants from niraparib, female patients should not breastfeed during treatment with niraparib and for 1 month after receiving the final dose.
6. Patient has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of study treatment.
7. Patient has a known history of human immunodeficiency virus (type 1 or 2 antibodies).
8. Patient has known active hepatitis B (e.g., hepatitis B surface antigen reactive) or hepatitis C (e.g., hepatitis C virus ribonucleic acid [qualitative] is detected).
9. Patient has an active autoimmune disease that has required systemic treatment in the past 2 years (i.e., with use of disease-modifying agents, corticosteroids, or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc) is not considered a form of systemic treatment.
10. Patient has not recovered (i.e., to Grade ≤1 or to baseline) from cytotoxic therapy-induced AEs. Note: Patients with Grade ≤2 neuropathy, Grade ≤2 alopecia, or Grade ≤2 fatigue are an exception to this criterion and may qualify for the study.

11. Patient is currently participating and receiving study treatment or has participated in a study of an investigational agent and received study treatment or used an investigational device within 4 weeks of the first dose of treatment.
12. Patient has had a prior cytotoxic therapy, anticancer targeted small molecules (e.g., tyrosine kinase inhibitors), hormonal agents within 5 half-lives, or monoclonal antibodies within 5 half-lives or 4 weeks (whichever is shorter) of that treatment prior to Day 1; radiation therapy encompassing >20% of the bone marrow within 2 weeks; or any radiation therapy within 1 week prior to Day 1.
13. Patient has not recovered adequately from AEs or complications from any major surgery prior to starting therapy.
14. Patient has received prior therapy with an anti-programmed death 1, anti-programmed death-ligand 1 (PD-L1), anti-programmed death-ligand 2, anti-cytotoxic T-lymphocyte-associated antigen-4 antibody (including ipilimumab), or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways.
15. Patient has received a live vaccine within 14 days of planned start of study treatment.
16. Patient has a heart-rate corrected QT interval (QTc) prolongation >480 ms at screening. Note: If a patient has a prolonged QT interval and the prolongation is deemed to be due to a pacemaker upon Investigator evaluation (i.e., the patient otherwise has no cardiac abnormalities), the patient may be eligible to participate in the study following discussion with the Sponsor's Medical Monitor.
17. Patient has a known hypersensitivity to TSR-042 components or excipients.

For Parts A and C only, patients will not be eligible for study entry if any of the following additional exclusion criteria are met:

18. Patient has undergone prior treatment with a known poly(ADP-ribose) polymerase inhibitor.
19. Patient has a known hypersensitivity to niraparib components or excipients.
20. Patient has had any known Grade 3 or 4 anemia, neutropenia, or thrombocytopenia due to prior chemotherapy that persisted >4 weeks related to the most recent prior treatment.
21. Known history or current diagnosis of MDS or AML, or current diagnosis of prostate cancer.

For Parts B, D, E, F, G, H, and I, patients will not be eligible for study entry if the following additional exclusion criterion is met:

22. Patient has a known hypersensitivity to any of the following relevant study treatments: carboplatin, paclitaxel, pemetrexed, nab-paclitaxel, or TSR-022 components or excipients.

For Parts C and D only, patients will not be eligible for study entry if any of the following additional exclusion criteria are met:

23. Patient has clinically significant cardiovascular disease (e.g., significant cardiac conduction abnormalities, uncontrolled hypertension, myocardial infarction, cardiac arrhythmia or unstable angina, New York Heart Association Grade 2 or greater congestive heart failure, serious cardiac arrhythmia requiring medication, Grade 2 or greater peripheral vascular disease, and history of cerebrovascular accident [CVA]) within 6 months of enrollment.

24. Patient has a history of bowel obstruction, including subocclusive disease, related to the underlying disease and history of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscesses. Evidence of recto-sigmoid involvement by pelvic examination or bowel involvement on CT scan or clinical symptoms of bowel obstruction.
25. 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).
26. Patient is at increased bleeding risk due to concurrent conditions (e.g., 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).
27. Patient has a known hypersensitivity to bevacizumab components or excipients.

For Parts E and F only, patients will not be eligible for study entry if any of the following additional exclusion criteria are met:

28. Patient is unable to interrupt aspirin or other nonsteroidal ant-inflammatory drugs (NSAIDs), other than an aspirin dose ≤ 1.3 g per day, for a 5-day period (8-day period for long -acting agents, such as piroxicam.
29. Patient is unable or unwilling to take folic acid or vitamin B_{12} supplement
30. Patient has symptomatic ascites or pleural effusion. A patient who is clinically stable following treatment for these conditions (including therapeutic thoraco- or paracentesis) is eligible.

For Parts G, H, and I only, patients will not be eligible for study entry if any of the following additional exclusion criteria are met:

31. Patient has pre-existing peripheral neuropathy that is Grade ≥2 by Common Terminology Criteria for Adverse Events (CTCAE) version 4 criteria.

For Parts E, F, G, H, and I only, patients will not be eligible for study entry if any of the following additional exclusion criteria are met:

32. Patient has interstitial lung disease or a history of pneumonitis that required oral or intravenous glucocorticoids to assist with management

Investigational Product, Dosage, and Mode of Administration:

Niraparib

Niraparib will be administered orally once daily (QD) continuously at the assigned dose. On Day 1 of each cycle, a niraparib dose will be administered upon completion of all infusions. Depending on the dose regimen, 2 or 3 capsules of 100-mg strength niraparib will be taken at each dose administration (total dose of 200 or 300 mg per dose, respectively). Subsequent to Amendment 1, only patients with a screening actual body weight ≥ 77 kg **and** screening platelet count ≥ 150,000 μL will be eligible to receive niraparib 300 mg as a stating dose. Patients will be instructed to take their niraparib dose 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 21-day cycle for up to 2 years or until disease progression, unacceptable toxicity, patient withdrawal, Investigator's decision, or death. The Pharmacy Manual contains descriptions of the packaging of niraparib and instructions for the preparation and administration of niraparib.

TSR-042

TSR-042 will be administered at the study site by 30-minute intravenous (IV) infusion on Day 1 of every 21-day cycle (Q3W) at 500 mg for the first 4 cycles. Beginning on Day 1 of Cycle 5, TSR-042 will be administered at 1,000 mg every other cycle (Q6W) to patients in Parts A, B, C, and D for up to 2 years or until disease progression, unacceptable toxicity, patient withdrawal, Investigator's decision, or death. Patients in Parts E, F, G, H, and I will continue to receive 500 mg on Day 1 of every cycle (Q3W) throughout the study. Continued treatment with TSR-042 beyond 2 years may be considered following discussion between the Sponsor and Investigator. The Pharmacy Manual contains descriptions of the packaging of TSR-042 and instructions for the preparation and administration of TSR-042.

TSR-022

TSR-022 will be administered at the study site by 30-minute IV infusion on Day 1 of every 21-day cycle (Q3W) at 900 mg (or 300 mg if lowered to dose level -1 for reasons of safety) for up to 2 years or until disease progression, unacceptable toxicity, patient withdrawal, Investigator's decision, or death. Continued treatment with TSR-022 beyond 2 years may be considered following discussion between the Sponsor and Investigator. The Pharmacy Manual contains descriptions of the packaging of TSR-022 and instructions for the preparation and administration of TSR-022.

Carboplatin-Paclitaxel

Paclitaxel will be administered at the study site by a 3-hour IV infusion on Day 1 of every 21-day cycle (Q3W) at 175 mg/m^2 for 4 to 6 cycles or until disease progression, unacceptable toxicity, patient withdrawal, Investigator's decision, or death. The paclitaxel package insert contains descriptions of the packaging of paclitaxel and instructions for preparation and administration of paclitaxel.

Carboplatin will be administered at the study site by a 30- or 60-minute IV infusion (30 minutes preferred) on Day 1 of every 21-day cycle (Q3W) at an area under the plasma or serum concentration-time curve (AUC) of 5 or 6, and will be administered for 4 to 6 cycles as clinically indicated. The carboplatin dose will be determined by the Investigator, taking into consideration the patient's prior anticancer therapies and pre-existing medical conditions. The carboplatin package insert contains descriptions of the packaging of carboplatin and instructions for preparation and administration of carboplatin.

Carboplatin-Pemetrexed

Pemetrexed will be administered at the study site by a 10-minute IV infusion on Day 1 of every 21-day cycle (Q3W) at 500 mg/m^2 for up to 2 years or until progression, unacceptable toxicity, patient withdrawal, Investigator's decision, or death. The pemetrexed package insert contains descriptions of

the packaging of pemetrexed and instructions for the preparation and administration of pemetrexed. Continued treatment with pemetrexed beyond 2 years may be considered following discussion between the Sponsor and Investigator. All patients should receive the appropriate supplementation of vitamin B12 and folic acid and corticosteroid prophylaxis as listed below:

- Folic acid 350 to 1,000 μg oral: At least 5 doses of folic acid must be taken during the 7 days preceding the first dose of pemetrexed, and folic acid dosing must continue during the full course of therapy and for 21 days after the last dose of pemetrexed.
- Vitamin B12 1,000 μg intramuscular injection will be administered in the week preceding the first dose of pemetrexed and once every 3 cycles thereafter. Subsequent vitamin B12 injections may be given the same day as pemetrexed administration.

Carboplatin will be administered at the study site by a 30- or 60-minute IV infusion (30 minutes preferred) on Day 1 of every 21-day cycle (Q3W) at an AUC of 5 or 6, and will be administered for 4 to 6 cycles as clinically indicated. The carboplatin dose will be determined by the Investigator, taking into consideration the patient's prior anticancer therapies and pre-existing medical conditions. The carboplatin package insert contains descriptions of the packaging of carboplatin and instructions for the preparation and administration of carboplatin.

Carboplatin–Nab-Paclitaxel

Nab-paclitaxel will be administered at the study site by a 30-minute IV infusion on Days 1, 8, and 15 of every week (Q1W) of every 3-week cycle, at 100 mg/m^2 for 4 to 6 cycles as clinically indicated or until disease progression, unacceptable toxicity, patient withdrawal, Investigator's decision, or death. The nab-paclitaxel package insert contains descriptions of the packaging of nab-paclitaxel and instructions for preparation and administration of nab-paclitaxel.

Carboplatin will be administered at the study site by a 30- or 60-minute IV infusion (30 minutes preferred) on Day 1 of every 21-day cycle (Q3W) at an AUC of 5 or 6, and will be administered for 4 to 6 cycles as clinically indicated. The carboplatin dose will be determined by the Investigator, taking into consideration the patient's prior anticancer therapies and pre-existing medical conditions. The carboplatin package insert contains descriptions of the packaging of carboplatin and instructions for preparation and administration of carboplatin.

Bevacizumab

Bevacizumab will be administrated at the study site by IV infusion based on local approved product label on Day 1 of every 21-day cycle (Q3W) at 15 mg/kg for up to 15 months or until progression, unacceptable toxicity, patient withdrawal, Investigator's decision or death. The bevacizumab package insert contains descriptions of the packaging of bevacizumab and instructions for preparation and administration of bevacizumab.

Note: The order of study drug administration for each part is listed below:

- Part A: TSR-042 followed by niraparib after completion of infusion
- Part B: TSR-042 followed by paclitaxel, then carboplatin
- Part C: TSR-042 followed by bevacizumab, then niraparib after completion of both infusions
- Part D: TSR-042 followed by paclitaxel, then carboplatin, then bevacizumab
- Part E: TSR-042 followed by pemetrexed, then carboplatin
- Part F: TSR-042 followed by TSR-022, then pemetrexed, then carboplatin
- Part G: TSR-042 followed by nab-paclitaxel, then carboplatin
- Part H: TSR-042 followed by TSR-022, then nab-paclitaxel, then carboplatin
- Part I: TSR-042 followed by TSR-022, then paclitaxel, then carboplatin

Duration of Treatment:

Planned Study Conduct Duration

The primary analysis will occur at approximately 6 months after the last patient is enrolled. The final analysis of primary and secondary endpoints will be conducted approximately 12 months after the last patient is enrolled.

Planned Study Treatment Duration

Patients enrolled in Part A may continue TSR-042 and niraparib combination treatment for up to 2 years or until disease progression, unacceptable toxicity, patient withdrawal, Investigator's decision, or death. Patients who have not progressed at 2 years will be given the option to continue on TSR-042 and niraparib combination treatment beyond 2 years if they are tolerating and benefiting from treatment and after consultation with the Sponsor. Patients with confirmed PD may continue study treatment at the Investigator's discretion 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 enrolled in Part B may continue TSR-042 and carboplatin-paclitaxel combination treatment for 4 to 6 cycles, as indicated, after which patients may continue TSR-042 monotherapy for up to 2 years or until disease progression, unacceptable toxicity, patient withdrawal, Investigator's decision, or death. Continued treatment with TSR-042 beyond 2 years may be considered following discussion between the Sponsor and Investigator.

Patients enrolled in Part C may continue TSR-042, niraparib and bevacizumab combination treatment for up to 15 months. Subsequently, they may continue TSR-042 and niraparib combination treatment for up to 2 years or until disease progression, unacceptable toxicity, patient withdrawal, Investigator's decision, or death. Continued treatment with TSR-042 and niraparib beyond 2 years may be considered following discussion between the Sponsor and Investigator.

Patients enrolled in Part D may continue TSR-042, carboplatin-paclitaxel, and bevacizumab combination treatment for 4 to 6 cycles, as indicated, after which patients may continue TSR-042 and bevacizumab treatment up to a total of 15 months. Subsequently, patients may continue TSR-042 treatment alone for up to 2 years or until disease progression, unacceptable toxicity, patient withdrawal, Investigator's decision, or death. Continued treatment with TSR-042 beyond 2 years may be considered following discussion between the Sponsor and Investigator.

Patients enrolled in Part E may continue TSR-042 and carboplatin-pemetrexed combination treatment for 4 to 6 cycles, as indicated, after which patients may continue TSR-042 and pemetrexed for up to 2 years or until disease progression, unacceptable toxicity, patient withdrawal, Investigator's decision, or death. Continued treatment with TSR-042 and pemetrexed beyond 2 years may be considered following discussion between the Sponsor and Investigator.

Patients enrolled in Part F may continue TSR-042, TSR-022, and carboplatin-pemetrexed combination treatment for 4 to 6 cycles, as indicated, after which patients may continue TSR-042, TSR-022, and pemetrexed combination therapy for up to 2 years or until disease progression, unacceptable toxicity, patient withdrawal, Investigator's decision, or death. Continued treatment with TSR-022, TSR-042, or pemetrexed beyond 2 years may be considered following discussion between the Sponsor and Investigator.

Patients enrolled in Part G may continue TSR-042 and carboplatin–nab-paclitaxel combination treatment for 4 to 6 cycles, as indicated, after which patients may continue TSR-042 monotherapy for up to 2 years or until disease progression, unacceptable toxicity, patient withdrawal, Investigator's decision, or death. Continued treatment with TSR-042 beyond 2 years may be considered following discussion between the Sponsor and the Investigator.

Patients enrolled in Part H may continue TSR-042, TSR-022, and carboplatin–nab-paclitaxel combination treatment for 4 to 6 cycles, as indicated, after which patients may continue TSR-042 and

TSR-022 combination therapy for up to 2 years or until disease progression, unacceptable toxicity, patient withdrawal, Investigator's decision, or death. Continued treatment with TSR-022 or TSR-042 beyond 2 years may be considered following discussion between the Sponsor and the Investigator.

Patients enrolled in Part I may continue TSR-042, TSR-022, and carboplatin-paclitaxel combination treatment for 4 to 6 cycles, as indicated, after which patients may continue TSR-042 and TSR-022 combination therapy for up to 2 years or until disease progression, unacceptable toxicity, patient withdrawal, Investigator's decision, or death. Continued treatment with TSR-022 or TSR-042 beyond 2 years may be considered following discussion between the Sponsor and the Investigator.

Criteria for Evaluation:

Efficacy

The following secondary efficacy endpoints will be evaluated based on Investigator assessment:

- ORR, defined as the proportion of patients who have achieved confirmed CR or PR, evaluated using RECIST v1.1 based on Investigator assessment
- DOR, defined as the time from first documentation of response (CR or PR) until the time of first documentation of disease progression by RECIST v1.1 based on Investigator assessment or death by any cause
- DCR, defined as the percentage of patients who have achieved CR, PR, or stable disease per RECIST v1.1 based on Investigator assessment
- PFS, defined as the time from the date of the first dose of study treatment to the earlier date of assessment of progression, or death by any cause in the absence of progression by RECIST v1.1 based on Investigator assessment

Safety

The primary endpoints in the safety analysis are as follows:

- Determination of the RP2D based on the number of DLTs observed during the first cycle (i.e., during the first 21 days of treatment [Day 1 to Day 21 of Cycle 1]).
- Incidence of treatment-emergent adverse events (TEAEs) occurring while patients are on treatment or up to 30 days after the last dose of study treatment
- Incidence of SAEs and adverse event of special interest (AESIs) occurring while patients are on study treatment or up to 90 days after the last dose of study treatment
- Changes in clinical laboratory parameters (hematology, serum chemistry, coagulation, thyroid function, and urinalysis), vital signs, ECOG performance status, ECG parameters (including QTc calculated using Fridericia's [QTcF]), physical examinations, and use of concomitant medications

Pharmacokinetics

Plasma and serum samples for PK determination will be collected from all patients.

For Part A (TSR-042 and niraparib combination treatment) and Part C (TSR-042, niraparib and bevacizumab combination treatment), plasma will be analyzed using liquid chromatography with mass spectrometry detection for niraparib and its major metabolite M1. The serum will be analyzed for TSR-042 using enzyme-linked immunosorbent assay (ELISA).

For Part B (TSR-042 and carboplatin-paclitaxel combination treatment), Part D (TSR-042, carboplatin-paclitaxel and bevacizumab combination treatment), Part E (TSR-042 and carboplatin-pemetrexed combination treatment), Part F (TSR-042, TSR-022, and carboplatin-pemetrexed combination treatment), Part G (TSR-042 and carboplatin–nab-paclitaxel combination treatment), Part H (TSR-042, TSR-022, and carboplatin–nab-paclitaxel), and Part I (TSR-042, TSR-022, and carboplatin-paclitaxel) serum samples will be analyzed for TSR-042 and TSR-022 using ELISA. The plasma samples will be analyzed for carboplatin using inductively coupled plasma mass spectrometry, and for paclitaxel and pemetrexed using liquid chromatography tandem-mass spectrometry, if appropriate.

Parameters of interest are AUC, minimum observed plasma or serum concentration (C_{min}), maximum observed plasma or serum concentration (C_{max}), clearance (after oral administration [CL/F] and after IV administration [CL]), volume of distribution (after oral administration [V_z/F] and after IV administration [V_z]), AUC at steady state (AUC_{ss}), minimum observed plasma or serum concentration at steady state ($C_{min,ss}$), and maximum observed plasma or serum concentration at steady state ($C_{max,ss}$).

Immunogenicity

Serum samples for the determination of TSR-042 and TSR-022 ADAs will be the same blood collections as those for the TSR-042 and TSR-022 PK assessments. ADAs will be analyzed in a tiered approach using electrochemiluminescence (i.e., screening, confirmation, titer, and competitive ligand binding assay as neutralizing antibody assay). Minimally, ADAs will be analyzed in predose samples from all cycles collected; additional samples for ADA determination will be collected upon treatment discontinuation at a post-treatment and safety follow-up visit (i.e., approximately 90 days after the last dose of TSR-042/TSR-022).

Biomarkers

Archival FFPE tumor tissue (mandatory [if available] for Parts F, H, and I; optional for Parts A, B, C, D, E, and G) and blood samples will be assessed for biomarkers that may correlate with clinical benefit from treatment with TSR-042 and niraparib combination treatment (Part A); TSR-042 and carboplatin-paclitaxel combination treatment (Part B); TSR-042, niraparib, and bevacizumab combination treatment (Part C); TSR-042, carboplatin-paclitaxel, and bevacizumab combination treatment (Part D); TSR-042 and carboplatin-pemetrexed combination treatment (Part E); TSR-042, TSR-022, and carboplatin-pemetrexed combination treatment (Part F); TSR-042 and carboplatin–nab-paclitaxel combination treatment (Part G); TSR-042, TSR-022, and carboplatin–nab-paclitaxel combination treatment (Part H); and TSR-042, TSR-022, and carboplatin-paclitaxel combination treatment (Part I), including but not limited to germline *BRCA* mutation (g*BRCA*mut), homologous recombination deficiency status, the phenotype and molecular profile of circulating immune cells, and circulating cytokines or chemokines prior to and during treatment. To enable these evaluations, blood samples for biomarker analysis will be obtained in Parts A, B, C, and D at the time of screening, at predose on Day 1 of Cycles 1 and 2, and at the time of EOT visit or disease progression. Blood samples for biomarker analysis will be obtained in Parts E, F, G, H, and I at the time of screening, at predose on Days 1 and 15 of Cycle 1 and Day 1 of Cycles 2, 4, and 6, and at the EOT visit or time of disease progression.

Statistical Methods:

Sample Size Considerations

Part A: An initial sample size of approximately 12 to 24 patients is estimated for Part A of the study to provide an initial understanding of the incidence of DLTs and safety profiles of TSR-042 and niraparib combination treatment.

Part B: A total of approximately 12 patients will be enrolled in Part B of the study to provide an initial understanding of the safety profiles of TSR-042 and carboplatin-paclitaxel combination treatment.

Part C: A sample size of approximately 6 to 24 patients is estimated for Part C of the study to provide an initial understanding of the incidence of DLTs and safety profiles of TSR-042, niraparib and bevacizumab combination treatment.

Part D: A total of approximately 6 to 12 patients will be enrolled in Part D of the study to provide an initial understanding of the safety profiles of TSR-042, carboplatin-paclitaxel and bevacizumab combination treatment.

Part E: A total of approximately 6 to 12 patients will be enrolled in Part E of the study to provide an initial understanding of the safety profiles of TSR-042 and carboplatin-pemetrexed combination treatment.

Part F: A total of approximately 6 to 24 patients will be enrolled in Part F of the study to provide an initial understanding of the safety profiles of TSR-042, TSR-022, and carboplatin-pemetrexed combination treatment.

Part G: A total of approximately 6 to 12 patients will be enrolled in Part G of the study to provide an initial understanding of the safety profiles of TSR-042 and carboplatin–nab-paclitaxel combination treatment.

Part H: A total of approximately 6 to 24 patients will be enrolled in Part H of the study to provide an initial understanding of the safety profiles of TSR-042, TSR-022, and carboplatin–nab-paclitaxel combination treatment.

Part I: A total of approximately 6 to 24 patients will be enrolled in Part I of the study to provide an initial understanding of the safety profiles of TSR-042, TSR-022, and carboplatin-paclitaxel combination treatment.

Analysis Populations

Three analysis populations will be defined as follows:

- Safety population: All patients who receive any amount of study treatment. All safety endpoints will be assessed in the safety population, with the exception of DLT assessment, which will include only those patients completing the first cycle of therapy, unless the patient discontinued study treatment due to a DLT. Analyses of baseline characteristics and the primary analysis of efficacy endpoints will be performed on the safety population.
- PK population: All patients who receive at least 1 dose of study treatment and have at least 1 PK sample.
- ADA population: All patients who receive at least 1 dose of study treatment and have provided a predose blood sample and at least 1 postdose blood sample at or after 96 hours.

General Methods

All analyses will include summary statistics, including the number and percentage for categorical variables and the number of patients, mean, standard deviation, median, minimum, and maximum for continuous variables. Time-to-event analyses will be performed using Kaplan-Meier methods. Further details will be provided in the study statistical analysis plan.

Efficacy Analysis

ORR and DCR will be summarized using descriptive statistics, including the number, percentage, and 2-sided 90% confidence intervals (CIs).

DOR and PFS will be summarized using Kaplan-Meier analysis, including the number and percentage of events, number and percentage of censored patients, and the 25th, 50th, and 75th percentiles of times-to-event with 95% CIs.

Safety Analysis

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

Additional safety summaries will be provided for clinical laboratory tests, vital signs, ECOG performance status, ECGs, physical examinations, and usage of concomitant medications.

Pharmacokinetics Analysis

The analysis set for the PK parameters will be the PK population. Noncompartmental methods will be used to evaluate the PK characteristics as appropriate.

Immunogenicity Analysis

The analysis set for ADA analyses will be the ADA population. The number and percent of patients who become positive for ADAs and who develop neutralizing antibodies will be summarized by dose and regimen, by visit, and overall.

Biomarkers Analysis

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

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

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3. 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
ADA	anti-drug antibody
ADL	activities of daily living
ADP	adenosine diphosphate
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
alt-NHEJ	alternative nonhomologous end joining
AML	acute myeloid leukemia
aPTT	activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
ATM	ataxia telangiectasia mutated
ATP	adenosine triphosphate
AUC	area under the plasma or serum concentration-time curve
AUC_{ss}	area under the plasma or serum concentration-time curve at steady state
BER	base excision repair
BIW	twice weekly
BP	blood pressure
BRCA	breast cancer gene
BRCA1	breast cancer 1
BRCA2	breast cancer 2
BRCA1/2	breast cancer 1 and breast cancer 2
BRCAmut	BRCA mutation
CA-125	cancer antigen 125
CBC	complete blood count
CD	cluster of differentiation
CD8 T	CD8+ T cytotoxic 1
CHK	check point kinases
CI	confidence interval
CL	clearance after intravenous administration
CL/F	clearance after oral administration

Table 1: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
C_{max}	maximum observed plasma or serum concentration
$C_{max,ss}$	maximum observed plasma or serum concentration at steady state
C_{min}	minimum observed plasma or serum concentration
$C_{min,ss}$	minimum observed plasma or serum concentration at steady state
CR	complete response
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
CYP	cytochrome P450
DCR	disease control rate
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
EC_{50}	50% maximum effective concentration
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ELISA	enzyme-linked immunosorbent assay
EMEA	European Medicines Agency
FDA	Food and Drug Administration
FFPE	formalin-fixed paraffin embedded
FT3	free triiodothyronine
FT4	free thyroxine
GARFT	glycinamide ribonucleotide formyltransferase
gBRCAmut	germline BRCA mutation
GCP	Good Clinical Practice
GCSF	granulocyte colony-stimulating factor
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HR	hazard ratio
HRD	homologous recombination deficiency
HRDneg	HRD negative
HRDpos	HRD positive
IB	Investigator's Brochure

Table 1: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
IC_{50}	50% maximum inhibitory concentration
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IRB	Independent Review Board
IFN-γ	interferon gamma
Ig	immunoglobulin
IL-2	interleukin-2
IP	intraperitoneal(ly)
ITSM	tyrosine-based switch motif
IV	intravenous
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MLR	mixed lymphocyte reaction
MRI	magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NHEJ	nonhomologous end joining
NSCLC	non-small cell lung cancer
ORR	objective response rate
PARP	poly(ADP-ribose) polymerase
PARP1	poly(ADP-ribose) polymerase 1
PARP2	poly(ADP-ribose) polymerase 2
PD	progressive disease
PD-1	programmed death-1
PD-L1	programmed death-ligand 1
PD-L2	programmed death-ligand 2
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic(s)
PO	orally
PR	partial response
PT	prothrombin time

Table 1: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
PTT	partial thromboplastin time
Q2W	every 2 weeks
Q3W	every 3 weeks
Q6W	every 6 weeks
QD	once daily
QTc	corrected QT interval
QTcF	corrected QT interval calculated using Fridericia's formula
RECIST	Response Evaluation Criteria in Solid Tumors
RECIST v1.1	Response Evaluation Criteria in Solid Tumors version 1.1
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction
T3	triiodothyronine
TEAE	treatment-emergent adverse event
Th1	T helper 1
TIL	tumor-infiltrating lymphocytes
TIM-3	T-cell immunoglobulin and mucin containing protein-3
TNFα	tumor necrosis factor alpha
TS	thymidylate synthase
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
V_z	volume of distribution after intravenous administration
V_z/F	volume of distribution after oral administration
WHO	World Health Organization

4. INTRODUCTION

4.1. Background

4.1.1. PARP and Homologous Recombination Deficiency

Poly(ADP-ribose) polymerase (PARP)1 and PARP2 are zinc-finger deoxyribonucleic acid (DNA)-binding enzymes that play a crucial role in DNA repair.[1] Upon formation of DNA breaks, PARP binds at the end of broken DNA strands, a process that activates its enzymatic activity.

Activated PARP catalyzes the addition of long polymers of adenosine diphosphate (ADP)-ribose onto PARP and several other proteins associated with chromatin, including histones and various DNA repair proteins.[2,3] This results in chromatin relaxation, fast recruitment of DNA repair proteins, and efficient repair of DNA breaks. In this manner, PARP plays a key role in sensing DNA damage and converting it into intracellular signals that activate the base excision repair (BER) and single-strand break repair pathways. Normal cells repair up to 10,000 DNA defects daily, and single-strand breaks are the most common form of DNA damage. Cells that are unable to repair this burden of DNA damage, such as those with defects in the homologous recombination or BER pathways, are at risk for accumulating multiple lesions that will ultimately trigger apoptosis. They enter the S phase (DNA replication) of the cell cycle with unrepaired single- and double-strand breaks. Pre-existing single-strand breaks are converted to double-strand breaks as the replication machinery passes. Accumulated double-strand breaks present during S phase are repaired by homologous recombination. Homologous recombination is the preferred repair pathway because it is associated with a much lower error rate than other forms of repair. Cells that are unable to perform DNA repair via homologous recombination (e.g., due to inactivation of genes required for homologous recombination, such as breast cancer [*BRCA1*]- or breast cancer 2 [*BRCA2*]-mutated cells) are at risk for accumulating multiple lesions that will ultimately trigger apoptosis. These cells accumulate stalled replication forks during S phase and are more likely to use the error-prone nonhomologous end joining (NHEJ) or alternative (alt)-NHEJ pathways to repair double-strand breaks in DNA. Accumulation of errors in DNA by NHEJ contributes to mutation burden that promotes the development of cancer. Over time, the buildup of excessive DNA errors in combination with the inability to complete S phase (because of stalled replication forks) contributes to cell death.[2,3]

Treatment with PARP inhibitors could represent a novel opportunity to selectively kill a subset of cancer cells with deficiencies in DNA repair pathways. For example, a tumor arising in a patient with a germline *BRCA* mutation (g*BRCA*mut) has a defective homologous recombination DNA repair pathway and would be increasingly dependent on NHEJ, alt-NHEJ, and BER for maintenance of genomic integrity. PARP inhibitors block alt-NHEJ and BER, forcing tumors with BRCA deficiencies to use the error-prone NHEJ to fix double-strand breaks.[1] Non-*BRCA* deficiencies in homologous recombination DNA repair genes could also enhance tumor cell sensitivity to PARP inhibitors.[4] The rationale for anticancer activity in a subset of non-g*BRCA*mut tumors is that they share distinctive DNA repair defects with g*BRCA*mut carriers, a phenomenon broadly described as "BRCAness."[5] DNA repair defects can be caused by germline or somatic alterations to the homologous recombination DNA repair pathway. In a recent analysis of approximately 500 high-grade serous ovarian adenocarcinoma tumors,

approximately 50% contained homologous recombination defects.[6] A subset of these tumors had biologically plausible molecular alterations that may make them sensitive to PARP inhibition by niraparib. A similar analysis of triple-negative breast cancer indicates that 43% to 44% of these patients have tumors with homologous recombination defects.[7] Homologous recombination is a complex pathway, and several genes other than *BRCA1* and *BRCA2* are required either to sense or repair DNA double-strand breaks via the homologous recombination pathway. Therefore, PARP inhibitors are also selectively cytotoxic for cancer cells with deficiencies in DNA repair proteins other than *BRCA1* and *BRCA2*.[1,5,8]

Recent clinical studies have shown PARP inhibitors to be active in breast and ovarian cancer. Clinical anticancer activity with PARP inhibitors has been seen in both patients with g*BRCA*mut and without g*BRCA*mut; however, activity is more robust in patients with the germline mutation.[1,4,9-15] In summary, treatment with PARP1/2 inhibitors represents a novel opportunity to selectively kill a subset of cancer cell types by exploiting their deficiencies in DNA repair. Human cancers exhibit genomic instability and an increased mutation rate due to underlying defects in DNA repair. These deficiencies render cancer cells more dependent on the remaining DNA repair pathways, and targeting these pathways is expected to have a much greater impact on the survival of the tumor cells than that of normal cells.

4.1.2. Immune Surveillance and PD-1 Inhibitors

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades.[16] Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes in cancer tissue and prognosis in various malignancies.[17-29] In particular, the presence of cluster of differentiation (CD)8+ T cells and the ratio of CD8+ effector T cells/FoxP3+ regulatory T cells seem to correlate with improved prognosis and long-term survival in many solid tumors.[25,30-36] The programmed death-1 (PD-1) receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control.[37] The normal function of PD-1, expressed on the cell surface of activated T cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an immunoglobulin (Ig) superfamily member related to CD28 and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (programmed death-ligand 1 [PD-L1] and programmed death-ligand 2 [PD-L2]). The structures of murine PD-1 alone[38] and in complex with its ligands were the first to be resolved,[39,40] and more recently the nuclear magnetic resonance-based structure of the human PD-1 extracellular region and analyses of its interactions with its ligands were also reported.[41] PD-1 and family members are Type I transmembrane glycoproteins containing an Ig variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail, which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif, and an immunoreceptor tyrosine-based switch motif (ITSM). Following T cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM within its cytoplasmic tail, leading to the dephosphorylation of effector molecules, such as CD3ζ, PKCθ, and ZAP70, which are involved in the CD3 T cell signaling cascade.[42] The mechanism by which PD-1 down-modulates T cell responses is similar to, but distinct from, that of CTLA-4.[43] PD-1 was shown to be expressed on activated lymphocytes, including peripheral CD4+ and CD8+ T cells,

B cells, T regs, and natural killer cells.[44] Expression has also been shown during thymic development on CD4-/CD8- (double-negative) T cells,[45] as well as subsets of macrophages[46] and dendritic cells.[47] The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types.[48] PD-L1 is expressed at low levels on various nonhematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is predominantly expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments.[48] Both ligands are Type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T cell activation triggered through the T cell receptor. PD-L2 is thought to control immune T cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T cell function in peripheral tissues. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T cell inhibitor,[49,50] which, via its interaction with the PD-1 receptor on tumor-specific T cells, plays a critical role in immune evasion by tumors.[51] As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in cancer.[52]

4.1.3. Anti-TIM-3 Monoclonal Antibody

In addition to PD-1, another immune protein that has been shown to mediate T-cell exhaustion is T-cell immunoglobulin and mucin containing protein-3 (TIM-3). TIM-3 was initially identified as a protein selectively expressed on interferon gamma (IFN-γ) producing CD4+ T helper 1 (Th1) and CD8+ T cytotoxic 1 (CD8 T) cells.[53] Early studies demonstrated blockade of TIM-3-enhanced Th1 cell proliferation and release of IFN-γ and interleukin-2 (IL-2).[53] These findings supported exploration of targeting TIM-3 for tumor immunotherapy. A role for TIM-3 in mediating T-cell exhaustion in cancer has been suggested in multiple preclinical murine models showing expression of TIM-3 and PD-1 on tumor-infiltrating lymphocytes (TILs).[54-56] The therapeutic efficacy of targeting these proteins demonstrated limited tumor control with TIM-3 or PD-1 blockade alone but enhanced immune-mediated control of tumor growth with concurrent TIM-3 and PD-1 blockade. These data demonstrate the expression of TIM-3 and PD-1 on TILs and implicated TIM-3 and PD-1 in limiting T-cell effector function in the tumor microenvironment.

Similar to the effects observed in murine models, TIM-3 expression on TILs in human tumors has also been shown to mediate immunosuppression. A wide variety of tumor types are infiltrated by CD8 T cells and these CD8 T cells express TIM-3 and PD-1 among other immunosuppressive proteins such as lymphocyte-activation gene-3 and CTLA-4.[57-59] Intriguingly, the presence of TIM-3+ T cells was increased in patients with non-small cell lung cancer (NSCLC) with more advanced disease. Additional studies have reported the expression of TIM-3 on tumor infiltrating regulatory T cells that correlates with enhanced immunosuppressive properties of these cells in an ex vivo assay.[60] In patients with melanoma, characterization of TIM-3 expression on CD8 T cells specific for a tumor antigen revealed that co-expression of TIM-3 and PD-1 marks TILs with the lowest proliferative potential that also fails to produce IL-2, tumor necrosis factor α (TNFα), and IFNγ.[61] Building on this phenotypic characterization of TIM-3 expression, the function of CD8 T cells from these patients that co-express TIM-3 and PD-1 demonstrate suppressed secretion of IFNγ, TNFα, and IL-2 following ex vivo stimulation

that can be improved via blockade of both TIM-3 and PD-1.[61] In addition to a role on CD8 T cells, regulatory T cells that suppress T-cell function can express TIM-3 and are enriched within the tumor microenvironment in human tumors and murine models. These TIM 3+ regulatory T cells exhibit superior suppressive capability relative to TIM-3-negative regulatory T cells resulting in limited CD8 T cell-mediated anti-tumor immunity.[60,62] Thus, the expression and function of TIM-3-expressing T cells in the tumor microenvironment in humans largely reflects the data generated in murine models and supports the exploration of TIM-3 blockade as a strategy to enhance anti-tumor immunity. The possibility of enhancing the clinical activity of tumor immunotherapy through TIM-3 blockade supports the value of developing an antibody that targets TIM-3 to utilize as monotherapy and in combination with other therapeutic approaches. TSR-022 is an IgG4-k isotype humanized monoclonal antibody that binds with high affinity to TIM-3. This antibody was generated based on a proprietary platform that utilizes affinity maturation to select antibodies with desired functional characteristics. Details on the nonclinical and clinical experience with TSR-022 are presented in Section 4.2.3.

Based on the preclinical data identifying TIM-3 expression on tumor infiltrating T cells in a broad range of tumors and TIM-3 blockade resulting in enhanced T-cell activity, TSR-022 is expected to result in clinical activity in patients with a variety of tumors and thus TSR-022 is being advanced for clinical development as an immunotherapy for advanced malignancies. To date, 46 patients have been treated with TSR-022 monotherapy, and 142 patients have been treated with TSR-022+TSR-042 combination therapy at 500 mg TSR-042 and 100, 300, or 900 mg TSR-022.

Please refer to the current TSR-022 Investigator's Brochure (IB) for additional information.

4.1.4. Carboplatin-Paclitaxel Chemotherapy

The main target of carboplatin is DNA, to which it binds efficiently, thereby inhibiting replication and transcription and inducing cell death.[63] Thrombocytopenia is chief among the potential side effects of carboplatin. To avoid severe thrombocytopenia, Calvert's formula is recommended in calculating the intravenous (IV) dose of carboplatin to be administered.[64]

Paclitaxel promotes tubulin polymerization, causing cell death by disrupting the normal microtubule dynamics required for cell division and vital interphase processes. Paclitaxel has shown activity against a broad range of tumor types, including breast, ovarian, lung, and head and neck cancers.[65]

Carboplatin in combination with paclitaxel has been shown to be efficacious against a variety of different tumor types, including NSCLC, ovarian cancer, endometrial cancer, and head and neck cancer.[66-69] Additional information on carboplatin and paclitaxel can be found in the prescribing information for each.

4.1.5. Carboplatin-Pemetrexed Chemotherapy

Pemetrexed is a folate analog metabolic inhibitor that exerts its action by disrupting folate-dependent metabolic processes essential for cell replication. In vitro studies have shown that pemetrexed inhibits thymidylate synthase (TS), dihydrofolate reductase, and glycinamide ribonucleotide formyltransferase (GARFT), which are folate-dependent enzymes involved in the de novo biosynthesis of thymidine and purine nucleotides. Pemetrexed is taken into cells by

membrane carriers such as the reduced folate carrier and membrane folate binding protein transport systems. Once in the cell, pemetrexed is converted to polyglutamate forms by the enzyme folylpolyglutamate synthetase. The polyglutamate forms are retained in cells and are inhibitors of TS and GARFT. Polyglutamation is a time- and concentration-dependent process that occurs in tumor cells and is thought to occur, to a lesser extent, in normal tissues. Polyglutamated metabolites are thought to have an increased intracellular half-life, resulting in prolonged drug action in malignant cells.[70]

Pemetrexed combined with cisplatin has been proven efficacious in a first-line setting for non-squamous NSCLC[71], and single-agent maintenance therapy with pemetrexed improved progression-free survival (PFS) and overall survival after induction therapy with a nonpemetrexed platinum doublet.[72] In addition, patients with advanced non-squamous NSCLC who continued single-agent pemetrexed maintenance therapy after induction therapy with pemetrexed-cisplatin showed a significant improvement in PFS compared with those who received placebo maintenance therapy after the same induction therapy.[73]

4.1.6. Carboplatin–Nab-Paclitaxel Chemotherapy

Nab-paclitaxel is a 130-nm albumin-bound formulation of paclitaxel that is indicated for locally advanced or metastatic NSCLC, as first-line treatment in combination with carboplatin in patients who are not candidates for curative surgery or radiation therapy.[74,75] It is suggested that nab-paclitaxel may reach the tumor microenvironment more efficiently than solvent-based paclitaxel via caveolae-mediated transcytosis and may be preferentially taken up by cancer cells.[75] Because of its saline medium, nab-paclitaxel can be administered safely at higher doses and for shorter durations without the need for the corticosteroid and antihistamine premedication that is needed to prevent solvent-related hypersensitivity reactions seen with solvent-based paclitaxel.[76,77] Nab-paclitaxel has shown increased ORR and time to progression in metastatic breast cancer compared with solvent-based paclitaxel[78] and has shown antitumor activity and improved ORR compared with solvent-based paclitaxel as first-line therapy in patients with NSCLC.[79,80]

4.1.7. Bevacizumab

Bevacizumab is an antiangiogenic recombinant humanized monoclonal immunoglobulin G1 antibody against the vascular endothelial growth factor (VEGF) protein. Bevacizumab (Avastin; Genentech/Roche 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 [FIGO] Stages IIIB, IIIC, and IV) ovarian cancer. In the US, bevacizumab is approved for the treatment of patients with platinum-sensitive recurrent ovarian cancer, either in combination with carboplatin and paclitaxel or in combination with carboplatin and gemcitabine, followed by bevacizumab as a single agent.

4.2. Study Treatments

4.2.1. Niraparib

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

4.2.1.1. Nonclinical Experience

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

Niraparib displayed strong antitumor activity in in vivo studies with *BRCA1*-mutant breast cancer (MDA-MB-436), *BRCA2*-mutant pancreatic cancer (CAPAN-1), and with patient-derived Ewing sarcoma mice models. Utilizing patient-derived ovarian and breast cancer xenograft models, niraparib demonstrated response in both *BRCAmut* and *BRCA* wild-type tumors.

4.2.1.2. Clinical Experience

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

Phase 1 Study of Niraparib Monotherapy in Advanced Solid Tumors

Clinical activity data for niraparib administered as monotherapy in patients with ovarian cancer are available from 1 early-phase clinical study. In Parts A and B of the Phase 1 study PN001 (ClinicalTrials.gov identifiers: MK-4827-001 and 2008_501), 100 patients with advanced solid tumors who had received a median of 3 prior therapies were enrolled; 49 patients had ovarian cancer (13 platinum-sensitive, 35 platinum-resistant, and 1 platinum-refractory).[11] An additional 4 patients were enrolled in Part D of the study, which assessed pharmacokinetics only.[81]

The most common nonhematological TEAEs were nausea, fatigue, anorexia, constipation, vomiting, and insomnia. These TEAEs were mainly mild to moderate in severity, self-limiting, and manageable with standard treatments. Hematological toxicity appeared to be dose proportional and most frequently arose in the setting of cumulative doses. Anemia was reported in 48 (48%) of 100 patients and was Grade ≥3 in 10 (10%) of 100 patients. Thrombocytopenia was less common (35 [35%] of 100 patients) and was Grade ≥3 in 15 (15%) of 100 patients. Neutropenia was the least commonly reported (24 [24%] of 100 patients), and was Grade 3 in 4 (4%) of 100 patients at niraparib doses of 300 and 400 mg. In all cases, hematological TEAEs were uncomplicated and reversible. Twenty patients required dose reductions (usually by 1 dose level) for recurrent anemia or thrombocytopenia. Treatment was discontinued due to AEs in 7 patients, including the 4 patients who had DLTs during the first cycle and 3 patients who had

Grade 3 vomiting, Grade 2 prolongation of QT interval, and Grade 3 prolongation of QT interval. No treatment-related deaths occurred.

Of the 49 patients, 22 had confirmed *BRCA1* or *BRCA2* mutation, of whom 20 were radiologically assessable. Eight (40%) of these 20 patients achieved a confirmed partial response (PR) by Response Evaluation Criteria in Solid Tumors (RECIST) and cancer antigen 125 (CA-125) Gynecologic Cancer Intergroup criteria at doses ranging from 80 to 400 mg per day. Median response duration was 387 days (range: 159 to 518 days). Three (33%) of 9 patients with platinum-resistant *BRCA*mut ovarian cancer had PR by RECIST and CA-125 criteria. In patients with platinum-sensitive disease, 5 (50%) of 10 patients (95% CI: 19 to 81) with BRCA1 or BRCA2 mutations had RECIST and CA-125 responses.

Phase 3 Study of Niraparib Monotherapy in Platinum-sensitive, Recurrent Ovarian Cancer
The selection of the 300 mg starting dose of niraparib for the NOVA study was based on data from the MSD-conducted Phase 1 MAD study PN001. There were no formal Phase 2 dose-ranging studies conducted. The Phase 1 study included both a dose escalation phase to determine the MTD and an expansion arm to further evaluate the selected dose. A total of 104 patients with advanced solid tumors were evaluated in this study, including 60 during dose escalation from 30 mg to 400 mg and 54 during expansion at the 300 mg dose level. The dose escalation stage determined that 400 mg exceeded the MTD (by traditional dose-limiting toxicity [DLT] evaluations and by using the pooled adjacent violators algorithm). No DLTs were observed at 290 or 300 mg dose levels.

In a Phase 3 study, niraparib was compared to placebo in 546 patients with platinum-sensitive recurrent ovarian cancer who had received at least 2 previous chemotherapy regimens and niraparib or placebo maintenance ("NOVA" study). In this pivotal study, daily niraparib improved progression-free survival (PFS) in a cohort of patients with g*BRCA* mutation as well as in a cohort of patients without g*BRCA* mutation. Within the g*BRCA*mut cohort, the median PFS was 21.0 months in patients on niraparib versus 5.5 months on placebo (hazard ratio [HR], 0.27; $p < 0.0001$). In recurrent ovarian cancer patients, efficacy was assessed in patients with HRD-positive tumors as identified by the Myriad's myChoice HRD test as well in the overall non-g*BRCA* mutation cohort regardless of HRD status. As observed in the g*BRCA*mut cohort, PFS was significantly longer with niraparib in the homologous recombination deficient-positive group of the non-g*BRCA*mut (without germline *BRCA* mutation) cohort (median, 12.9 months vs 3.8 months; HR, 0.38; $p < 0.0001$). Lastly, PFS was significantly improved in the overall non-g*BRCA*mut cohort (median, 9.3 months vs 3.9 months; HR, 0.45; $p < 0.0001$). Secondary endpoints, including chemotherapy-free interval, time to first subsequent therapy (TFST), and progression-free survival 2 (PFS2), confirmed the PFS benefit of niraparib treatment in both cohorts. This provides compelling evidence that niraparib does not diminish responsiveness to subsequent therapy and that the niraparib treatment effect persists. Subsequently in 2017, a recommendation to consider niraparib maintenance therapy in this setting in cases of CR and PR was added to the National Comprehensive Cancer Network (NCCN) guidelines.[7]

In the NOVA study, the most commonly observed non-hematologic treatment-emergent adverse events (TEAEs) of any National Cancer Institute - Common Terminology Criteria for Adverse Events (NCI-CTCAE) grade were nausea, fatigue, constipation, and vomiting; the majority of the non-hematologic TEAEs were mild to moderate in severity. The most commonly observed

hematologic TEAEs (any grade) were anemia (48.5%), thrombocytopenia 66.2%), and neutropenia (31.4%). The incidence of myelodysplastic syndrome (MDS) and/or acute myeloid leukemia (AML) in patients who received niraparib in the NOVA study was similar to that in patients who received placebo (1.4% and 1.0%, respectively). MDS/AML and secondary cancers (new malignancies other than MDS or AML) are potential risks of PARP inhibitors. Guidance on monitoring patients for new AEs of MDS/AML and the follow-up of patients with suspected MDS/AML is provided in Section 10.6.7.

TEAE's leading to treatment interruption, reduction or discontinuation were 68.9%, 66.5% and 14.7% respectively. Approximately 50% of patients required dose interruption during the first month of niraparib therapy, and 47% required dose reduction during the second month of therapy. Most patient achieved their individual maximal tolerated dose by the third month. The average dose of niraparib during the study was 206 mg. After Month 3 or 4, new incident thrombocytopenia was reported in < 1% of patients. Although Grade 3 or 4 hematologic laboratory events were common at the initiation of treatment, no severe clinical sequelae were observed, and relatively few patients discontinued due to these AEs (discontinuation rate was 3.3% for thrombocytopenia, 1.4% for anemia and 1.9% for neutropenia). Dose adjustment based on individual tolerability during the first 3 cycles substantially reduced the incidence of these events beyond Cycle 3.

Baseline Platelet Count and Weight as Predictors of Thrombocytopenia.

An analysis was conducted using the data collected in ENGOT-OV16/NOVA and the initial phase I study, PN001. This analysis determined that only baseline platelets had an impact on platelet nadir; lower baseline platelets (<180 10^9/L) were associated with an increased frequency of thrombocytopenia Grade ≥1 (76%) or Grade ≥ 3 (45%) compared to patients with higher baseline platelet counts. Further, an exploratory analysis of clinical data versus baseline body weight from ENGOT-OV16/NOVA was conducted. For this analysis, the weight categories were based on quartiles with the lowest quartile (patients with a body weight less than 58 kg at baseline) compared to the highest quartile (patients with a body weight greater than or equal to 77 kg at baseline). While TEAEs occurred in most patients regardless of body weight, Grade ≥3 TEAEs, SAEs, and TEAEs leading to dose modification or treatment discontinuation occurred more commonly in the weight <58 kg cohort than in the ≥77 kg cohort. In the cohort of patients with a body weight <58 kg, approximately 80% of patients had a dose reduction compared to 59% of patients with a weight greater than or equal to 77 kg. Treatment discontinuations were increased in the patients with lower body weight (24%) compared to patients in the highest quartile (10%).

The potential relationship between body weight and TEAEs was further explored in an analysis to evaluate the correlation of grade 3 or 4 thrombocytopenia and baseline body weight. The lowest platelet count in the first 30 days was plotted versus baseline body weight to determine if low body weight identified a subgroup of patients with higher levels of thrombocytopenia during Cycle 1. In the first 30 days of treatment, a baseline body weight ≥77 kg is associated with a lower incidence of grade 3 or 4 thrombocytopenia (14%) relative to the group with body weight <58 kg (43%).

Finally, a classification tree approach was used to refine the best cut-off points for predicting the likelihood of a patient developing ≥Grade 3 thrombocytopenia within 30 days after the first dose

of niraparib. The results of the model show that the subgroup of patients with a baseline body weight <77 kg **or** baseline platelet count <150,000 µL had a grade 3/4 thrombocytopenia rate in the first 30 days of 35.4% compared to 11.5% in the group of patients with a body weight >77 kg **and** a platelet count >150,000 µL. Further, the average daily dose was 258 mg through the first two cycles for patients with a body weight >77 kg and platelet count >150,000 µL, and was only 206 mg for patients with body weight < 77 kg or platelet count <150,000 µL. Thus, the actual delivered dose approximated a starting dose of 200 mg despite the intended delivery of a starting dose of 300 mg. These observations are to be confirmed in the present study with the inclusion of study treatment dosed at 200 mg (2 capsules of niraparib or placebo) in patients whose baseline weight is <77 kg or baseline platelet count is <150,000 µL.

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

4.2.2. TSR-042

TSR-042 is an IgG4 humanized monoclonal antibody that binds with high affinity to PD-1, resulting in inhibition of binding to PD-L1 and PD-L2. This antibody was generated based on a proprietary platform that utilizes affinity maturation to select highly-specific antibodies with desired functional characteristics. The functional antagonist activity of TSR-042 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 IB.

4.2.2.1. 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 (IC_{50}) 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 (EC_{50}) 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 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.

The safety of TSR-042 was characterized in a single-dose, a 4-week repeat-dose (5 doses), and a 13-week repeat-dose (14 doses) toxicity study in cynomolgus monkeys when administered as IV doses of 10, 30, or 100 mg/kg. In the repeat-dose studies, the dose frequency was once a week. TSR-042 was well tolerated in cynomolgus monkeys, with a systemic exposure ($AUC_{0\text{-}168h}$) of up to approximately 419,000 h × µg/mL over the course of the 4-week repeat-dose study. No findings of toxicological significance were observed in either single-dose or 4-week repeat-dose toxicity study with TSR-042, and the no observed adverse effect level (NOAEL) was ≥ 100 mg/kg. In addition, no findings of toxicological relevance were observed in the in vitro tissue cross-reactivity study using human and cynomolgus monkey tissues.

In the 13-week repeat-dose toxicity study, microscopic findings of an immune-mediated nature were observed in animals dosed with TSR-042 at ≥ 10 mg/kg/week. Additionally, 1 male dosed at 10 mg/kg/week was euthanized because of chronic, unresolved generalized skin findings. Microscopic findings in the skin of this animal were indicative of an immune reaction. Considering the mechanism of action of TSR-042, these findings could be the results of a pharmacological effect of TSR-042. Because of the euthanasia of 1 male in the 10 mg/kg dose group, the NOAEL could not be determined in this study.

4.2.2.2. Clinical Experience

As of 21 January 2018, there were 4 ongoing Phase 1 studies with TSR-042: Study 4010-01-001 (TSR-042 monotherapy), Study 4020-01-001 (TSR-042 combination therapy), Study 3000-01-002 (TSR-042 combination therapy), and Study 4040-01-001 (TSR-042 combination therapy).

Study 4010-01-001 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 recurrent or 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 (i.e., 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 (RP2D) are being evaluated in patients with specific tumor types.

Dose escalation in Part 1 of the study continued to a maximally administered dose of 10 mg/kg Q2W, and a maximum tolerated dose was not identified. No dose-limiting toxicities (DLTs) were observed. Following completion of Part 1, Part 2A evaluated safety and tolerability of TSR-042 at 2 fixed dosing schedules of 500 mg Q3W and 1,000 mg Q6W. No DLTs were observed in Part 2A. Based on the PK/pharmacodynamic profile and safety and tolerability data

from the dose regimens evaluated in Part 1 and Part 2A, the RP2D was determined to be 500 mg Q3W for 4 cycles followed by 1,000 mg Q6W thereafter.

As of 21 January 2018, 135 patients with heavily pretreated advanced solid tumors have been treated with TSR-042 in Study 4010-01-001: 21 patients in Part 1 and 114 patients in Parts 2A and 2B. The majority of these patients (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 patients (9.6%). The majority of these events occurred in only 1 patient each, with the exception of aspartate aminotransferase increased (3 patients), alanine aminotransferase increased (2 patients), and fatigue (2 patients). Serious adverse events (SAEs) occurred in 38 patients (28.1%), for 5 of these patients the event was considered study drug-related. Eight patients had an adverse event (AE) leading to study drug discontinuation. Six patients had an AE leading to study drug discontinuation which was considered study drug-related. Three patients had an AE leading to death. None of the AEs leading to death were considered to be related to the study drug.

As of 21 January 2018, a total of 51 patients with heavily pretreated advanced solid tumors have been treated with TSR-042 in combination with other therapeutic agents: 28 patients received TSR-042 in combination with TSR-022 in Study 4020-01-001, 9 patients received TSR-042 in combination with niraparib in Part A of Study 3000-01-002, and 14 patients received TSR-042 in combination with carboplatin and paclitaxel in Part B of Study 3000-01-002. The majority (80.4%) of patients receiving TSR-042 combination therapy reported at least 1 TEAE, with events of fatigue and dyspnoea being the most frequently reported. One DLT (Grade 3 aspartate aminotransferase increased) was reported in a patient in Part B of Study 3000-01-002. Serious AEs occurred in 14 patients, none of these events were considered study drug-related. One patient had at least 1 AE leading to study drug discontinuation (alanine aminotransferase increased and aspartate aminotransferase increased). Both events were considered study drug-related. No patient had an AE leading to death.

4.2.3. TSR-022

4.2.3.1. Nonclinical Experience

TSR-022 is an IgG4-κ isotype humanized monoclonal antibody that binds with high affinity to TIM-3. Binding of TSR-022 to TIM-3 has been demonstrated in nonclinical assays and is similar for human and monkey proteins. Full TIM-3 receptor occupancy was observed ex vivo in human peripheral blood mononuclear cells (PBMCs) at a concentration of approximately 0.6 µg/mL. TSR-022 is unlikely to independently induce cytokine release, activate the complement system, or elicit complement-dependent cytotoxicity (CDC) or antibody-dependent cell-mediated cytotoxicity (ADCC) at clinically relevant doses. TSR-022 augments T cell activity as measured by enhanced IL-2 production in multiple assays. This agonist activity is further enhanced by the addition of an anti-PD-1 antibody.

The PK properties of TSR-022 were characterized in cynomolgus monkeys using both single- and repeat-dose studies. TSR-022 exhibits kinetics typical of mAbs, with a limited volume of distribution and a slow to moderate clearance. Consecutive weekly dosing of 10, 30, and 100 mg/kg in cynomolgus monkeys showed a moderate accumulation of TSR-022.

The results from the 2 repeat-dose toxicity studies indicated that weekly administration of TSR-022 at doses up to 100 mg/kg for a total of 3 or 5 doses was well tolerated in cynomolgus monkeys. No study drug-related findings of toxicological significance were observed in either repeat-dose toxicity study, and the NOAEL was ≥100 mg/kg in both studies. ADA formation was observed in several animals in both repeat-dose studies but was not associated with any toxicity.

4.2.3.2. Clinical Experience

As of the clinical cutoff date of 19 May 2018, there is 1 ongoing study with TSR-022: Study 4020-01-001, a first-in-human study of TSR-022 to evaluate the safety and tolerability, PK, pharmacodynamic, immunogenicity, and clinical activity of TSR-022 in patients with advanced solid tumors. The study is conducted in 2 parts:

- Part 1 (dose escalation, safety, and tolerability) of the study is conducted in 3 subparts (Part 1a, Part 1b, and Part 1c) to evaluate the safety and tolerability of TSR-022 monotherapy or combination therapy. All 3 subparts use a 3 + 3 design.
  - In Part 1a, the safety and tolerability of TSR-022 administration Q2W were evaluated based on weight (0.03, 0.1, 0.3, 1, 3, or 10 mg/kg doses) or as a fixed dose of 1,200 mg.
  - In Part 1b, the safety and tolerability of TSR-022 at 1 mg/kg Q2W in combination with nivolumab at 3 mg/kg Q2W were evaluated.
  - In Part 1c, the safety and tolerability of TSR-022 (100, 300, or 900 mg) in combination with TSR-042 (500 mg) administered Q3W are being evaluated.
- Part 2 (antitumor activity) of the study will evaluate the efficacy of TSR-022 as monotherapy and in combination with TSR-042.

As of 19 May 2018, 194 patients in this study have been treated with TSR-022 as monotherapy or in combination with nivolumab or TSR-042. Dose escalation in Part 1a of the study continued to a maximally administered dose of 1,200 mg Q2W, and a maximum tolerated dose was not identified. The majority (95.7%) of the 46 patients who were treated with TSR-022 monotherapy in Part 1a reported at least 1 TEAE, with fatigue and nausea being the most frequently reported. Grade ≥3 TEAEs considered by the Investigator to be related to study drug were experienced by 2 patients. For 1 of the 2 patients, the event was considered dose-limiting (Grade 3 lipase increased; 10 mg/kg TSR-022). SAEs were reported in 26.1% of patients; only 1 patient (2.2%) had an SAE assessed by the Investigator to be related to study drug. Two patients (4.3%) discontinued the study drug due to a TEAE, and for 1 patient (2.2%), this was assessed as related to study drug by the Investigator. No patient had a TEAE leading to death.

As of 19 May 2018, a total of 7 patients were treated with TSR-022 in combination with nivolumab, and 142 patients were treated with TSR-022 in combination with TSR-042. Because 2 patients treated with TSR-022 in combination with nivolumab experienced a DLT (Grade 3 diarrhea [1 patient] and Grade 3 alanine aminotransferase increased with Grade 3 aspartate aminotransferase increased [1 patient]), Part 1b of the study was discontinued. All 7 patients who were treated with TSR-022 + nivolumab combination therapy reported at least 1 TEAE; 6 patients (85.7%) experienced TEAEs considered by the Investigator to be related to study drug.

TEAEs of Grade ≥3 were reported in 6 patients (85.7%), and 2 patients (28.6%) experienced Grade ≥3 TEAEs considered by the Investigator to be related to study drug. SAEs were reported in 4 patients (57.1%), and no patients had SAEs assessed to be related to study drug by the Investigator. Four patients (57.1%) discontinued the study drug due to a TEAE, and for 1 patient (14.3%), this was assessed as related to study drug by the Investigator. No patient had a TEAE leading to death.

As of 19 May 2018, the majority (85.2%) of the 142 patients who received TSR-022 in combination with TSR-042 experienced TEAEs; 42.3% experienced TEAEs considered by the Investigator to be related to study drug. TEAEs of Grade ≥3 were reported in 35.9% of patients, and 6.3% experienced Grade ≥3 TEAEs considered by the Investigator to be related to study drug. SAEs were reported in 27.5% of patients; 6.3% experienced SAEs considered by the Investigator to be related to study drug. Seven patients (4.9%) discontinued study drug due to a TEAE; 1 patient (0.7%) experienced a TEAE leading to study drug discontinuation that was considered by the Investigator to be related to study drug. Two patients (1.4%) had TEAEs leading to death; neither were assessed as related to study drug by the Investigator.

4.2.4. Bevacizumab

4.2.4.1. Clinical Experience

Bevacizumab has been evaluated in multiple clinical studies, including in 1,873 patients with newly diagnosed, Stage III (incompletely resected) or Stage IV epithelial ovarian cancer who had undergone debulking surgery as part of a Phase 3 study (GOG218).[82] Patients receiving bevacizumab administered concurrently with chemotherapy and as a maintenance treatment showed statistically significant improvement in PFS compared to placebo (14.1 months vs 10.3 months; HR, 0.717; $p < 0.001$).

Bevacizumab was also evaluated in 1,528 patients with ovarian cancer, regardless of FIGO stage as part of a Phase 3 study (ICON7).[83] Patients receiving bevacizumab administered concurrently with chemotherapy and as a maintenance treatment showed statistically significant improvement in PFS compared to chemotherapy alone (19.0 months vs 17.3 months; HR, 0.81; $p = 0.004$), with maximum improvement compared to chemotherapy alone at 12 months (15.1%; 95% confidence interval [CI], 10.7-19.5). The improvement was even more pronounced in patients at high risk of progression (i.e., FIGO Stage IV or FIGO Stage III and >1.0 cm of residual disease after debulking surgery; 15.9 months vs 10.5 months; HR, 0.68; $p = <0.001$).

4.2.5. TSR-042 and Niraparib Combination Treatment

4.2.5.1. 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 *BRCA* null genetic background,[84] as PARP inhibition was previously shown to increase immune cell infiltration in *BRCA*-deficient models.[85] In a study of a ovarian carcinoma mouse model,[86] niraparib (50 mg/kg orally [PO] QD) and anti-mPD-1 (5 mg/kg intraperitoneally [IP] 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, one 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.[87] 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%).[88] Together, these data support the therapeutic approach of combining niraparib with anti PD-1 agent in either *BRCA1/2* mutant or wild-type tumors.

4.2.5.2. Clinical Experience

This study is the first to assess TSR-042 and niraparib combination treatment; therefore, no clinical data are currently available for TSR-042 and niraparib combination treatment.

4.2.6. Carboplatin-Paclitaxel in Combination With PD-1 or PD-L1 Antibodies

4.2.6.1. Nonclinical Experience

There is accumulating evidence that, in addition to direct cytostatic and cytotoxic effects, the mechanism of action of conventional chemotherapies may also involve activation of tumor-targeted immune responses, including increasing the immunogenicity of cancer cells and reducing immunosuppression of tumors.[89] In nonclinical models, platinum-based agents have been suggested to increase direct cytostatic-mediated activation of T cells by several mechanisms, including down-regulation of PD-L2, increased adenosine triphosphate, and increased high mobility group protein box-1 release from dying cells.[90] Several immunostimulatory effects of paclitaxel on the immune system have also been reported; among these are the induction of endoplasmic reticulum stress, which can lead to calreticulin exposure and dendritic cell stimulation,[91] depletion of myeloid-derived suppressor cells,[92,93] and boosting of T-cell priming.[94] These data suggest that chemotherapy agents may modulate the tumor microenvironment, an effect that could be enhanced by the addition of immune checkpoint inhibitors, such as those targeting PD-1 or PD-L1.

4.2.6.2. Clinical Experience

Carboplatin-paclitaxel in combination with anti-PD-1 antibody agents has been studied in patients with advanced NSCLC in several studies. The combination has been well tolerated and

has shown encouraging anti-tumor activity. Nivolumab 5 or 10 mg/kg and carboplatin-paclitaxel combination treatment was evaluated in the CheckMate 012 study, a Phase 1, multicohort study exploring the safety and efficacy of nivolumab monotherapy and nivolumab in combination with current standard therapies in first-line advanced NSCLC. The safety profile of combination treatment was found to be manageable, and the clinical activity of nivolumab 5 mg/kg and carboplatin-paclitaxel combination treatment showed evidence of efficacy.[95]

Carboplatin-paclitaxel was administered in combination with the anti-PD-1 antibody pembrolizumab in the KEYNOTE-021 study in patients with advanced non-squamous NSCLC. The study concluded that pembrolizumab and carboplatin-paclitaxel combination treatment may be an effective and tolerable first-line treatment option for patients with advanced non-squamous NSCLC.[96]

This study is the first to assess TSR-042 and carboplatin-paclitaxel combination treatment; therefore, no clinical data are currently available for TSR-042 and carboplatin-paclitaxel combination treatment.

4.2.7. Carboplatin-Paclitaxel in Combination with Bevacizumab

Carboplatin-paclitaxel and bevacizumab combination treatment was evaluated in patients with recurrent or advanced non–small-cell lung (Stage IIIB or IV) cancer (Eastern Cooperative Oncology Group (ECOG-4599)). These patients were assigned to treatment with carboplatin-paclitaxel alone or carboplatin-paclitaxel plus bevacizumab. The median survival was 12.3 months for patients assigned to carboplatin-paclitaxel plus bevacizumab treatment, whereas the median survival for patients assigned to carboplatin-paclitaxel alone was 10.3 months (HR, 0.79; P = 0.003). It was concluded that the addition of bevacizumab to carboplatin-paclitaxel had a significant survival benefit. However, patients showed an increased toxic effect, particularly febrile neutropenia and pulmonary hemorrhage.[97]

The combination of chemotherapy and bevacizumab has also been evaluated in in patients with recurrent, persistent, or metastatic cervical cancer (GOG 240). The addition of bevacizumab to combination chemotherapy in these patients was associated with an improvement of 3.7 months in median overall survival. Bevacizumab, as compared with chemotherapy alone, was associated with an increased incidence of hypertension of grade 2 or higher (25% vs. 2%), thromboembolic events of grade 3 or higher (8% vs. 1%), and gastrointestinal fistulas of grade 3 or higher (3% vs. 0%).[98]

4.2.8. Carboplatin-Pemetrexed in Combination With Anti-PD-1 Inhibitors

The addition of the PD-l inhibitor pembrolizumab to carboplatin and pemetrexed has shown improved efficacy and a favorable benefit-risk profile in patients with chemotherapy-naive, advanced non-squamous NSCLC[99].

The comparison of the combination of pemetrexed and a platinum-based drug plus either pembrolizumab or placebo in patients with non-squamous NSCLC with any level of PD-L1 expression has been studied in the KEYNOTE-189 study. Addition of pembrolizumab to standard chemotherapy of pemetrexed and a platinum-based drug resulted in significantly longer overall survival and PFS than chemotherapy alone. Median progression-free survival was 8.8 months vs 4.9 months (HR = 0.52, P < .001). Progression-free survival at 12 months was 34.1%

vs 17.3%. Overall survival at 12 months was 69.2% in the pembrolizumab group vs 49.4% in the placebo group (hazard ratio [HR] = 0.49, P < .001). Median overall survival was not reached in the pembrolizumab group vs 11.3 months in the placebo group (hazard ratio for disease progression or death, 0.52; 95% CI, 0.43 to 0.64; P<0.001).

The addition of pembrolizumab to pemetrexed and chemotherapy showed a similar incidence of adverse events as chemotherapy regimens involving only pemetrexed and a platinum-based drug. The incidence of most immune-mediated adverse events was not higher with pembrolizumab combination therapy than that previously observed with pembrolizumab monotherapy.

4.2.9. Carboplatin–Nab-Paclitaxel in Combination With Anti-PD-1 Inhibitors

In the Keynote 407 study, pembrolizumab plus carboplatin and paclitaxel or nab-paclitaxel showed significant improvement in OS over chemotherapy alone in patients with metastatic squamous NSCLC. Pembrolizumab plus chemotherapy significantly improved OS (median, 15.9 months vs 11.3 months; HR, 0.64; P = 0.0008) over chemotherapy alone. PFS (median, 6.4 months vs 4.8 months; HR, 0.56; P < 0.0001) and ORR (57.9% vs 38.4%; P = 0.0004) were also improved with pembrolizumab plus chemotherapy, and responses were more durable. The safety profile was consistent with safety profiles of pembrolizumab and chemotherapy, and no new safety signals were identified.[100]

The Impower 131 study met its primary endpoint of investigator-assessed PFS with atezolizumab plus carboplatin and nab-paclitaxel compared to nab-paclitaxel alone in patients with advanced squamous NSCLC (median PFS, 6.3 months vs 5.6 months; HR, 0.71). The combination had a manageable safety profile consistent with the known safety risks of the individual therapies, and no new safety signals were observed.[101]

4.2.10. Combination of Niraparib and Bevacizumab

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

As described earlier, 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 DNA breaks within tumor cells due to increased levels of reactive oxygen species. 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) or olaparib combined with cediranib (Phase II), irrespective of their *BRCA* mutation or HRD status. 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 myChoice® HRD test.

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).[102] 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 intravenous (IV) infusion every 3 weeks. 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. AEs observed to date are consistent with those of the individual components and are readily managed through routine laboratory testing (i.e., CBC), clinical surveillance (i.e., blood pressure monitoring), and adherence to the recommended dose modifications.

4.2.11. Combination of PD-L1 Inhibitor, PARP Inhibitor, and Anti-Angiogenic Agent

There is no previous clinical experience of combination treatment that includes a PD-1 inhibitor. However, the efficacy and safety of the combination of a PD-L1 inhibitor, PARP inhibitor and an anti-angiogenic agent have been studied in a Phase 1/2 study in women's cancers.[103,104] Data from the study indicates anti-cancer activity of the triplet combination, especially in ovarian cancer. At the dosing levels explored, the combination was tolerable and hemotoxicity and cardiovascular toxicity observed in the study were consistent with PARPi-class and anti-VEGFR treatments, respectively.

4.2.12. Combination of TSR-042 and TSR-022

While a significant proportion of patients with NSCLC benefit from anti-PD-1 monotherapy, there are many patients who do not benefit from anti-PD-1 treatment. The lack of benefit in these patients may be due to additional immunosuppressive mechanisms such as those mediated by TIM-3. Early combination treatment enables the assessment of TIM-3 and PD-1 blockade to address de novo resistance to anti-PD-1 blockade while preventing one of the mechanisms that may result in resistance to anti-PD-1 monotherapy.

There are several lines of evidence that suggest that the activity of anti-TIM-3 will be optimized in the setting of concurrent treatment with anti-PD-1. First, the blockade of TIM-3 may result in an increase in IFNγ and IFNγ-induced PD-L1 expression.[27, 28] Second, the majority of TIM-3 expressing cells also express PD-1.[57-59] Third, treatment with anti-PD-1 has been shown to increase TIM-3 expression.[24] Combination therapy of anti-TIM-3 and anti-PD-1 may therefore provide improved clinical activity compared to either monotherapy.

The combination of TSR-042 and TSR-022 treatment is currently being evaluated in patients with advanced solid tumors as part of an ongoing Phase 1 study (Study 4020-01-001). In Part 1c of the study, patients receive TSR-042 (500 mg) in combination with TSR-022 (100, 300, or 900 mg) via IV infusion every 3 weeks.

As of 19 May 2018, 142 subjects were treated with TSR-022 in combination with TSR-042. The majority (85.2%) of the 142 subjects who received TSR-022 in combination with TSR-042

experienced TEAEs; 42.3% experienced TEAEs considered by the Investigator to be related to study drug. TEAEs of Grade ≥3 were reported in 35.9% of subjects, and 6.3% experienced Grade ≥3 TEAEs considered by the Investigator to be related to study drug. SAEs were reported in 27.5% of subjects; 6.3% experienced SAEs considered by the Investigator to be related to study drug. Seven subjects (4.9%) discontinued study drug due to a TEAE; 1 subject (0.7%) experienced a TEAE leading to study drug discontinuation that was considered by the Investigator to be related to study drug. Two subjects (1.4%) had TEAEs leading to death; neither were assessed as related to study drug by the Investigator.

Please refer to the current TSR-022 IB for further information.

4.3. Rationale for the Current Study

It is possible that increased DNA damage from treatment with a PARP inhibitor or chemotherapy agents (e.g., carboplatin-paclitaxel or carboplatin-pemetrexed) combined with reduced angiogenesis due to treatment with a VGFR inhibitor may lead to an increase in the neoantigen expression and a more robust antigenic environment. In this stimulated immune environment, treatment with an anti-PD-1 inhibitor may result in improved clinical efficacy.

Synergistic interactions have been observed between immune checkpoint inhibitors and PARP inhibitors; nonclinical studies in syngeneic mouse models have shown an increased response rate to combination of anti-PD-1 and niraparib over either agent alone, further supporting the investigation of this combination in patients (see Section 4.2.5.1). The combination was well tolerated in all of these nonclinical studies including models of BRCA1-deficient ovarian cancer, BRCA1-null ovarian cancer, ovarian carcinoma, and lung squamous cell cancer.[84-88] PARP inhibitor can increase the number of CD8+ T cells and natural killer cells, as well as their production of interferon-gamma and tumor necrosis factor alpha, resulting in an improved response to checkpoint blockade.[85]

Combination treatment with an anti-PD-1 antibody agent and PARP inhibitor 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.[105] Given the unmet medical need of patients with advanced or metastatic cancer, their non-overlapping safety and metabolic profiles (see the niraparib IB and the TSR-042 IB for details), and nonclinical and clinical data suggesting possible synergistic interaction between immune checkpoint inhibitors and PARP inhibitors along with a potential overlap in PD-l- and PARP-sensitive patient populations, the present clinical study is designed to evaluate TSR-042 and niraparib combination treatment in this patient population.

Accumulating nonclinical data suggest that chemotherapy agents such as carboplatin and paclitaxel may activate immune responses targeting tumor cells, in addition to their direct cytotoxic effects (see Section 4.2.6.1).[69] In nonclinical models, platinum-based agents have been suggested to increase direct cytostatic-mediated activation of T cells by several mechanisms, including down-regulation of PD-L2 and increased ATP and high mobility group protein box-1 release from dying cells, whereas for paclitaxel, several immunostimulatory effects on the immune system have been reported.[90-94] These data suggest that chemotherapy agents may modulate the tumor microenvironment, suggesting a potential synergistic interaction between chemotherapy and immune checkpoint inhibitors, such as those targeting PD-1 or PD-L1.

Carboplatin-paclitaxel in combination with anti-PD-1 antibody agents has been evaluated in patients with advanced NSCLC in several studies (see Section 4.2.6.2). The combination of carboplatin-paclitaxel with nivolumab was well tolerated with encouraging anti-tumor activity as a first-line therapy in patients with advanced NSCLC.[95] In patients with advanced non-squamous NSCLC, combination treatment with carboplatin-paclitaxel and pembrolizumab was shown to be an effective and tolerable first-line treatment option.[96] These data suggest a potential synergistic anti-cancer effect of carboplatin-paclitaxel and an anti-PD-1 inhibitor, such as TSR-042.

The addition of the PD-l inhibitor pembrolizumab to carboplatin and pemetrexed has shown improved efficacy and a favorable benefit-risk profile in patients with chemotherapy-naive, advanced non-squamous NSCLC.[99]

Pembrolizumab plus carboplatin and paclitaxel or nab-paclitaxel showed significant improvement in OS over chemotherapy alone in patients with metastatic squamous NSCLC. PFS and ORR were also improved with pembrolizumab plus chemotherapy, and responses were more long-lasting.[101]

As mentioned above, the strategy of combining a PARP inhibitor, VEGF inhibitor, and an immune checkpoint inhibitor was tested in a Phase 1/2 study and showed acceptable safety data and encouraging anti-cancer effects, suggesting potential synergistic effect of the combination.[103]

In the IMPOWER-150 study, carboplatin-paclitaxel-bevacizumab in combination with the anti-PD-L1 antibody, atezolizumab, was studied in previously untreated advanced non-squamous cell lung cancer patients.[106] Results showed significant improvement in OS and PFS: the median OS with atezolizumab/ bevacizumab/chemotherapy was 19.8 months compared with 14.9 months for bevacizumab/chemotherapy (HR 0.76; 95% CI 0.63, 0.93) and the median PFS was 8.3 versus 6.8 months (hazard ratio [HR] 0.62; 95% CI 0.52, 0.74). The overall safety profile of the combination was acceptable.

The combination of TSR-042 (500 mg) and TSR-022 (900 mg) treatment is currently being evaluated in patients with advanced solid tumors as part of an ongoing Phase 1 study (Study 4020-01-001). Results to date, although limited, indicate that TSR-042/TSR-022 combination therapy is safe and has a manageable safety profile.

This study is the first to assess TSR-042 and niraparib combination treatment; TSR-042 and carboplatin-paclitaxel combination treatment; TSR-042, niraparib, and bevacizumab combination treatment;TSR-042, carboplatin-paclitaxel, and bevacizumab combination treatment; TSR-042 and carboplatin-pemetrexed combination treatment; TSR-042, TSR-022, and carboplatin-pemetrexed combination treatment; TSR-042 and carboplatin–nab-paclitaxel combination treatment; TSR-042, TSR-022, and carboplatin–nab-paclitaxel combination treatment; and TSR-042, TSR-022, and carboplatin-paclitaxel combination treatment; therefore, the PK profiles of niraparib, TSR-042, and TSR-022 will be evaluated. Anti-drug antibodies (ADAs) for TSR-042 and TSR-022 (as applicable) during all combination treatments will be evaluated as well. The study will be conducted in conformance with the protocol, Good Clinical Practice (GCP), and applicable regulatory requirements.

5. STUDY OBJECTIVES AND PURPOSE

5.1. Primary Objectives

The primary objectives for Part A of this study are as follows:

- To evaluate DLTs of TSR-042 and niraparib combination treatment during the first cycle of treatment in patients with advanced or metastatic cancer and to establish a RP2D.
- To evaluate the safety and tolerability of TSR-042 and niraparib combination treatment

The primary objectives for Part B of this study are as follows:

- To evaluate DLTs of TSR-042 and carboplatin-paclitaxel combination treatment during the first cycle of treatment in patients with advanced or metastatic cancer and to confirm an RP2D
- To evaluate the safety and tolerability of TSR-042 and carboplatin-paclitaxel combination treatment

The primary objectives for Part C of this study are as follows:

- To evaluate DLTs of TSR-042, niraparib, and bevacizumab combination treatment during the first cycle of treatment in patients with advanced or metastatic cancer and to establish an RP2D
- To evaluate the safety and tolerability of TSR-042, niraparib, and bevacizumab combination treatment

The primary objectives for Part D of this study are as follows:

- To evaluate DLTs of TSR-042, carboplatin-paclitaxel, and bevacizumab combination treatment during the first cycle of treatment in patients in whom carboplatin-paclitaxel and bevacizumab combination treatment is considered a reasonable therapy, and to confirm an RP2D
- To evaluate the safety and tolerability of TSR-042, carboplatin-paclitaxel, and bevacizumab combination treatment

The primary objectives for Part E of this study are as follows:

- To evaluate DLTs of TSR-042 and carboplatin-pemetrexed combination treatment during the first cycle of treatment, as first-line treatment in patients with advanced or metastatic non-squamous NSCLC, and to confirm an RP2D
- To evaluate the safety and tolerability of TSR-042 and carboplatin-pemetrexed combination treatment

The primary objectives for Part F of this study are as follows:

- To evaluate DLTs of TSR-042, TSR-022, and carboplatin-pemetrexed combination treatment during the first cycle of treatment, as first-line treatment in patients with advanced or metastatic non-squamous NSCLC, and to confirm an RP2D
- To evaluate the safety and tolerability of TSR-042, TSR-022, and carboplatin-pemetrexed combination treatment

The primary objectives for Part G of this study are as follows:

- To evaluate DLTs of TSR-042 and carboplatin–nab-paclitaxel combination treatment during the first cycle of treatment, as first-line treatment in patients with advanced or metastatic NSCLC, and to confirm an RP2D
- To evaluate the safety and tolerability of TSR-042 and carboplatin–nab-paclitaxel combination treatment

The primary objectives for Part H of this study are as follows:

- To evaluate DLTs of TSR-042, TSR-022, and carboplatin–nab-paclitaxel combination treatment during the first cycle of treatment, as first-line treatment in patients with advanced or metastatic NSCLC, and to confirm an RP2D
- To evaluate the safety and tolerability of TSR-042, TSR-022, and carboplatin–nab-paclitaxel combination treatment

The primary objectives for Part I of this study are as follows:

- To evaluate DLTs of TSR-042, TSR-022, and carboplatin-paclitaxel combination treatment during the first cycle of treatment, as first-line treatment in patients with advanced or metastatic NSCLC, and to confirm an RP2D
- To evaluate the safety and tolerability of TSR-042, TSR-022, and carboplatin-paclitaxel combination treatment

5.2. Secondary Objectives

The secondary objectives for Part A of the study are as follows:

- To evaluate measures of clinical benefit as assessed by the Investigators, including objective response rate (ORR), duration of response (DOR), disease control rate (DCR), and PFS by Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1)
- To evaluate the PK of niraparib, its major metabolite M1, and TSR-042 during TSR-042 and niraparib combination treatment
- To evaluate ADAs of TSR-042 during TSR-042 and niraparib combination treatment

The secondary objectives for Part B of the study are as follows:

- To evaluate measures of clinical benefit as assessed by the Investigators, including ORR, DOR, DCR, and PFS by RECIST v1.1

- To evaluate the PK of TSR-042 during TSR-042 and carboplatin-paclitaxel combination treatment
- To evaluate ADAs of TSR-042 during TSR-042 and carboplatin-paclitaxel combination treatment

The secondary objectives for Part C of the study are as follows:

- To evaluate measures of clinical benefit as assessed by the Investigators, including ORR, DOR, DCR, and PFS by RECIST v1.1
- To evaluate the PK of niraparib, its major metabolite M1, and TSR-042 during TSR-042, niraparib and bevacizumab combination treatment
- To evaluate ADAs of TSR-042 during TSR-042, niraparib and bevacizumab combination treatment

The secondary objectives for Part D of the study are as follows:

- To evaluate measures of clinical benefit as assessed by the Investigators, including ORR, DOR, DCR, and PFS by RECIST v1.1
- To evaluate the PK of TSR-042 during TSR-042, carboplatin-paclitaxel and bevacizumab combination treatment
- To evaluate ADAs of TSR-042 during TSR-042, carboplatin-paclitaxel and bevacizumab combination treatment

The secondary objectives for Part E of the study are as follows:

- To evaluate measures of clinical benefit as assessed by the Investigators, including ORR, DOR, DCR, and PFS by RECIST v1.1
- To evaluate the PK of TSR-042 during TSR-042 and carboplatin-pemetrexed combination treatment
- To evaluate ADAs of TSR-042 during TSR-042 and carboplatin-pemetrexed combination treatment

The secondary objectives for Part F of the study are as follows:

- To evaluate measures of clinical benefit as assessed by the Investigators, including ORR, DOR, DCR, and PFS by RECIST v1.1
- To evaluate the PK of TSR-042 and TSR-022 during TSR-042, TSR-022, and carboplatin-pemetrexed combination treatment
- To evaluate ADAs of TSR-042 and TSR-022 during TSR-042, TSR-022, and carboplatin-pemetrexed combination treatment

The secondary objectives for Part G of the study are as follows:

- To evaluate measures of clinical benefit as assessed by the Investigators, including ORR, DOR, DCR, and PFS by RECIST v1.1

- To evaluate the PK of TSR-042 during TSR-042 and carboplatin–nab-paclitaxel combination treatment
- To evaluate ADAs of TSR-042 during TSR-042 and carboplatin–nab-paclitaxel combination treatment

The secondary objectives for Part H of the study are as follows:

- To evaluate measures of clinical benefit as assessed by the Investigators, including ORR, DOR, DCR, and PFS by RECIST v1.1
- To evaluate the PK of TSR-042 and TSR-022 during TSR-042, TSR-022, and carboplatin–nab-paclitaxel combination treatment
- To evaluate ADAs of TSR-042 and TSR-022 during TSR-042, TSR-022, and carboplatin–nab-paclitaxel combination treatment

The secondary objectives for Part I of the study are as follows:

- To evaluate measures of clinical benefit as assessed by the Investigators, including ORR, DOR, DCR, and PFS by RECIST v1.1
- To evaluate the PK of TSR-042 and TSR-022 during TSR-042, TSR-022, and carboplatin-paclitaxel combination treatment
- To evaluate ADAs of TSR-042 and TSR-022 during TSR-042, TSR-022, and carboplatin-paclitaxel combination treatment

5.3. Exploratory Objectives

The exploratory objectives for Part A of the study are as follows:

- To explore biomarkers that may be predictive of benefit from TSR-042 and niraparib combination treatment based on the pretreatment biomarker profile
- To explore changes in biomarkers (e.g., immune cells and immune proteins) in the blood following TSR-042 and niraparib combination treatment and correlate with clinical benefit

The exploratory objectives for Part B of the study are as follows:

- To explore biomarkers that may be predictive of benefit from TSR-042 and carboplatin-paclitaxel combination treatment based on the pretreatment biomarker profile
- To explore changes in biomarkers (e.g., immune cells and immune proteins) in the blood following TSR-042 and carboplatin-paclitaxel combination treatment and correlate with clinical benefit

The exploratory objectives for Part C of the study are as follows:

- To explore biomarkers that may be predictive of benefit from TSR-042, niraparib and bevacizumab combination treatment based on the pretreatment biomarker profile

- To explore changes in biomarkers (e.g., immune cells and immune proteins) in the blood following TSR-042, niraparib and bevacizumab combination treatment and correlate with clinical benefit

The exploratory objectives for Part D of the study are as follows:

- To explore biomarkers that may be predictive of benefit from TSR-042, carboplatin-paclitaxel and bevacizumab combination treatment based on the pretreatment biomarker profile
- To explore changes in biomarkers (e.g., immune cells and immune proteins) in the blood following TSR-042, carboplatin-paclitaxel and bevacizumab combination treatment and correlate with clinical benefit

The exploratory objectives for Part E of the study are as follows:

- To explore biomarkers that may be predictive of benefit from TSR-042 and carboplatin-pemetrexed combination treatment based on the pretreatment biomarker profile
- To explore changes in biomarkers (e.g., immune cells and immune proteins) in the blood following TSR-042 and carboplatin-pemetrexed combination treatment and correlate with clinical benefit

The exploratory objectives for Part F of the study are as follows:

- To explore biomarkers that may be predictive of benefit from TSR-042, TSR-022, and carboplatin-pemetrexed combination treatment based on the pretreatment biomarker profile
- To explore changes in biomarkers (e.g., immune cells and immune proteins) in the blood following TSR-042, TSR-022, and carboplatin-pemetrexed treatment and correlate with clinical benefit

The exploratory objectives for Part G of the study are as follows:

- To explore biomarkers that may be predictive of benefit from TSR-042 and carboplatin–nab-paclitaxel combination treatment based on the pretreatment biomarker profile
- To explore changes in biomarkers (e.g., immune cells and immune proteins) in the blood following TSR-042 and carboplatin–nab-paclitaxel combination treatment and correlate with clinical benefit

The exploratory objectives for Part H of the study are as follows:

- To explore biomarkers that may be predictive of benefit from TSR-042, TSR-022, and carboplatin–nab-paclitaxel combination treatment based on the pretreatment biomarker profile
- To explore changes in biomarkers (e.g., immune cells and immune proteins) in the blood following TSR-042, TSR-022, and carboplatin–nab-paclitaxel treatment and correlate with clinical benefit

The exploratory objectives for Part I of the study are as follows:

- To explore biomarkers that may be predictive of benefit from TSR-042, TSR-022, and carboplatin-paclitaxel combination treatment based on the pretreatment biomarker profile
- To explore changes in biomarkers (e.g., immune cells and immune proteins) in the blood following TSR-042, TSR-022, and carboplatin-paclitaxel treatment and correlate with clinical benefit

6. INVESTIGATIONAL PLAN

6.1. Overall Study Design and Plan

This is a multicenter, open-label, 9-part Phase 1b study evaluating the safety and preliminary efficacy of niraparib or niraparib/bevacizumab in combination with TSR-042 treatment and confirming the safety and tolerability of carboplatin-paclitaxel, carboplatin-paclitaxel/ bevacizumab, carboplatin-pemetrexed, carboplatin-pemetrexed/TSR-022, carboplatin–nab-paclitaxel, TSR-022/carboplatin–nab-paclitaxel, and TSR-022/carboplatin-paclitaxel in combination with TSR-042 treatment in patients with advanced or metastatic cancer. Specifically, patients eligible for this study are as follows:

- Part A (dose finding—TSR-042 and niraparib combination treatment): All comers, defined as patients with previously treated advanced or metastatic cancer
- Part B (safety and tolerability evaluation—TSR-042 and carboplatin-paclitaxel combination treatment): Patients with advanced or metastatic cancer for which treatment with carboplatin and paclitaxel is indicated (e.g., including, but not limited to, NSCLC, ovarian cancer, and cervical cancer)
- Part C (dose finding—TSR-042, niraparib and bevacizumab combination treatment): All comers, defined as patients with previously treated advanced or metastatic cancer
- Part D (safety and tolerability evaluation—TSR-042, carboplatin-paclitaxel and bevacizumab combination treatment): in patients where carboplatin-paclitaxel and bevacizumab is considered a reasonable therapy
- Part E (safety and tolerability evaluation—TSR-042 and carboplatin-pemetrexed combination treatment): as first-line treatment in patients with advanced or metastatic non-squamous NSCLC
- Part F (safety and tolerability evaluation—TSR-042, TSR-022, and carboplatin-pemetrexed combination treatment): as first-line treatment in patients with advanced or metastatic non-squamous NSCLC
- Part G (safety and tolerability evaluation—TSR-042 and carboplatin–nab-paclitaxel combination treatment): as first-line treatment in patients with advanced or metastatic NSCLC
- Part H (safety and tolerability evaluation—TSR-042, TSR-022, and carboplatin–nab-paclitaxel combination treatment): as first-line treatment in patients with advanced or metastatic NSCLC
- Part I (safety and tolerability evaluation—TSR-042, TSR-022, and carboplatin-paclitaxel combination treatment): as first-line treatment in patients with advanced or metastatic NSCLC

The study will include 9 parts: Parts A, B, C, D, E, F, G, H, and I. Part A will be a dose-finding evaluation conducted in all comers (12 to 24 patients) to determine the RP2D of niraparib in combination with TSR-042. Part B will evaluate the safety and tolerability of TSR-042 and carboplatin-paclitaxel combination treatment in approximately 12 patients with advanced or

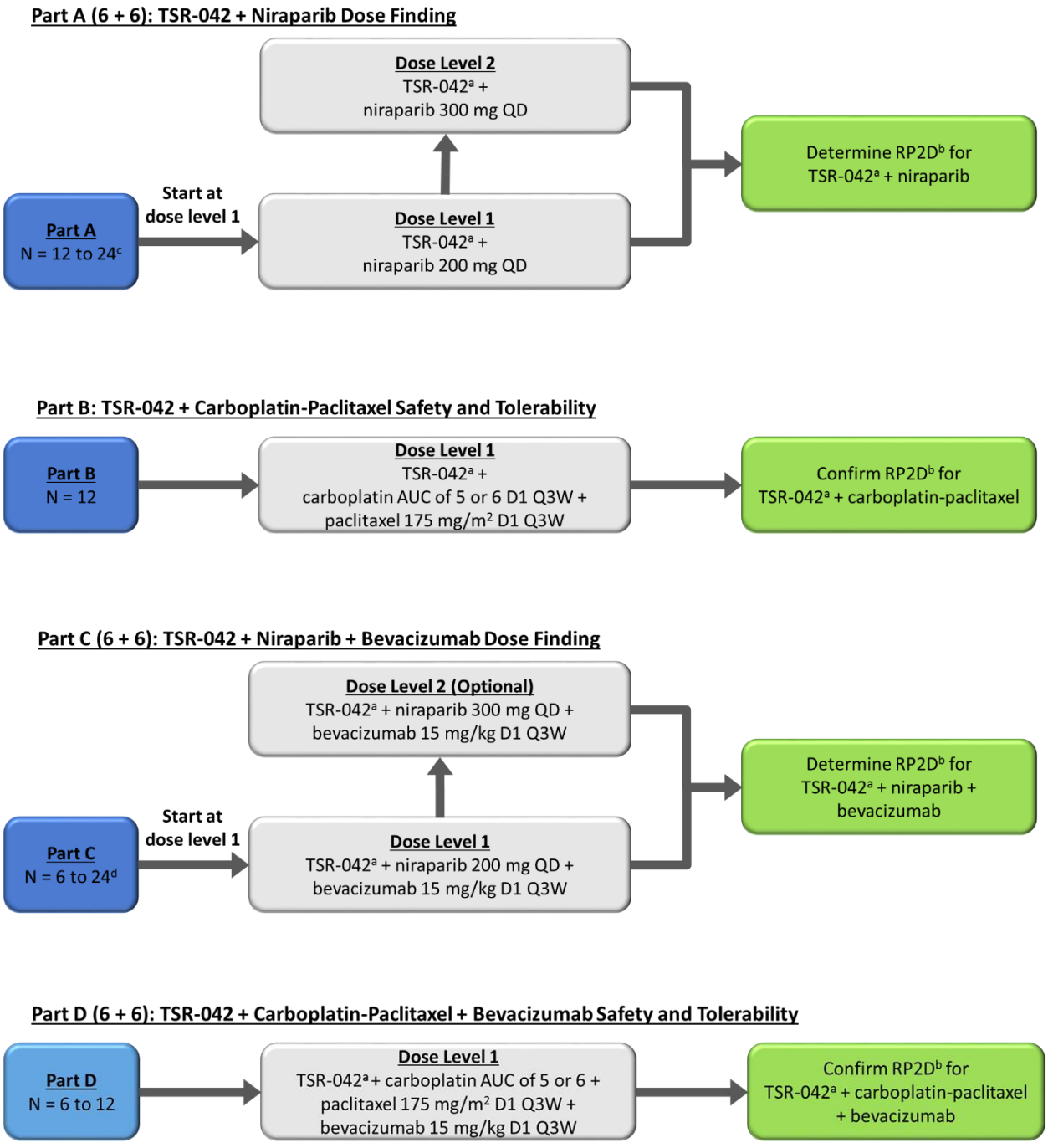
metastatic cancer for which carboplatin-paclitaxel is indicated. Part C will be a dose-finding evaluation conducted in all comers (6 to 24 patients) to determine the RP2D of niraparib and bevacizumab in combination with TSR-042. Part D will evaluate the safety and tolerability of TSR-042, carboplatin-paclitaxel and bevacizumab combination treatment in 6 to 12 patients, in patients in whom carboplatin-paclitaxel and bevacizumab combination treatment is considered a reasonable therapy. Part E will evaluate the safety and tolerability of TSR-042 and carboplatin-pemetrexed combination treatment as first-line treatment in 6 to 12 patients with advanced or metastatic non-squamous NSCLC. Part F will evaluate the safety and tolerability of TSR-042, TSR-022, and carboplatin-pemetrexed combination treatment as first-line treatment in 6 to 24 patients with advanced or metastatic non-squamous NSCLC. Part G will evaluate the safety and tolerability of TSR-042 and carboplatin–nab-paclitaxel combination treatment as first-line treatment in 6 to 12 patients with advanced or metastatic NSCLC. Part H will evaluate the safety and tolerability of TSR-042, TSR-022, and carboplatin–nab-paclitaxel combination treatment as first-line treatment in 6 to 24 patients with advanced or metastatic NSCLC. Part I will evaluate the safety and tolerability of TSR-042, TSR-022, and carboplatin-paclitaxel combination treatment as first-line treatment in 6 to 24 patients with advanced or metastatic NSCLC.

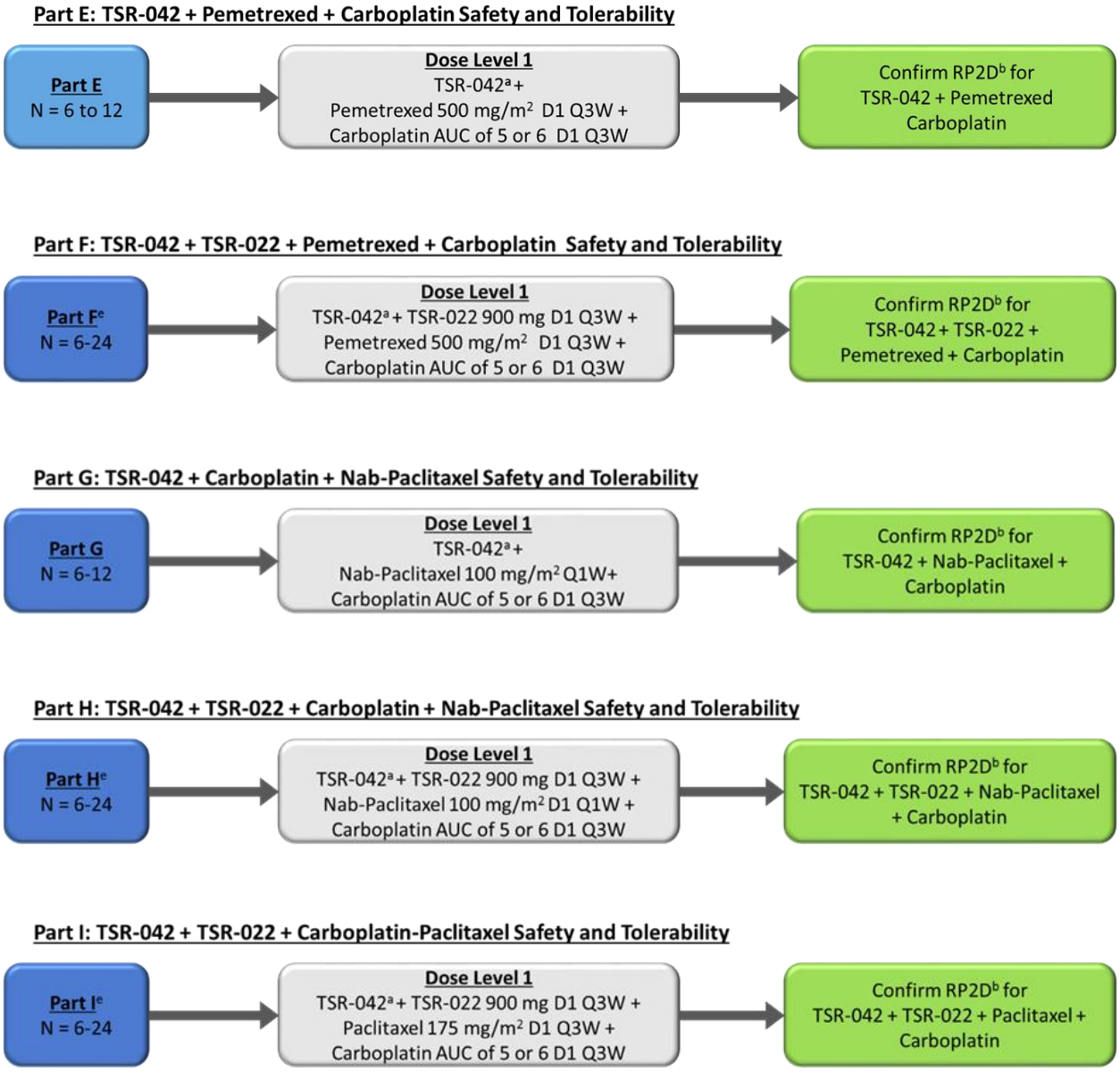
Enrollment of patients into Parts A, B, D, E, G, and I will occur concurrently. Part C will be initiated after dose level 1 (niraparib 200 mg) in Part A is determined to be safe. Part F will be initiated after TSR-042 and carboplatin-pemetrexed combination treatment in Part E is determined to be safe. Part H will be initiated after TSR-042 and carboplatin–nab-paclitaxel combination treatment in Part G is determined to be safe.

6.1.1. Overview

The study design is provided in Figure 1.

Figure 1: Study Design





Abbreviations: AE = adverse event; AUC = area under the plasma or serum concentration-time curve; D1 = Day 1; D21 = Day 21; DLT = dose-limiting toxicity; PK = pharmacokinetics; Q1W = every week; Q3W = every 3 weeks; Q6W = every 6 weeks; RP2D = recommended Phase 2 dose.

[a] In addition to receiving niraparib (Part A), carboplatin-paclitaxel (Part B), niraparib and bevacizumab (Part C), carboplatin-paclitaxel and bevacizumab (Part D), carboplatin-pemetrexed (Part E), carboplatin-pemetrexed and TSR-022 (Part F), carboplatin–nab-paclitaxel (Part G), TSR-022 and carboplatin–nab-paclitaxel (Part H), and TSR-022 and carboplatin-paclitaxel (Part I) at the specified regimen, all patients will be administered TSR-042 at 500 mg on Day 1 of every cycle (Q3W) for 4 cycles. Beginning on Day 1 of Cycle 5, TSR-042 will be administered to patients in Parts A, B, C, and D at 1,000 mg on Day 1 of every other cycle (Q6W) until the patient discontinues study treatment. Patients in Parts E, F, G, H, and I will continue to receive 500 mg on Day 1 of every cycle (Q3W) throughout the study.

[b] The RP2D for TSR-042 and niraparib combination treatment (Part A); TSR-042 and carboplatin-paclitaxel combination treatment (Part B); TSR-042, niraparib, and bevacizumab combination treatment (Part C); TSR-042, carboplatin-paclitaxel, and bevacizumab combination treatment (Part D); TSR-042 and carboplatin-pemetrexed

(Part E); TSR-042, carboplatin-pemetrexed, and TSR-022 (Part F); TSR-042 and carboplatin–nab-paclitaxel (Part G); TSR-042, TSR-022, and carboplatin–nab-paclitaxel (Part H); and TSR-042, TSR-022, and carboplatin-paclitaxel (Part I) will be determined or confirmed based on an evaluation of multiple endpoints, which may include the DLT rate in first and subsequent cycles of combination treatment, the rate of dose modifications for non-DLT AEs, the ability to manage toxicities, PK, niraparib dose intensity, and signs of clinical efficacy.

[c] 12 to 24 patients will be enrolled in Part A to determine the RP2D for TSR-042 and niraparib combination treatment.

[d] Initially, dose level 1 in Part C will enroll 6 to 12 patients to determine the RP2D for TSR-042, niraparib, and bevacizumab combination treatment. Dose level 2 is optional.

[e] 900 mg of TSR-022 is the highest dose tested in dose escalation in combination with TSR-042 that provides maximal pharmacodynamic effect; this dose may be lowered to dose level -1 (300 mg) if needed. Based on available safety information, the Sponsor may decide to test additional dose levels.

6.1.2. General Study Conduct

6.1.2.1. Part A: Dose Finding for TSR-042 and Niraparib Combination Treatment

Determination of the RP2D for TSR-042 and niraparib combination treatment will be conducted using the dose levels described in Table 2.

Table 2: Dose Regimen for TSR-042 and Niraparib Combination Treatment

Dose Level	Niraparib Dose	TSR-042 Dose
1	200 mg administered on Days 1 to 21 repeated Q3W	500 mg on Day 1 of every cycle (Q3W) for 4 cycles, followed by 1,000 mg on Day 1 of every other cycle (Q6W) beginning on Day 1/Cycle 5
2	300 mg administered on Days 1 to 21 repeated Q3W	

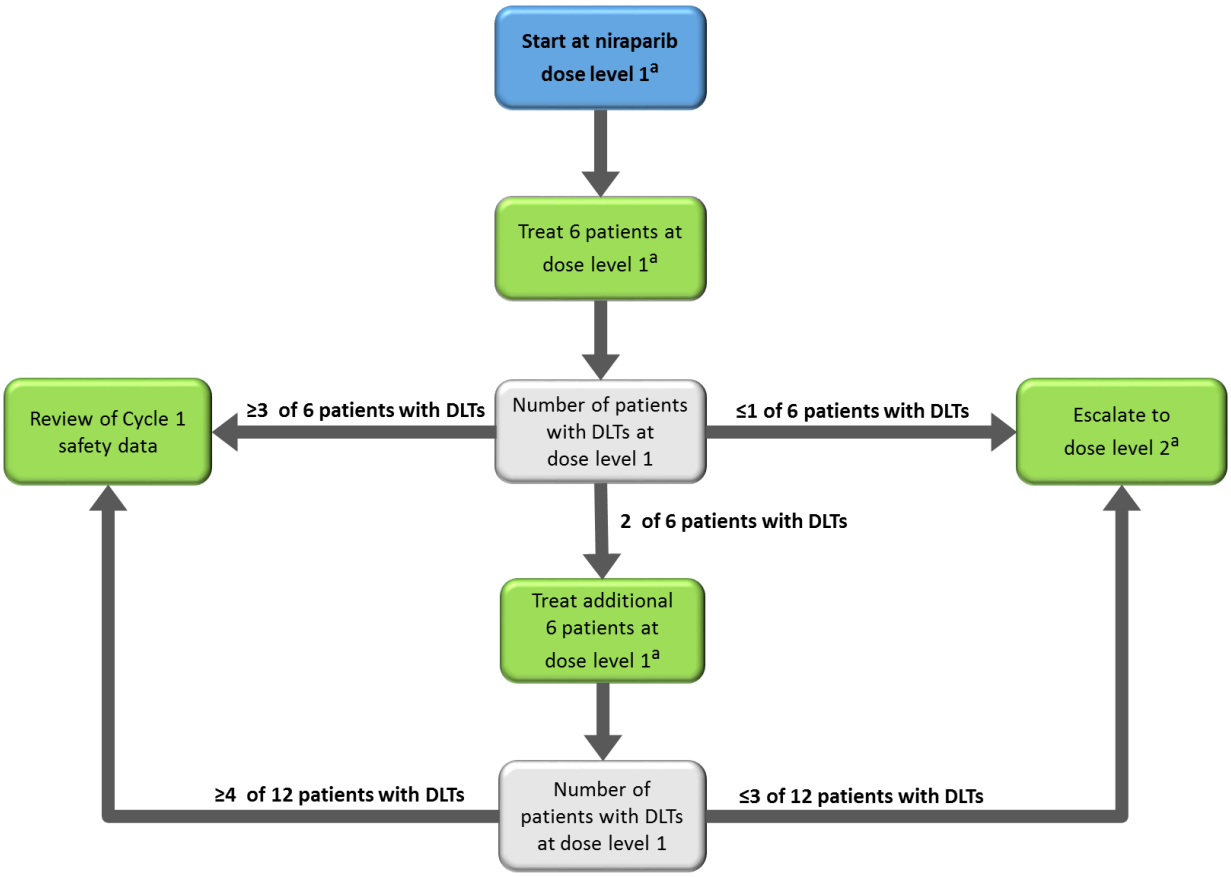
Abbreviations: Q3W = every 3 weeks; Q6W = every 6 weeks.

At dose level 1, a cohort of 6 patients will be enrolled initially. After all patients in dose level 1 who are evaluable for safety have completed Cycle 1 of combination treatment, if ≤1 patient experiences a DLT (see DLT definition in Section 6.1.2.3), dose level 1 will be considered safe. If 2 of 6 patients experience DLTs, 6 additional patients will be enrolled at dose level 1. If 12 patients are enrolled at dose level 1 and ≤3 of 12 patients experience DLTs, dose level 1 will be considered safe. The combination therapy will be considered unsafe if ≥3 of 6 or ≥4 of 12 patients experience DLTs during Cycle 1 (see Part A dose-finding scheme below). However, when determining the RP2D, the Sponsor will review and consider safety data from all patients treated with the combination therapy. Note: Part A has been completed as of Amendment 2.

Once dose level 1 (200 mg) is determined to be safe, the decision to open the next higher dose level (dose level 2) will be made based on evaluation of safety data from dose level 1. Dose level 2 (300 mg) will be opened only if less than one-third of evaluable patients (i.e., ≤1 of 6 patients or ≤3 of 12 patients) at dose level 1 experience a DLT during Cycle 1. Patients at dose level 2 will be enrolled using the same 6 + 6 scheme used at dose level 1. For patients in Part A, the dose of niraparib may be increased after Cycle 2 to a higher dose level that has been found to be safe during the dose-escalation phase following discussion with the Sponsor. No further dose escalation will be evaluated if dose level 2 is reached.

The Part A dose-finding scheme is summarized in Figure 2.

Figure 2: Part A Dose-Finding Scheme for TSR-042 and Niraparib Combination Treatment



Abbreviations: DLT = dose-limiting toxicity; Q3W = every 3 weeks; Q6W = every 6 weeks.

[a] Niraparib will be administered at the specified dose level as described in Table 2. In addition to receiving niraparib at the specified regimen, all patients will be administered TSR-042 at 500 mg on Day 1 of every cycle (Q3W) for 4 cycles. Beginning on Day 1 of Cycle 5, TSR-042 will be administered at 1,000 mg on Day 1 of every other cycle (Q6W).

Recommended Phase 2 Dose for TSR-042 and Niraparib Combination Treatment

The RP2D for TSR-042 and niraparib combination treatment will be a dose with DLTs observed in less than one-third of evaluable patients (i.e., ≤1 of 6 patients or ≤3 of 12 patients) during Cycle 1 of combination treatment and will be determined following discussion and agreement between the Investigators and Sponsor based on evaluation of multiple endpoints, which may include the DLT rate in first and subsequent cycles of combination treatment, the rate of dose modifications for non-DLT AEs, the ability to manage toxicities, PK, niraparib dose intensity, and signs of clinical efficacy. The goal will be to identify the dose and regimen of niraparib with the greatest dose intensity that can be safely combined with the recommended dose and regimen of TSR-042.

Duration of Study Treatment

Patients enrolled in Part A may continue TSR-042 and niraparib combination treatment for up to 2 years or until disease progression, unacceptable toxicity, patient withdrawal, Investigator's

decision, or death. Patients who have not progressed at 2 years will be given the option to continue on TSR-042 and niraparib combination treatment beyond 2 years if they are tolerating and benefiting from treatment and after consultation with the Sponsor. Patients with confirmed PD may continue study treatment at the Investigator's discretion 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.

6.1.2.2. Part B: Safety and Tolerability Evaluation for TSR-042 and Carboplatin-Paclitaxel Combination Treatment

Confirmation of the RP2D for TSR-042 and carboplatin-paclitaxel combination treatment will be conducted using the dose level described in Table 3.

Table 3: Dose Regimen for TSR-042 and Carboplatin-Paclitaxel Combination Treatment

Dose Level	Carboplatin-Paclitaxel Dose	TSR-042 Dose
1	Carboplatin[a] AUC of 5 or 6 on Day 1 Q3W and paclitaxel 175 mg/m^2 on Day 1 Q3W administered for 4 to 6 cycles as clinically indicated	500 mg on Day 1 of every cycle Q3W for 4 cycles, followed by 1,000 mg on Day 1 of every other cycle (Q6W) beginning on Day 1/Cycle 5

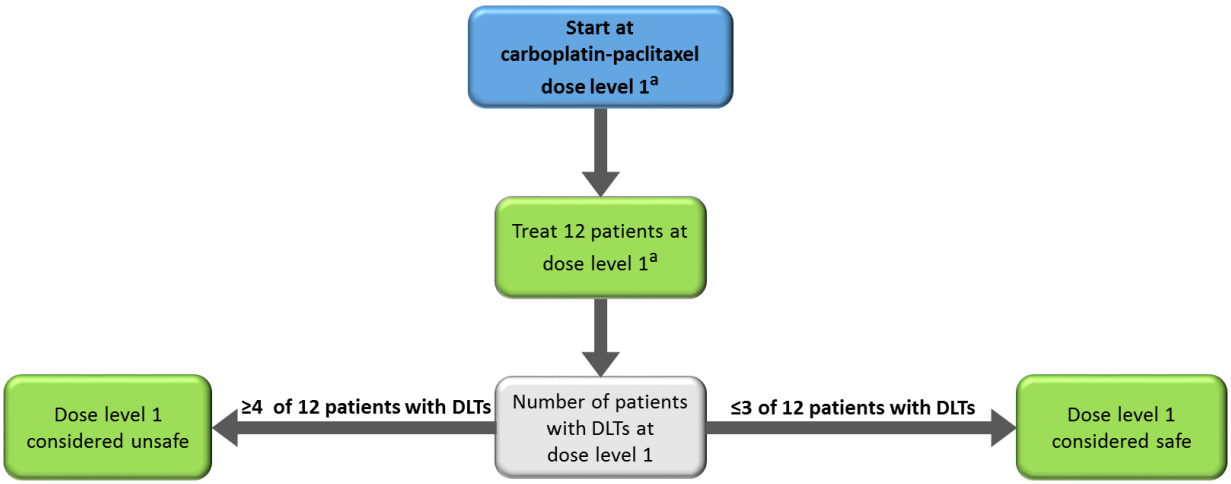
Abbreviations: AUC = area under the plasma or serum concentration-time curve; Q3W = every 3 weeks; Q6W = every 6 weeks.

[a] The carboplatin dose will be determined by the Investigator, taking into consideration the patient's prior anticancer therapies and pre-existing medical conditions.

A cohort of approximately 12 patients will be enrolled at dose level 1 in Part B. After all patients who are evaluable for safety have completed Cycle 1 of combination treatment, if ≤3 patients experience a DLT (see DLT definition in Section 6.1.2.3), TSR-042 and carboplatin-paclitaxel combination treatment will be considered safe. The combination therapy will be considered unsafe if ≥4 of 12 patients experience DLTs during Cycle 1 (see Part B dose confirmation scheme below). However, when determining the RP2D, the Sponsor will review and consider safety data from all patients treated with the combination therapy. Note: Part B has been completed as of Amendment 2.

The Part B dose confirmation scheme is summarized in Figure 3.

Figure 3: Part B Dose Confirmation Scheme for TSR-042 and Carboplatin-Paclitaxel Combination Treatment



Abbreviations: DLT = dose-limiting toxicity; Q3W = every 3 weeks; Q6W = every 6 weeks.
[a] Carboplatin-paclitaxel will be administered at the specified dose level as described in Table 3. In addition to receiving carboplatin-paclitaxel at the specified regimen, patients will be administered TSR-042 at 500 mg on Day of every cycle (Q3W) for 4 cycles. Beginning on Day 1 of Cycle 5, TSR-042 will be administered at 1,000 mg on Day 1 of every other cycle (Q6W).

Recommended Phase 2 Dose for Carboplatin-Paclitaxel and TSR-042

The RP2D for TSR-042 and carboplatin-paclitaxel combination treatment will be confirmed following discussion and agreement between the Investigators and Sponsor based on evaluation of multiple endpoints, which may include the DLT rate in first and subsequent cycles of combination treatment, the rate of dose modifications for non-DLT AEs, the ability to manage toxicities, PK, and signs of clinical efficacy.

Duration of Study Treatment

Patients enrolled in Part B may continue TSR-042 and carboplatin-paclitaxel combination treatment for 4 to 6 cycles, as indicated, after which patients may continue TSR-042 monotherapy for up to 2 years or until disease progression, unacceptable toxicity, patient withdrawal, Investigator's decision, or death. Continued treatment with TSR-042 beyond 2 years may be considered following discussion between the Sponsor and Investigator.

6.1.2.3. Part C: Dose Finding for TSR-042, Niraparib, and Bevacizumab Combination Treatment

Determination of the RP2D for TSR-042, niraparib, and bevacizumab combination treatment will be conducted using the dose levels described in Table 4.

Table 4: Dose Regimen for TSR-042, Niraparib and Bevacizumab Combination Treatment

Dose Level	Niraparib Dose	TSR-042 Dose	Bevacizumab Dose
1	200 mg administered on Days 1 to 21 repeated Q3W	500 mg on Day 1 of every cycle (Q3W) for 4 cycles, followed by 1,000 mg on Day 1 of every other cycle (Q6W) beginning on Day 1/Cycle 5	15 mg/kg on Day 1 of every 21-day cycle Q3W for up to 15 months
2 (optional)	300 mg administered on Days 1 to 21 repeated Q3W		

Abbreviations: Q3W = every 3 weeks; Q6W = every 6 weeks.

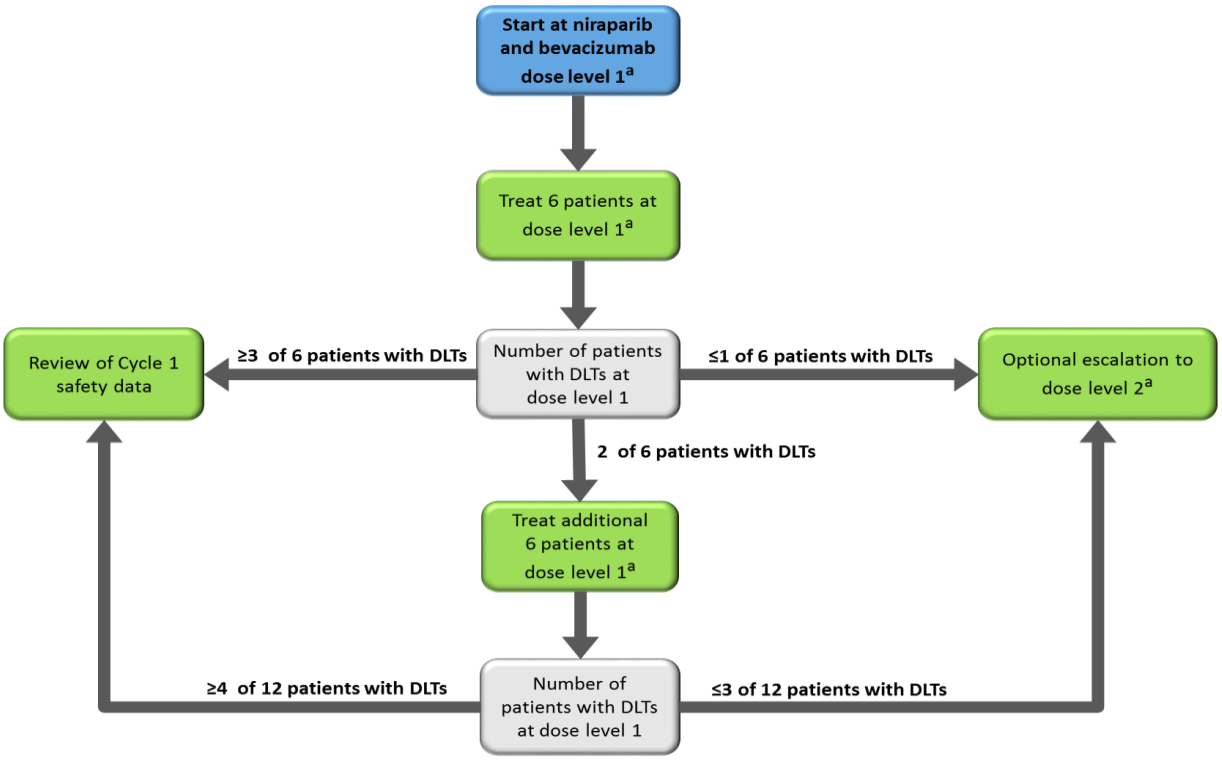
At dose level 1 (200 mg), a cohort of 6 patients will be enrolled initially. After all patients in dose level 1 who are evaluable for safety have completed Cycle 1 of combination treatment, if ≤1 patient experiences a DLT (see DLT Assessment below), dose level 1 will be considered safe. If 2 of 6 patients experience DLTs, 6 additional patients will be enrolled at dose level 1. If 12 patients are enrolled at dose level 1 and ≤3 of 12 patients experience DLTs, dose level 1 will be considered safe. The combination therapy will be considered unsafe if ≥3 of 6 or ≥4 of 12 patients experience DLTs during Cycle 1 (see Part C dose-finding scheme below). However, when determining the RP2D, the Sponsor will review and consider safety data from all patients treated with the combination therapy.

For patients in Part C, the dose of niraparib may be increased after Cycle 2 to a higher dose level that has been found to be safe during the dose-escalation phase following discussion with the Sponsor. No further dose escalation will be evaluated if dose level 2 is reached.

The decision to open dose level 2 (300 mg) will be made by the Sponsor based on evaluation of safety data from dose level 1. Dose level 2 will be optional and opened only if less than one-third of evaluable patients (i.e., ≤1 of 6 patients or ≤3 of 12 patients) at dose level 1 experience a DLT during Cycle 1.

The Part C dose-finding scheme is summarized in Figure 4.

Figure 4: Part C Dose-Finding Scheme for TSR-042, Niraparib, and Bevacizumab Combination Treatment



Abbreviations: DLT = dose-limiting toxicity; Q3W = every 3 weeks; Q6W = every 6 weeks.

[a] Niraparib and bevacizumab will be administered at the specified dose level as described in Table 4 (Dose Regimen for TSR-042, Niraparib and Bevacizumab Combination Treatment). In addition to receiving niraparib at the specified regimen, all patients will be administered TSR-042 at 500 mg on Day 1 of every cycle (Q3W) for 4 cycles. Beginning on Day 1 of Cycle 5, TSR-042 will be administered at 1,000 mg on Day 1 of every other cycle (Q6W). Bevacizumab 15 mg/kg will be administered on Day 1 of every 21-day cycle Q3W for up to 15 months.

Recommended Phase 2 Dose for TSR-042, Niraparib, and Bevacizumab Combination Treatment

The RP2D for TSR-042, niraparib, and bevacizumab combination treatment will be a dose with DLTs observed in less than one-third of evaluable patients (i.e., ≤1 of 6 patients or ≤3 of 12 patients) during Cycle 1 of combination treatment and will be determined following discussion and agreement between the Investigators and Sponsor based on evaluation of multiple endpoints, which may include the DLT rate in first and subsequent cycles of combination treatment, the rate of dose modifications for non-DLT AEs, the ability to manage toxicities, PK, niraparib dose intensity, and signs of clinical efficacy. The goal will be to identify the dose and regimen of niraparib with the greatest dose intensity that can be safely combined with the recommended dose and regimens of TSR-042 and bevacizumab.

Duration of Study Treatment

Patients enrolled in Part C may continue TSR-042, niraparib, bevacizumab combination treatment for up to 15 months followed by TSR-042 and niraparib combination treatment for the remainder of 2 years or until disease progression, unacceptable toxicity, patient withdrawal,

Investigator's decision, or death. Patients who have not progressed at 2 years will be given the option to continue on TSR-042 and niraparib combination treatment beyond 2 years if they are tolerating and benefiting from treatment and after consultation with the Sponsor. Patients with confirmed PD may continue study treatment at the Investigator's discretion 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.

6.1.2.4. Part D: Safety and Tolerability Evaluation for TSR-042, Carboplatin-Paclitaxel and Bevacizumab Combination Treatment

Confirmation of the RP2D for TSR-042, carboplatin-paclitaxel and bevacizumab combination treatment will be conducted using the dose level described in the table below:

Table 5: Dose Regimen for TSR-042 and Carboplatin-Paclitaxel Combination Treatment

Dose Level	Carboplatin-Paclitaxel Dose	TSR-042 Dose	Bevacizumab Dose
1	Carboplatin[a] AUC of 5 or 6 on Day 1 Q3W and paclitaxel 175 mg/m^2 on Day 1 Q3W administered for 4 to 6 cycles as clinically indicated	500 mg on Day 1 of every cycle (Q3W) for 4 cycles, followed by 1,000 mg on Day 1 of every other cycle (Q6W) beginning on Day 1/Cycle 5	15 mg/kg on Day 1 of every 21-day cycle Q3W for up to 15 months

Abbreviations: AUC = area under the plasma or serum concentration-time curve; Q3W = every 3 weeks; Q6W = every 6 weeks.

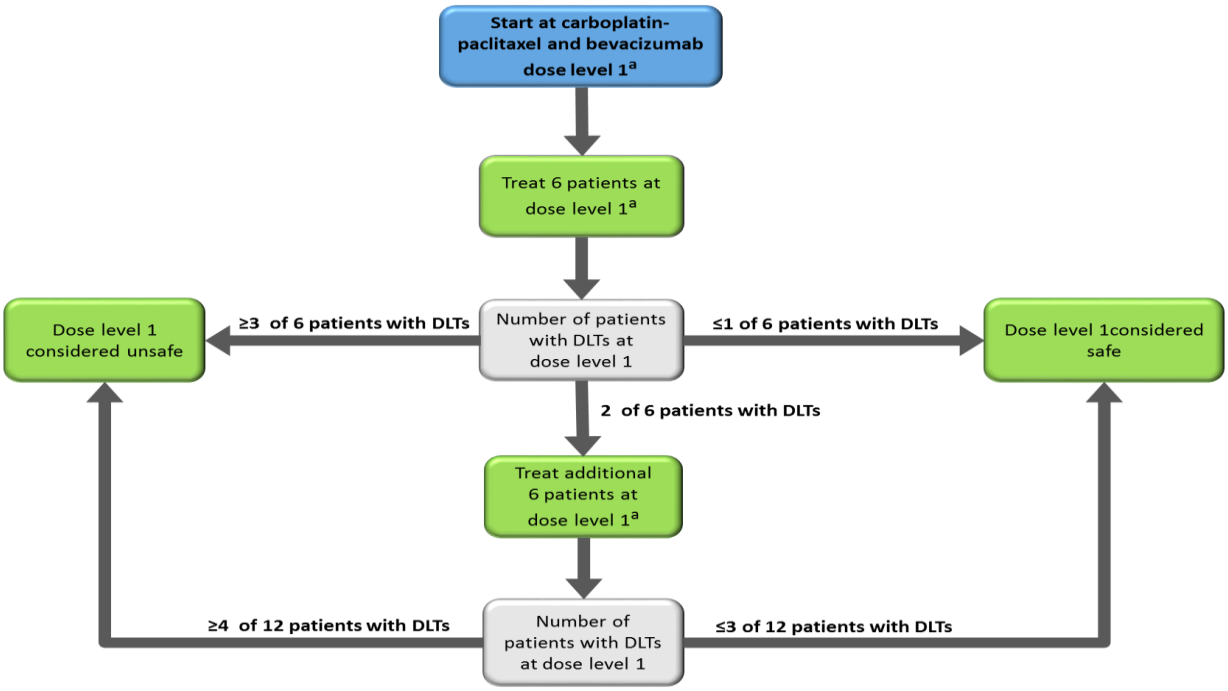
[a] The carboplatin dose will be determined by the Investigator, taking into consideration the patient's prior anticancer therapies and pre-existing medical conditions.

At dose level 1, a cohort of 6 patients will be enrolled initially. After all patients in dose level 1 who are evaluable for safety have completed Cycle 1 of combination treatment, if ≤1 patient experiences a DLT (see DLT Assessment below), dose level 1 will be considered safe. If 2 patients experience DLTs, 6 additional patients will be enrolled at dose level 1. If ≤3 of 12 patients experience DLTs at dose level 1, the combination will be considered safe. The combination therapy will be considered unsafe if ≥3 of 6 or ≥4 of 12 patients experience DLTs during Cycle 1 (see Part D dose confirmation scheme below). However, when determining the RP2D, the Sponsor will review and consider safety data from all patients treated with the combination therapy. Note: Part D has been completed as of Amendment 2.

The RP2D for TSR-042, carboplatin-paclitaxel and bevacizumab combination treatment will be confirmed following discussion and agreement between the Investigators and Sponsor based on evaluation of multiple endpoints, which may include the DLT rate in first and subsequent cycles of combination treatment, the rate of dose modifications for non-DLT AEs, the ability to manage toxicities, PK, and signs of clinical efficacy.

The Part D dose confirmation scheme is summarized in Figure 5.

Figure 5: Part D Dose Confirmation Scheme for TSR-042, Carboplatin-Paclitaxel and Bevacizumab Combination Treatment



Abbreviations: DLT = dose-limiting toxicity; Q3W = every 3 weeks; Q6W = every 6 weeks.

[a] Carboplatin-paclitaxel and bevacizumab will be administered at the specified dose level as described in Table 5 (Dose Regimen for TSR-042, Carboplatin-Paclitaxel and Bevacizumab Combination Treatment). In addition to receiving carboplatin-paclitaxel and bevacizumab the specified regimen, patients will be administered TSR-042 at 500 mg on Day 1 of every cycle (Q3W) for 4 cycles. Beginning on Day 1 of Cycle 5, TSR-042 will be administered at 1,000 mg on Day 1 of every other cycle (Q6W). Bevacizumab 15 mg/kg will be administered on Day 1 of every 21-day cycle (Q3W) for up to 15 months.

Recommended Phase 2 Dose for Carboplatin-Paclitaxel, TSR-042, and Bevacizumab

The RP2D for TSR-042, carboplatin-paclitaxel, and bevacizumab combination treatment will be confirmed following discussion and agreement between the Investigators and Sponsor based on evaluation of multiple endpoints, which may include the DLT rate in first and subsequent cycles of combination treatment, the rate of dose modifications for non-DLT AEs, the ability to manage toxicities, PK, and signs of clinical efficacy.

Duration of Study Treatment

Patients enrolled in Part D may continue TSR-042, carboplatin-paclitaxel, and bevacizumab combination treatment for 4 to 6 cycles, as indicated, after which, patients may continue bevacizumab for up to 15 months and TSR-042 for up to 2 years or until disease progression, unacceptable toxicity, patient withdrawal, Investigator's decision, or death. Continued treatment with TSR-042 beyond 2 years may be considered following discussion between the Sponsor and Investigator.

6.1.2.5. Part E: Safety and Tolerability for TSR-042 and Carboplatin-Pemetrexed Combination Treatment

Confirmation of the RP2D for TSR-042, pemetrexed, and carboplatin combination treatment will be conducted using the dose levels described in Table 6.

Table 6: Dose Regimen for TSR-042 and Carboplatin-Pemetrexed Combination Treatment

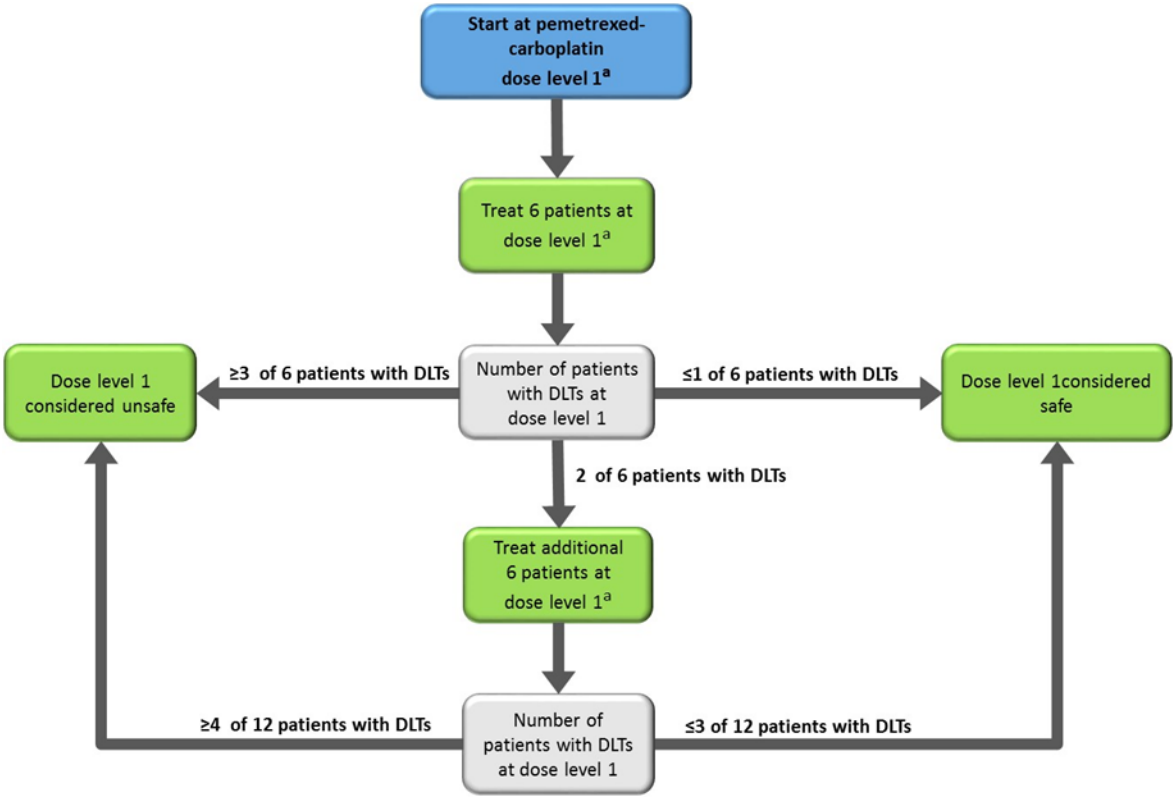
Dose Level	TSR-042 Dose	Pemetrexed Dose	Carboplatin Dose[a]
1	500 mg on Day 1 of every cycle Q3W	500 mg/m^2 Day 1 Q3W (with vitamin supplementation)	AUC of 5 or 6 on Day 1 Q3W administered for 4 to 6 cycles as clinically indicated

Abbreviations: AUC = area under the plasma or serum concentration-time curve; Q3W = every 3 weeks.
[a] The carboplatin dose will be determined by the Investigator, taking into consideration the patient's prior anticancer therapies and pre-existing medical conditions.

At dose level 1, a cohort of 6 patients will be enrolled initially. After all patients in dose level 1 who are evaluable for safety have completed Cycle 1 of combination treatment, if ≤ 1 patient experiences a DLT (see DLT Assessment below), dose level 1 will be considered safe. If 2 of 6 patients experience DLTs, 6 additional patients will be enrolled at dose level 1. If ≤ 3 of 12 patients experience DLTs, the combination will be considered safe. The combination therapy will be considered unsafe if ≥3 of 6 or ≥4 of 12 patients experience DLTs during Cycle 1 (see Part E dose confirmation scheme below). However, when determining the RP2D, the Sponsor will review and consider safety data from all patients treated with the combination therapy.

The Part E dose confirmation scheme is summarized in Figure 6.

Figure 6: Part E Dose Confirmation Scheme for TSR-042 and Carboplatin-Pemetrexed Combination Treatment



Abbreviations: DLT = dose-limiting toxicity; Q3W = every 3 weeks.

[a] Carboplatin-pemetrexed will be administered at the specified dose level as described in Table 6. In addition to receiving carboplatin-pemetrexed at the specified regimen, patients will be administered TSR-042 at 500 mg on Day 1 of every cycle Q3W.

Recommended Phase 2 Dose for TSR-042 and Carboplatin-Pemetrexed

The RP2D for TSR-042 and carboplatin-pemetrexed combination treatment will be confirmed following discussion and agreement between the Investigators and Sponsor based on evaluation of multiple endpoints, which may include the DLT rate in first and subsequent cycles of combination treatment, the rate of dose modifications for non-DLT AEs, the ability to manage toxicities, PK, and signs of clinical efficacy.

Duration of Study Treatment

Patients enrolled in Part E may continue TSR-042 and carboplatin-pemetrexed combination treatment for 4 to 6 cycles, as indicated, after which patients may continue TSR-042 and pemetrexed for up to 2 years or until disease progression, unacceptable toxicity, patient withdrawal, Investigator's decision, or death. Continued treatment with TSR-042 and pemetrexed beyond 2 years may be considered following discussion between the Sponsor and Investigator.

6.1.2.6. Part F: Safety and Tolerability for TSR-042, TSR-022, and Carboplatin-Pemetrexed Combination Treatment

Part F will begin after combination therapy in Part E has been determined as safe. Confirmation of the RP2D for TSR-042, TSR-022, and carboplatin-pemetrexed combination treatment will be conducted using the dose levels described in Table 7.

Table 7: Dose Regimen for TSR-042, TSR-022, and Carboplatin-Pemetrexed Combination Treatment

Dose Level	TSR-042 Dose	TSR-022 Dose	Pemetrexed Dose	Carboplatin Dose[a]
1	500 mg on Day 1 of every cycle Q3W	900 mg on Day 1 Q3W[b]	500 mg/m^2 Day 1 Q3W (with vitamin supplementation)	AUC of 5 or 6 on Day 1 Q3W administered for 4 to 6 cycles as clinically indicated
-1	500 mg on Day 1 of every cycle Q3W	300 mg on Day 1 Q3W[b]	500 mg/m^2 Day 1 Q3W (with vitamin supplementation)	AUC of 5 or 6 on Day 1 Q3W administered for 4 to 6 cycles as clinically indicated

Abbreviations: AUC = area under the plasma or serum concentration-time curve; Q3W = every 3 weeks.

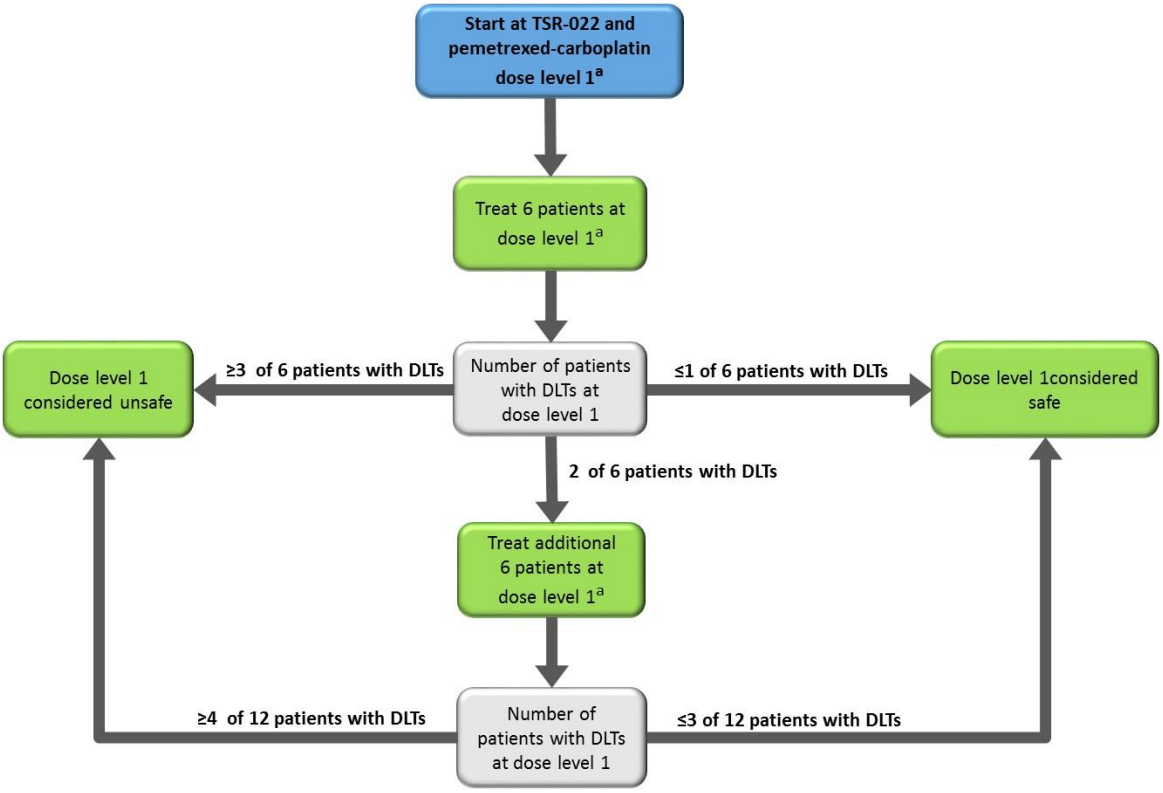
[a] The carboplatin dose will be determined by the Investigator, taking into consideration the patient's prior anticancer therapies and pre-existing medical conditions.

[b] 900 mg of TSR-022 is the highest dose tested in dose escalation in combination with TSR-042 that provides maximal pharmacodynamic effect; this dose may be lowered to dose level -1 if needed. Based on available safety information, the Sponsor may decide to test additional dose levels of TSR-022.

At dose level 1 (900 mg TSR-022), a cohort of 6 patients will be enrolled initially. After all patients in dose level 1 who are evaluable for safety have completed Cycle 1 of combination treatment, if ≤ 1 patient experiences a DLT (see DLT Assessment below), dose level 1 will be considered safe. If 2 of 6 patients experience DLTs, 6 additional patients will be enrolled at dose level 1. If ≤ 3 of 12 patients experience DLTs, dose level 1 will be considered safe. If ≥ 4 of 12 patients experience DLTs at dose level 1, dose level -1 will enroll 6 patients. After all patients in dose level -1 who are evaluable for safety have completed Cycle 1 of combination treatment, if ≤ 1 patient experiences a DLT, dose level -1 will be considered safe. If 2 of 6 patients experience DLTs, 6 additional patients will be enrolled at dose level -1. If ≤ 3 of 12 patients experience DLTs, dose level -1 will be considered safe. The combination therapy, dose level -1, will be considered unsafe if ≥3 of 6 or ≥4 of 12 patients experience DLTs during Cycle 1 (see Part F dose confirmation scheme below). However, when determining the RP2D, the Sponsor will review and consider safety data from all patients treated with the combination therapy.

The Part F dose confirmation scheme is summarized in Figure 7.

Figure 7: Part F Dose Confirmation Scheme for TSR-042, TSR-022, and Carboplatin-Pemetrexed Combination Treatment



Abbreviations: DLT = dose-limiting toxicity; Q3W = every 3 weeks.
[a] Carboplatin-pemetrexed will be administered at the specified dose level as described in Table 7. In addition to receiving carboplatin-pemetrexed at the specified regimen, patients will be administered TSR-042 at 500 mg on Day 1 of every cycle Q3W and TSR-022 at 900 mg on Day 1 Q3W.
[b] Patients at dose level -1 will be enrolled using the same 6 + 6 scheme used at dose level 1.

Recommended Phase 2 Dose for TSR-042, TSR-022, and Carboplatin-Pemetrexed

The RP2D for TSR-042, TSR-022, and combination treatment will be confirmed following discussion and agreement between the Investigators and Sponsor based on evaluation of multiple endpoints, which may include the DLT rate in first and subsequent cycles of combination treatment, the rate of dose modifications for non-DLT AEs, the ability to manage toxicities, PK, and signs of clinical efficacy.

Duration of Study Treatment

Patients enrolled in Part F may continue TSR-042, TSR-022, and carboplatin-pemetrexed combination treatment for 4 to 6 cycles, as indicated, after which, patients may continue TSR-042,TSR-022, and pemetrexed combination therapy for up to 2 years or until disease progression, unacceptable toxicity, patient withdrawal, Investigator's decision, or death. Continued treatment with TSR-022, TSR-042, or pemetrexed beyond 2 years may be considered following discussion between the Sponsor and Investigator.

6.1.2.7. Part G: Safety and Tolerability for TSR-042 and Carboplatin–Nab-Paclitaxel Combination Treatment

Confirmation of the RP2D for TSR-042 and carboplatin–nab-paclitaxel combination treatment will be conducted using the dose level described in Table 8.

Table 8: Dose Regimen for TSR-042 and Carboplatin–Nab-Paclitaxel Combination Treatment

Dose Level	TSR-042 Dose	Nab-Paclitaxel Dose	Carboplatin Dose[a]
1	500 mg on Day 1 of every cycle Q3W	100 mg/m^2 on Days 1, 8, and 15 (Q1W) of every 3-week cycle, administered for 4 to 6 cycles as clinically indicated	AUC of 5 or 6 on Day 1 Q3W administered for 4 to 6 cycles as clinically indicated

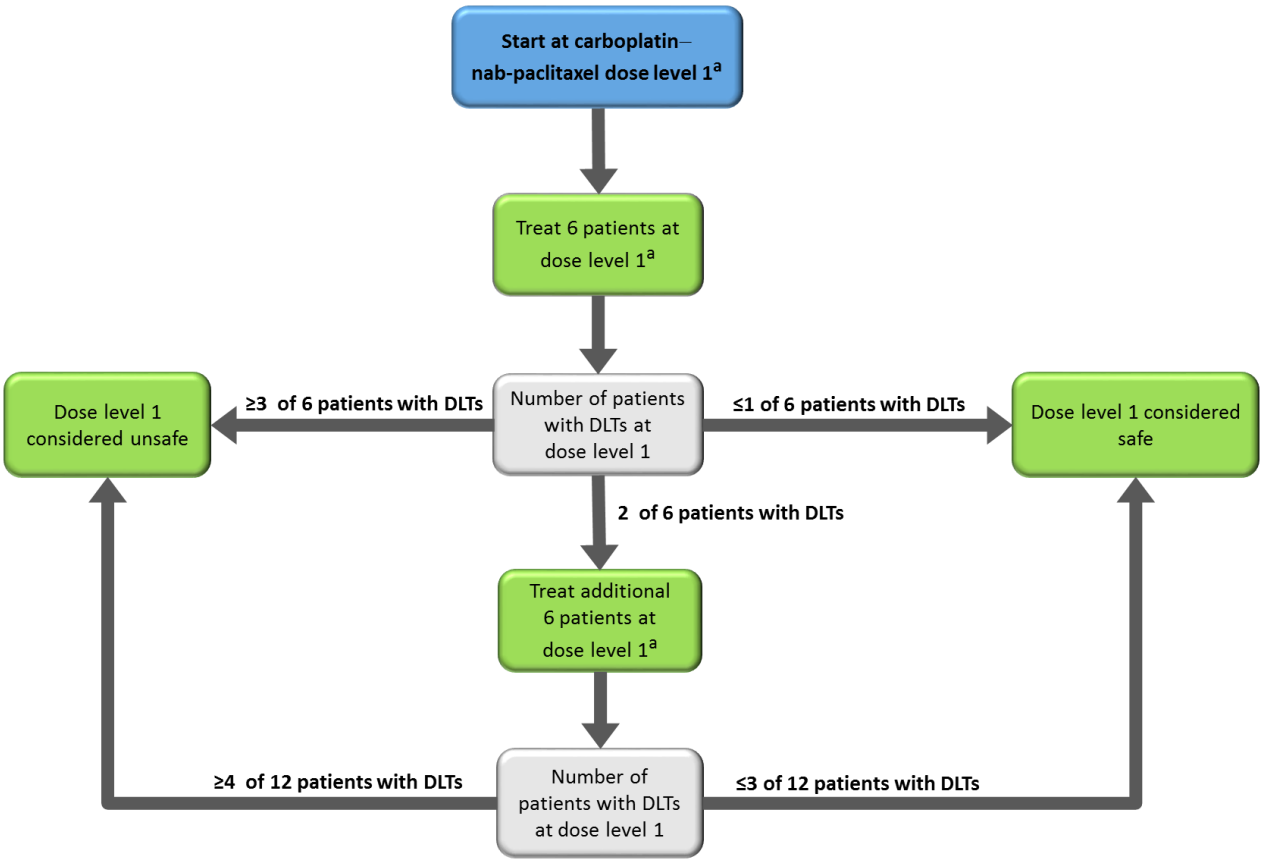
Abbreviations: AUC = area under the plasma or serum concentration-time curve; Q1W = every week; Q3W = every 3 weeks.

[a] The carboplatin dose will be determined by the Investigator, taking into consideration the patient's prior anticancer therapies and pre-existing medical conditions.

At dose level 1, a cohort of 6 patients will be enrolled initially. After all patients in dose level 1 who are evaluable for safety have completed Cycle 1 of combination treatment, if ≤ 1 patient experiences a DLT (see DLT Assessment below), dose level 1 will be considered safe. If 2 of 6 patients experience DLTs, 6 additional patients will be enrolled at dose level 1. If ≤ 3 of 12 patients experience DLTs, dose level 1 will be considered safe. The combination therapy will be considered unsafe if ≥3 of 6 or ≥4 of 12 patients experience DLTs during Cycle 1 (see Part G dose confirmation scheme below). However, when determining the RP2D, the Sponsor will review and consider safety data from all patients treated with the combination therapy.

The Part G dose confirmation scheme is summarized in Figure 8.

Figure 8: Part G Dose Confirmation Scheme for TSR-042 and Carboplatin–Nab-Paclitaxel Combination Treatment



Abbreviations: DLT = dose-limiting toxicity.

[a] Carboplatin–nab-paclitaxel will be administered at the specified dose level as described in Table 8. In addition to receiving carboplatin–nab-paclitaxel at the specified regimen, patients will be administered TSR-042 at 500 mg on Day 1 of every cycle (Q3W).

Recommended Phase 2 Dose for TSR-042 and Carboplatin–Nab-paclitaxel

The RP2D for TSR-042 and carboplatin–nab-paclitaxel combination treatment will be confirmed following discussion and agreement between the Investigators and Sponsor based on evaluation of multiple endpoints, which may include the DLT rate in first and subsequent cycles of combination treatment, the rate of dose modifications for non-DLT AEs, the ability to manage toxicities, PK, and signs of clinical efficacy.

Duration of Study Treatment

Patients enrolled in Part G may continue TSR-042 and carboplatin–nab-paclitaxel combination treatment for 4 to 6 cycles, as indicated, after which patients may continue TSR-042 monotherapy for up to 2 years or until disease progression, unacceptable toxicity, patient withdrawal, Investigator's decision, or death. Continued treatment with TSR-042 beyond 2 years may be considered following discussion between the Sponsor and the Investigator.

6.1.2.8. Part H: Safety and Tolerability for TSR-042, TSR-022, and Carboplatin–Nab-Paclitaxel Combination Treatment

Part H will begin after combination therapy in Part G has been determined as safe. Confirmation of the RP2D for TSR-042, TSR-022, and carboplatin–nab-paclitaxel combination treatment will be conducted using the dose levels described in Table 9.

Table 9: Dose Regimen for TSR-042, TSR-022, and Carboplatin–Nab-Paclitaxel Combination Treatment

Dose Level	TSR-042 Dose	TSR-022 Dose	Nab-Paclitaxel Dose	Carboplatin Dose[a]
1	500 mg on Day 1 of every cycle Q3W	900 mg on Day 1 Q3W[b]	100 mg/m^2 on Days 1, 8, and 15 (Q1W) of every 3-week cycle, administered for 4 to 6 cycles as clinically indicated	AUC of 5 or 6 on Day 1 Q3W administered for 4 to 6 cycles as clinically indicated
-1	500 mg on Day 1 of every cycle Q3W	300 mg on Day 1 Q3W[b]	100 mg/m^2 on Days 1, 8, and 15 (Q1W) of every 3-week cycle, administered for 4 to 6 cycles as clinically indicated	AUC of 5 or 6 on Day 1 Q3W administered for 4 to 6 cycles as clinically indicated

Abbreviations: AUC = area under the plasma or serum concentration-time curve; Q1W = every week; Q3W = every 3 weeks.

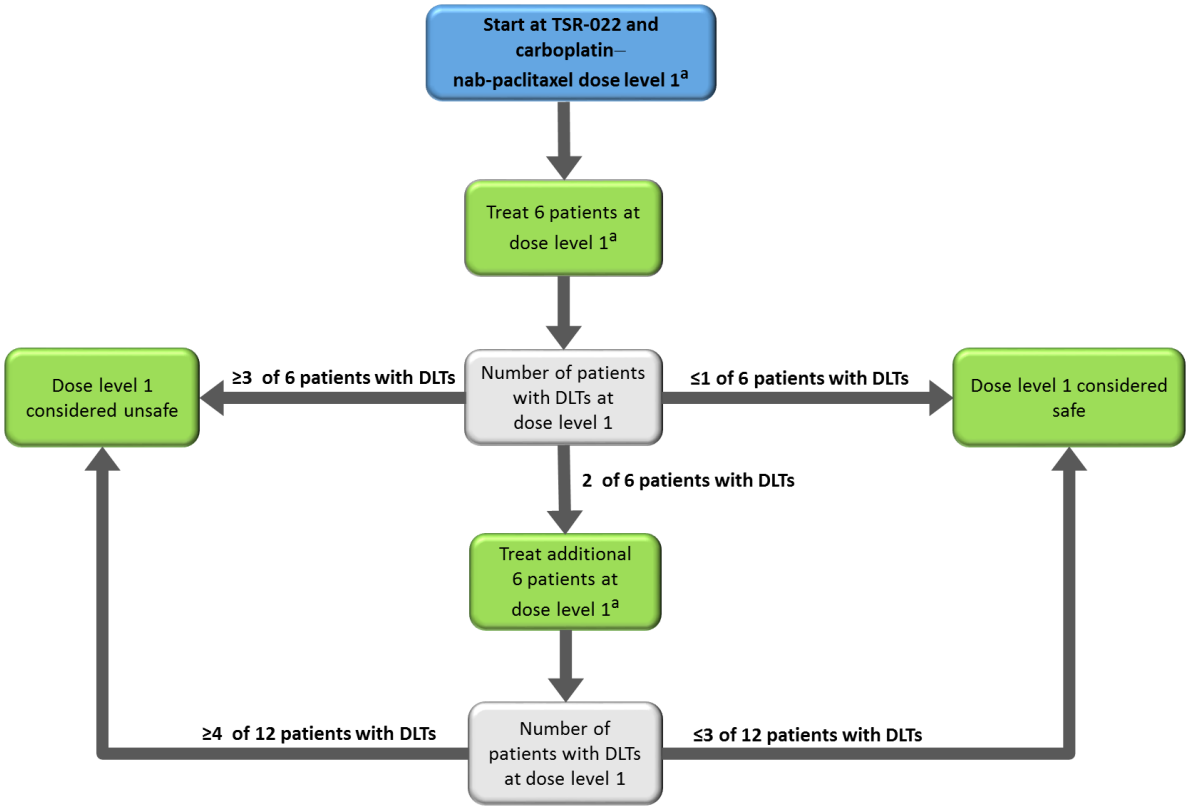
[a] The carboplatin dose will be determined by the Investigator, taking into consideration the patient's prior anticancer therapies and pre-existing medical conditions.

[b] 900 mg of TSR-022 is the highest dose tested in dose escalation in combination with TSR-042 that provides maximal pharmacodynamic effect; this dose may be lowered to dose level -1 if needed. Based on available safety information, the Sponsor may decide to test additional dose levels of TSR-022.

At dose level 1, a cohort of 6 patients will be enrolled initially. After all patients in dose level 1 who are evaluable for safety have completed Cycle 1 of combination treatment, if ≤ 1 patient experiences a DLT (see DLT Assessment below), dose level 1 will be considered safe. If 2 of 6 patients experience DLTs, 6 additional patients will be enrolled at dose level 1. If ≤ 3 of 12 patients experience DLTs, dose level 1 will be considered safe. If ≥ 4 of 12 patients experience DLTs at dose level 1, dose level -1 will enroll 6 patients. After all patients in dose level -1 who are evaluable for safety have completed Cycle 1 of combination treatment, if ≤ 1 patient experiences a DLT, dose level -1 will be considered safe. If 2 of 6 patients experience DLTs, 6 additional patients will be enrolled at dose level -1. If ≤ 3 of 12 patients experience DLTs, dose level -1 will be considered safe. The combination therapy, dose level -1, will be considered unsafe if ≥3 of 6 or ≥4 of 12 patients experience DLTs during Cycle 1 (see Part H dose confirmation scheme below). However, when determining the RP2D, the Sponsor will review and consider safety data from all patients treated with the combination therapy.

The Part H dose confirmation scheme is summarized in Figure 9.

Figure 9: Part H Dose Confirmation Scheme for TSR-042, TSR-022, and Carboplatin–Nab-Paclitaxel Combination Treatment



Abbreviations: DLT = dose-limiting toxicity.

[a] Carboplatin–nab-paclitaxel will be administered at the specified dose level as described in Table 9. In addition to receiving carboplatin–nab-paclitaxel at the specified regimen, patients will be administered TSR-042 at 500 mg on Day 1 of every cycle Q3W and TSR-022 at 900 mg on Day 1 Q3W.

[b] Patients at dose level -1 will be enrolled using the same 6 + 6 scheme used at dose level 1.

Recommended Phase 2 Dose for TSR-042, TSR-022, and Carboplatin–Nab-Paclitaxel

The RP2D for TSR-042, TSR-022, and carboplatin–nab-paclitaxel combination treatment will be confirmed following discussion and agreement between the Investigators and Sponsor based on evaluation of multiple endpoints, which may include the DLT rate in first and subsequent cycles of combination treatment, the rate of dose modifications for non-DLT AEs, the ability to manage toxicities, PK, and signs of clinical efficacy.

Duration of Study Treatment

Patients enrolled in Part H may continue TSR-042, TSR-022, and carboplatin–nab-paclitaxel combination treatment for 4 to 6 cycles, as indicated, after which patients may continue TSR-042 and TSR-022 combination therapy for up to 2 years or until disease progression, unacceptable toxicity, patient withdrawal, Investigator's decision, or death. Continued treatment with TSR-022 or TSR-042 beyond 2 years may be considered following discussion between the Sponsor and the Investigator.

6.1.2.9. Part I: Safety and Tolerability for TSR-042, TSR-022, and Carboplatin-Paclitaxel Combination Treatment

Confirmation of the RP2D for TSR-042, TSR-022, and carboplatin-paclitaxel combination treatment will be conducted using the dose levels described in Table 10.

Table 10: Dose Regimen for TSR-042, TSR-022, and Carboplatin-Paclitaxel Combination Treatment

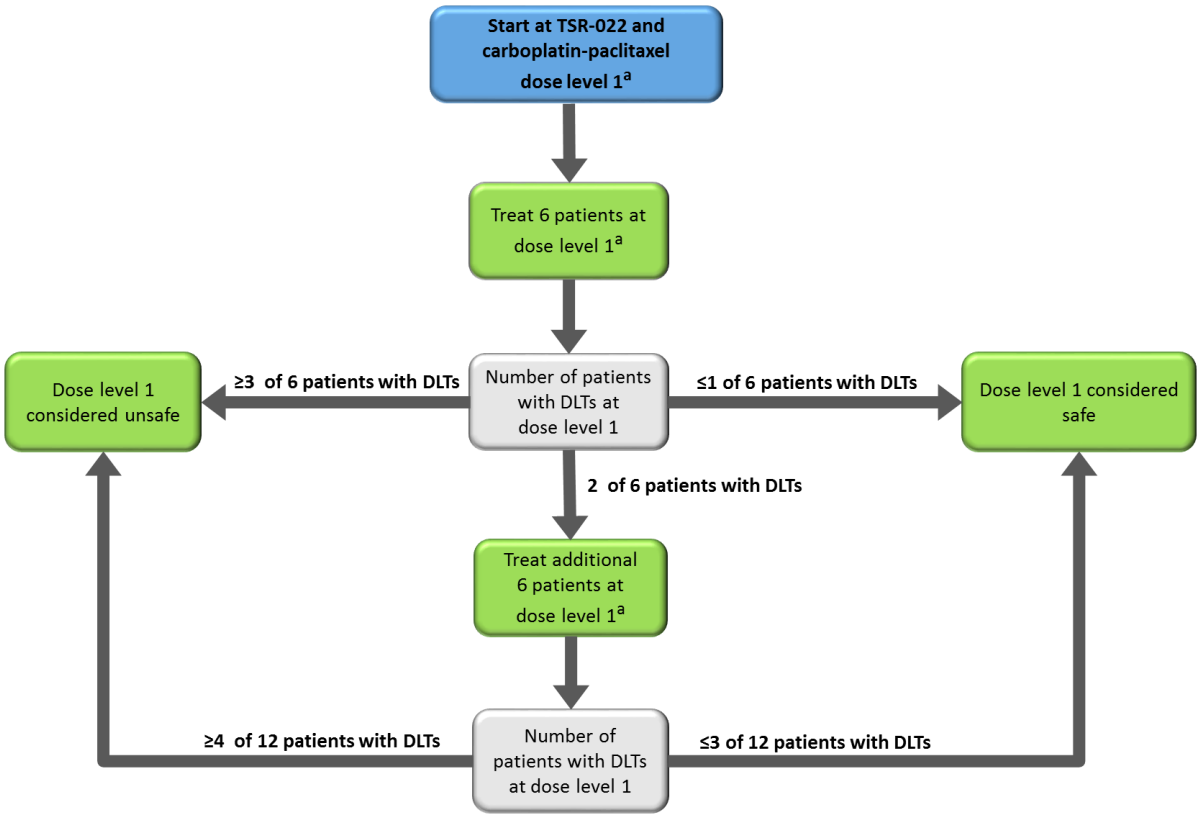
Dose Level	TSR-042 Dose	TSR-022 Dose	Carboplatin-Paclitaxel Dose
1	500 mg on Day 1 of every cycle Q3W	900 mg on Day 1 Q3W[b]	Carboplatin[a] AUC of 5 or 6 on Day 1 Q3W and paclitaxel 175 mg/m^2 on Day 1 Q3W administered for 4 to 6 cycles as clinically indicated
-1	500 mg on Day 1 of every cycle Q3W	300 mg on Day 1 Q3W[b]	Carboplatin[a] AUC of 5 or 6 on Day 1 Q3W and paclitaxel 175 mg/m^2 on Day 1 Q3W administered for 4 to 6 cycles as clinically indicated

Abbreviations: AUC = area under the plasma or serum concentration-time curve; Q3W = every 3 weeks.
[a] The carboplatin dose will be determined by the Investigator, taking into consideration the patient's prior anticancer therapies and pre-existing medical conditions.
[b] 900 mg of TSR-022 is the highest dose tested in dose escalation in combination with TSR-042 that provides maximal pharmacodynamic effect; this dose may be lowered to dose level -1 if needed. Based on available safety information, the Sponsor may decide to test additional dose levels of TSR-022.

At dose level 1, a cohort of 6 patients will be enrolled initially. After all patients in dose level 1 who are evaluable for safety have completed Cycle 1 of combination treatment, if ≤ 1 patient experiences a DLT (see DLT Assessment below), dose level 1 will be considered safe. If 2 of 6 patients experience DLTs, 6 additional patients will be enrolled at dose level 1. If ≤ 3 of 12 patients experience DLTs, dose level 1 will be considered safe. If ≥ 4 of 12 patients experience DLTs in dose level 1, dose level -1 will enroll 6 patients. After all patients in dose level -1 who are evaluable for safety have completed Cycle 1 of combination treatment, if ≤ 1 patient experiences a DLT, dose level -1 will be considered safe. If 2 of 6 patients experience DLTs, 6 additional patients will be enrolled at dose level -1. If ≤ 3 of 12 patients experience DLTs, dose level -1 will be considered safe. The combination therapy, dose level -1, will be considered unsafe if ≥3 of 6 or ≥4 of 12 patients experience DLTs during Cycle 1 (see Part I dose confirmation scheme below). However, when determining the RP2D, the Sponsor will review and consider safety data from all patients treated with the combination therapy.

The Part I dose confirmation scheme is summarized in Figure 10.

Figure 10: Part I Dose Confirmation Scheme for TSR-042, TSR-022, and Carboplatin-Paclitaxel Combination Treatment



Abbreviations: DLT = dose-limiting toxicity.

[a] Carboplatin-paclitaxel will be administered at the specified dose level as described in Table 10. In addition to receiving carboplatin-paclitaxel at the specified regimen, patients will be administered TSR-042 at 500 mg on Day 1 of every cycle Q3W and TSR-022 at 900 mg on Day 1 Q3W.

[b] Patients at dose level -1 will be enrolled using the same 6 + 6 scheme used at dose level 1.

Recommended Phase 2 Dose for TSR-042, TSR-022, and Carboplatin-Paclitaxel

The RP2D for TSR-042, TSR-022, and carboplatin-paclitaxel combination treatment will be confirmed following discussion and agreement between the Investigators and Sponsor based on evaluation of multiple endpoints, which may include the DLT rate in first and subsequent cycles of combination treatment, the rate of dose modifications for non-DLT AEs, the ability to manage toxicities, PK, and signs of clinical efficacy.

Duration of Study Treatment

Patients enrolled in Part I may continue TSR-042, TSR-022, and carboplatin-paclitaxel combination treatment for 4 to 6 cycles, as indicated, after which patients may continue TSR-042 and TSR-022 combination therapy for up to 2 years or until disease progression, unacceptable toxicity, patient withdrawal, Investigator's decision, or death. Continued treatment with TSR-022 or TSR-042 beyond 2 years may be considered following discussion between the Sponsor and the Investigator.

6.1.2.10. Dose-Limiting Toxicity Assessment

DLTs will be assessed during Cycle 1 (i.e., during the first 21 days of treatment on Day 1 to Day 21). DLT criteria are as follows:

- Any treatment-related Grade 4 nonhematologic clinical (nonlaboratory) AE
- Any treatment-related Grade 3 nonhematologic clinical (nonlaboratory) AE lasting >3 days despite optimal medical intervention
- Any treatment-related Grade 3 or 4 nonhematologic laboratory abnormality if any of the following also occur:
  - The abnormality leads to hospitalization.
  - The abnormality persists for ≥7 days from the time of AE onset and patient is symptomatic from the AE.
- Any treatment-related hematologic toxicity defined as any of the following:
  - Grade 4 thrombocytopenia persists for ≥7 days from the time of AE onset or Grade 3 or 4 thrombocytopenia associated with clinically significant bleeding
  - Grade 4 neutropenia, Grade 3 or 4 neutropenia associated with infection, or Grade 3 or 4 febrile neutropenia persists for ≥7 days
  - Grade 4 anemia or Grade 3 anemia requiring blood transfusion
- Any treatment-related toxicity leading to prolonged delay (>2 weeks) in initiating Cycle 2
- Any treatment-related Grade 5 AE

A patient will be considered nonevaluable for DLTs if, for any reason other than safety, the patient is unable to complete the 21-day combination treatment DLT observation period or is unable to take >80% of the intended dose of either agent. For patients who skip niraparib doses due to hematologic AEs based on dose modification table (Table 13) which do not meet the DLT criteria, it is allowed to miss up to 10 days of niraparib during Cycle 1 to be considered as evaluable for DLTs. Patients considered nonevaluable may be replaced after consultation between the Sponsor and Investigator.

Niraparib administration has been safely managed with dose interruptions or adjustments for AEs, including laboratory abnormalities, while maintaining activity in the single-agent setting. Therefore, niraparib dose interruption, dose reduction, or both, for an AE that does not meet a DLT definition as described above will be considered a non-DLT modification. Non-DLT dose modifications will be considered in determining the RP2D for TSR-042 and niraparib combination treatment. However, patients requiring a non-DLT dose modification that makes them unable to take >80% of the intended dose during Cycle 1 will be considered nonevaluable for DLTs.

Appropriate dose modification of niraparib is described in Section 6.4.1.1.

6.2. Number of Subjects

In Part A, approximately 12 to 24 patients will be enrolled.

In Part B, approximately 12 patients will be enrolled.

In Part C, approximately 6 to 24 patients may be enrolled. Dose level 1 will enroll 6 to 12 patients. Dose level 2 is optional.

In Part D, approximately 6 to 12 patients will be enrolled.

In Part E, approximately 6 to 12 patients will be enrolled.

In Part F, approximately 6 to 24 patients will be enrolled.

In Part G, approximately 6 to 12 patients will be enrolled.

In Part H, approximately 6 to 24 patients will be enrolled.

In Part I, approximately 6 to 24 patients will be enrolled.

6.3. Treatment Assignment

6.3.1. Part A: Dose Finding for TSR-042 and Niraparib Combination Treatment

An initial cohort of 6 to 12 patients will be enrolled at dose level 1 of TSR-042 and niraparib combination treatment, and dose escalation will be conducted as described in Section 6.1.2. Once dose level 1 is determined to be safe, an additional cohort of 6 to 12 patients will be enrolled at dose level 2.

6.3.2. Part B: TSR-042 and Carboplatin-Paclitaxel Combination Treatment Safety and Tolerability

A cohort of approximately 12 patients will be enrolled at dose level 1 in Part B.

6.3.3. Part C: Dose Finding for TSR-042, Niraparib, and Bevacizumab Combination Treatment

A cohort of approximately 6 to 12 patients will be enrolled at dose level 1 of TSR-042, niraparib, and bevacizumab combination treatment. Dose level 2 is optional.

6.3.4. Part D: TSR-042, Carboplatin-Paclitaxel, and Bevacizumab Combination Treatment

A cohort of approximately 6 to 12 patients will be enrolled at dose level 1 in Part D.

6.3.5. Part E: TSR-042 and Carboplatin-Pemetrexed Combination Treatment

A cohort of approximately 6 to 12 patients will be enrolled at dose level 1 in Part E.

6.3.6. Part F: TSR-042, TSR-022, and Carboplatin-Pemetrexed Combination Treatment

A cohort of approximately 6 to 12 patients will be enrolled at dose level 1 in Part F. If dose level 1 is determined to be not safe, an additional cohort of 6 to 12 patients will be enrolled at dose level -1.

6.3.7. Part G: TSR-042 and Carboplatin–Nab-Paclitaxel Combination Treatment

A cohort of approximately 6 to 12 patients will be enrolled at dose level 1 in Part G.

6.3.8. Part H: TSR-042, TSR-022, and Carboplatin–Nab-Paclitaxel Combination Treatment

A cohort of approximately 6 to 12 patients will be enrolled at dose level 1 in Part H. If dose level 1 is determined to be not safe, an additional cohort of 6 to 12 patients will be enrolled at dose level -1.

6.3.9. Part I: TSR-042, TSR-022, and Carboplatin-Paclitaxel Combination Treatment

A cohort of approximately 6 to 12 patients will be enrolled at dose level 1 in Part I. If dose level 1 is determined to be not safe, an additional cohort of 6 to 12 patients will be enrolled at dose level -1.

6.4. Dose Adjustment Criteria

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

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

6.4.1. Safety Criteria for Adjustment or Stopping Doses

6.4.1.1. Niraparib

Intrapatient Dose Escalation

After Cycle 2, the dose of niraparib may be increased to a higher dose level that has been found to be safe during the dose-escalation phase following discussion with the Sponsor.

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 11). 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 12). If the event recurs at 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 (i.e., 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, and/or the patient has already undergone a maximum of 2 dose reductions (to a minimum dose of 100 mg QD), the patient must permanently discontinue treatment with niraparib.

The dose interruption and modification criteria for niraparib for hematologic parameters will be based on blood counts and are outlined in Table 13. If the hematologic toxicity has not recovered to the specified levels within 4 weeks (28 days) of the dose interruption period, and/or the patient has already undergone a maximum of 2 dose reductions (to a minimum dose of 100 mg QD), the patient must permanently discontinue treatment with niraparib.

Table 11: Niraparib Dose Modifications for Nonhematologic Adverse Reactions

Abnormality	Intervention
Non-hematologic 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. Up to 2 dose reductions are permitted.
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 12: Niraparib Dose Reductions for Nonhematologic Toxicity

Event	Dose[a]
Initial dose	300[b] mg QD
First dose reduction for treatment-related CTCAE Grade 3 or 4 AE or SAE where prophylaxis is not considered feasible	200 mg QD
Second dose reduction for treatment-related CTCAE Grade 3 or 4 AE or SAE where prophylaxis is not considered feasible	100 mg QD
Continued treatment-related CTCAE Grade 3 or 4 AE or SAE lasting >28 days	Discontinue niraparib

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

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

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

Table 13: Niraparib Dose Modifications for Hematologic Toxicity

Laboratory Abnormality	Intervention
Monitor complete blood counts weekly for the first month, monthly for the next 11 months of treatment, and periodically after this time.	
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.
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 and/or transfusion at a higher platelet count. 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 12.

In the case of thrombocytopenia, following the first occurrence, resumption of therapy may occur at the same dose or 1 dose level lower when the hematologic toxicity has resolved. Subsequent occurrences should trigger dose reduction upon resumption of therapy. If the platelet count has not reverted within 28 days of interruption to ≥100,000/μL, then study treatment should be discontinued.

If dose interruption and/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 4 weeks may resume. CBC monitoring will continue every 4 weeks (i.e., monthly) for the next 11 months of treatment, and periodically after this time.

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 MDS/AML 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.

6.4.1.2. TSR-042 and TSR-022

AEs (both nonserious and serious) associated with TSR-042 or TSR-022 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 and TSR-022 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 and/or TSR-022 will be permanently discontinued for any drug-related Grade 4 AE. TSR-042 and/or TSR-022 must be permanently discontinued for certain irAEIs as described in Table 14. The recent joint American Society of Clinical Oncology (ASCO) and NCCN guideline for diagnosis and management of immune-related adverse events treated with immune checkpoint inhibitor therapy[107] may be used as a supplement to Table 14.

The specific immune-related AEs typically observed with anti-PD-1 antibodies will be managed according to the guidelines summarized below.[108]

The reason for interruption or discontinuation of TSR-042 and/or TSR-022 should be recorded in the eCRF.

Immune-related Adverse Events of Interest and Guidelines for Management

Given the mechanisms of action of TSR-042 and TSR-022, 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 14 for details on the management of TSR-042 and/or TSR-022 dose delays and discontinuation for specific irAEIs. Detailed guidance for the administration of rescue medications and supportive care is available in Section 9.7.4. For all irAEIs listed in Table 14, TSR-042 and/or TSR-022 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 and/or TSR-022.

All treatment delays (including any missed doses) and discontinuations, and the reason for delays or discontinuation of TSR-042 and/or TSR-022, should be recorded in the eCRF.

Table 14: Guidelines for Treatment of Immune-related Adverse Events of Interest

Toxicity	Hold Treatment For Grade	Restarting Treatment/ discontinuation
Diarrhea/colitis	2-3	Restart dosing when toxicity resolves to Grade 0-1.
	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 0-1.
	3-4 (AST or ALT > 5 × ULN or total bilirubin > 3 × ULN)	Permanently discontinue (see exception below)[a]
Type 1 diabetes mellitus (TIDM) or hyperglycemia	3-4 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	2-4	For Grade 2-3 hold until hormonal therapy results in return to adequate levels by laboratory values and restart dosing when toxicity resolves to Grade 0-1. For recurrence or worsening of ≥ Grade 2 hypophysitis after steroid taper has been completed and is on adequate hormone replacement therapy, permanently discontinue. For Grade 4, permanently discontinue.
Adrenal insufficiency	2-3	Hold until hormonal therapy results in return to adequate levels by laboratory values and restart dosing when toxicity resolves to Grade 0-1. For recurrent or worsening ≥Grade 2 adrenal insufficiency while adequate hormonal replacement is continuing, permanently discontinue study drug.
	4	Permanently discontinue.

Table 14: Guidelines for Treatment of Immune-related Adverse Events of Interest (Continued)

Toxicity	Hold Treatment For Grade	Restarting Treatment/ discontinuation
Hypo- and hyperthyroidism	3	Hold until hormonal therapy results in return to adequate levels by laboratory values and restart dosing when toxicity resolves to Grade 0-1.
	4	Permanently discontinue.
Infusion-related reaction	2[b]	Restart dosing when toxicity resolves to Grade 0-1.
	3-4	Permanently discontinue.
Pneumonitis	2	Restart dosing when toxicity resolves to Grade 0-1. If Grade 2 recurs, permanently discontinue.
	3-4	Permanently discontinue.
Rash	3	Restart dosing when toxicity resolves to Grade 0-1
	4	Permanently discontinue
Renal failure or nephritis	2	Restart dosing when toxicity resolves to Grade 0-1.
	3-4	Permanently discontinue.
Recurrence of AEs after resolution to ≤ Grade 1	3-4	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 (e.g., 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 9.7.4 for further management details.

6.4.1.3. Carboplatin-Paclitaxel

Hematological and nonhematological AEs attributable to carboplatin and/or paclitaxel will be managed as indicated in the labeling information and by local institutional practice.

6.4.1.4. Carboplatin-Pemetrexed

Hematological and nonhematological AEs attributable to carboplatin and/or pemetrexed will be managed as indicated in the labeling information and by local institutional practice.

6.4.1.5. Carboplatin–Nab-Paclitaxel

Hematological and nonhematological AEs attributable to carboplatin and/or nab-paclitaxel will be managed as indicated in the labeling information and by local institutional practice.

6.4.1.6. Bevacizumab

Hematological and nonhematological AEs attributable to carboplatin and/or nab-paclitaxel will be managed as indicated in the labeling information and by local institutional practice. Dose reductions of bevacizumab are not permitted in this study.[109,110]

Interrupt bevacizumab treatment for the following adverse events: 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.[103] 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.

6.4.2. Pharmacokinetic Criteria for Adjustment or Stopping Doses

Not applicable.

6.5. Criteria for Study Termination

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

7. STUDY POPULATION

7.1. Inclusion Criteria

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

1. Patient is male or female and at least 18 years of age.
2. Patient has histologically or cytologically proven advanced (unresectable) or metastatic cancer as outlined below according to study part and disease type:
    a. Part A: Patients with previously treated advanced or metastatic cancer. Patient may have received no more than 4 lines of treatment for advanced or metastatic cancer. Hormonal treatment will not be considered a prior line of treatment.
    b. Part B: Patients with advanced or metastatic cancer for which treatment with carboplatin-paclitaxel is considered appropriate therapy. Patient may have received no more than 1 prior line of chemotherapy in the metastatic setting. Hormonal treatment will not be considered a prior line of treatment.
    c. Part C: Patients with previously treated advanced or metastatic cancer. Patient may have received no more than 4 lines of treatment for advanced or metastatic cancer. Hormonal treatment will not be considered a prior line of treatment.
    d. Part D: Patients in whom carboplatin-paclitaxel and bevacizumab is considered appropriate therapy. Patient may have received no more than 1 prior line of chemotherapy in the metastatic setting. Hormonal treatment will not be considered a prior line of treatment.
    e. Parts E, F, G, H, I: Patients who have not received prior systemic therapy, including targeted therapy and biologic agents, for their advanced or metastatic (Stage ≥ IIIB or IV) NSCLC. Patients who have received neoadjuvant or adjuvant therapy are eligible as long as development of advanced or metastatic disease occurred at least 12 months after completion of neoadjuvant or adjuvant therapy.
3. Patient has an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1.
4. Patient has adequate organ function defined as follows (Note: CBC test should be obtained without transfusion or receipt of colony-stimulating factors in the 2 weeks before obtaining sample):
    a. Absolute neutrophil count ≥ 1,500/μL
    b. Platelets ≥ 100,000/μL
    c. Hemoglobin ≥ 9 g/dL or ≥ 5.6 mmol/L
    d. Serum creatinine ≤ 1.5 × upper limit of normal (ULN) or calculated creatinine clearance ≥ 50 mL/min using Cockcroft-Gault equation for patients with creatinine levels > 1.5 × institutional ULN
    e. Total bilirubin ≤ 1.5 × ULN or direct bilirubin ≤ 1 × ULN
    f. AST and ALT ≤ 2.5 × ULN unless liver metastases are present, in which case they must be ≤5 × ULN
    g. International normalized ratio or prothrombin time (PT) ≤ 1.5 × ULN unless the patient is receiving anticoagulant therapy as long as PT or partial thromboplastin time (PTT) is within therapeutic range of intended use of anticoagulants

h. Activated partial thromboplastin time (aPTT) ≤ 1.5 × ULN unless the patient is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

5. Female patient has a negative serum pregnancy test within 72 hours prior to taking study treatment if of childbearing potential and agrees to abstain from activities that could result in pregnancy from screening through 180 days after the last dose of study treatment, or is of nonchildbearing potential. Nonchildbearing potential is defined as follows (by other than medical reasons):
   a. ≥45 years of age and has not had menses for >1 year
   b. Patients who have been amenorrheic for <2 years without history of a hysterectomy and oophorectomy must have a follicle stimulating hormone value in the postmenopausal range upon screening evaluation
   c. Post-hysterectomy, post-bilateral oophorectomy, or post-tubal ligation. Documented hysterectomy or oophorectomy must be confirmed with medical records of the actual procedure or confirmed by an ultrasound. Tubal ligation must be confirmed with medical records of the actual procedure, otherwise the patient must be willing to use effective contraception throughout the study, starting with the screening visit through 180 days after the last dose of study treatment. See Section 9.7.3 for a list of acceptable birth control methods. Information must be captured appropriately within the site's source documents. Note: Abstinence is acceptable if this is the established and preferred contraception for the patient.
6. Male patient agrees to use an adequate method of contraception (see Section 9.7.3 for a list of acceptable birth control methods) and not donate sperm starting with the first dose of study treatment through 90 days after the last dose of study treatment. Note: Abstinence is acceptable if this is the established and preferred contraception for the patient.
7. Patient has measurable lesions by RECIST v1.1.

For Parts A and C, in addition to the general inclusion criteria, patients must also meet the following additional criteria to be considered eligible to participate in this study:

8. Patient is able to take oral medications.
9. For patients to be eligible for any parts of the study using niraparib 300 mg as a starting dose, a screening actual body weight ≥ 77 kg **and** screening platelet count ≥ 150,000 u/L is necessary.

7.2. Exclusion Criteria

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

1. Patient has known active central nervous system metastases, carcinomatous meningitis, or both. Note: Patients with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging [using the identical imaging modality for each assessment, either magnetic resonance imaging [MRI] or computer tomography [CT] scan] for at least 4 weeks prior to the first dose of study treatment and any neurologic symptoms have returned to baseline), have no evidence of new or

enlarging brain metastases, and have not been using steroids for at least 7 days prior to study treatment. Carcinomatous meningitis precludes a patient from study participation regardless of clinical stability.

2. Patient has a known additional malignancy that progressed or required active treatment within the last 2 years. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin that has undergone potentially curative therapy, or in situ cervical cancer.
3. Patient is considered a poor medical risk due to a serious, uncontrolled medical disorder, nonmalignant systemic disease, or active infection that requires systemic therapy. Specific examples include, but are not limited to, history of (noninfectious) pneumonitis that required steroids or current pneumonitis, uncontrolled ventricular arrhythmia, recent (within 90 days) myocardial infarction, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, or any psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the study (including obtaining informed consent).
4. Patient has a condition (such as transfusion-dependent anemia or thrombocytopenia), therapy, or laboratory abnormality that might confound the study results or interfere with the patient's participation for the full duration of the study treatment including the following:
    a. Patients who received a transfusion (platelets or red blood cells) within 6 weeks of the first dose of study treatment are not eligible.
    b. Patients who received colony-stimulating factors (e.g., granulocyte colony-stimulating factor, granulocyte macrophage colony-stimulating factor, or recombinant erythropoietin) within 4 weeks prior to the first dose of study treatment are not eligible.
5. Patient is pregnant or expecting to conceive children within the projected duration of the study, starting with the screening visit through 180 days after the last dose of study treatment.
    a. No data are available regarding the presence of niraparib or its metabolites in human milk, or on its effects on the breastfed infant or milk production. Because of the potential for serious adverse reactions in breastfed infants from niraparib, female patients should not breastfeed during treatment with niraparib and for 1 month after receiving the final dose.
6. Patient has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of study treatment.
7. Patient has a known history of human immunodeficiency virus (type 1 or 2 antibodies).
8. Patient has known active hepatitis B (e.g., hepatitis B surface antigen [HBsAg] reactive) or hepatitis C (e.g., hepatitis C virus [HCV] ribonucleic acid [qualitative] is detected).
9. Patient has an active autoimmune disease that has required systemic treatment in the past 2 years (i.e., with use of disease-modifying agents, corticosteroids, or

immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

10. Patient has not recovered (i.e., to Grade ≤1 or to baseline) from cytotoxic therapy-induced AEs. Note: Patients with Grade ≤2 neuropathy, Grade ≤2 alopecia, or Grade ≤2 fatigue are an exception to this criterion and may qualify for the study.
11. Patient is currently participating and receiving study treatment or has participated in a study of an investigational agent and received study treatment or used an investigational device within 4 weeks of the first dose of treatment.
12. Patient has had a prior cytotoxic therapy, anticancer targeted small molecules (e.g., tyrosine kinase inhibitors), hormonal agents within 5 half-lives, or monoclonal antibodies within 5 half-lives or 4 weeks (whichever is shorter) of that treatment prior to Day 1; radiation therapy encompassing >20% of the bone marrow within 2 weeks; or any radiation therapy within 1 week prior to Day 1.
13. Patient has not recovered adequately from AEs or complications from any major surgery prior to starting therapy.
14. Patient has received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA-4 (including ipilimumab), or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways.
15. Patient has received a live vaccine within 14 days of planned start of study treatment.
16. Patient has a heart-rate QTc prolongation >480 ms at screening. Note: If a patient has a prolonged QT interval and the prolongation is deemed to be due to a pacemaker upon Investigator evaluation (i.e., the patient otherwise has no cardiac abnormalities), the patient may be eligible to participate in the study following discussion with the Sponsor's Medical Monitor.
17. Patient has a known hypersensitivity to TSR-042 components or excipients.

For Parts A and C only, patients will not be eligible for study entry if any of the following additional exclusion criteria are met:

18. Patient has undergone prior treatment with a known PARP inhibitor.
19. Patient has a known hypersensitivity to niraparib components or excipients.
20. Patient has had any known Grade 3 or 4 anemia, neutropenia, or thrombocytopenia due to prior chemotherapy that persisted >4 weeks related to the most recent prior treatment.
21. Known history or current diagnosis of MDS or AML, or current diagnosis of prostate cancer.

For Parts B, D, E, F, G, H, and I, patients will not be eligible for study entry if any of the following additional exclusion criterion are met:

22. Patient has a known hypersensitivity to any of the following relevant study treatments: carboplatin, paclitaxel, pemetrexed, nab-paclitaxel, or TSR-022 components or excipients.

For Parts C and D only, patients will not be eligible for study entry if the following additional exclusion criterion is met:

23. Patient has clinically significant cardiovascular disease (e.g., significant cardiac conduction abnormalities, uncontrolled hypertension, myocardial infarction, cardiac arrhythmia or unstable angina, New York Heart Association Grade 2 or greater congestive heart failure, serious cardiac arrhythmia requiring medication, Grade 2 or greater peripheral vascular disease, and history of cerebrovascular accident [CVA]) within 6 months of enrollment.
24. Patient has a history of bowel obstruction, including subocclusive disease, related to the underlying disease and history of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscesses. Evidence of recto-sigmoid involvement by pelvic examination or bowel involvement on CT scan or clinical symptoms of bowel obstruction.
25. 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).
26. Patient is at increased bleeding risk due to concurrent conditions (e.g., 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).
27. Patient has a known hypersensitivity to bevacizumab components or excipients

For Parts E and F only, patients will not be eligible for study entry if any of the following additional exclusion criteria are met:

28. Patient is unable to interrupt aspirin or other nonsteroidal ant-inflammatory drugs, other than an aspirin dose ≤ 1.3 g per day, for a 5-day period (8-day period for long -acting agents, such as piroxicam.
29. Patient is unable or unwilling to take folic acid, vitamin B_{12} supplement.
30. Patient has symptomatic ascites or pleural effusion. A patient who is clinically stable following treatment for these conditions (including therapeutic thoraco- or paracentesis) is eligible.

For Parts G, H, and I only, patients will not be eligible for study entry if any of the following additional exclusion criteria are met:

31. Patient has pre-existing peripheral neuropathy that is Grade ≥ 2 by Common Terminology Criteria for Adverse Events (CTCAE) version 4 criteria.
32. Patient has interstitial lung disease or a history of pneumonitis that required oral or intravenous glucocorticoids to assist with management.

7.3. Patient Discontinuation and Replacement

7.3.1. Discontinuation from Study Treatment

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

- AE
- Disease progression as outlined in Section 10.1 or based on clinical criteria by Investigator
- Risk to patient as judged by the Investigator and/or Sponsor
- Severe noncompliance with the protocol as judged by the Investigator and/or Sponsor
- Patient request
- Patient becomes pregnant
- Sponsor decision to terminate study
- Death

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

Details of required niraparib dose modifications, including interruptions, dose reductions, and permanent discontinuations, related to toxicity are provided in Section 6.4.1.1. Details of required TSR-042 and TSR-022 dose interruptions and permanent discontinuation related to toxicity are provided in Section 6.4.1.2. Details of required carboplatin-paclitaxel dose interruptions and permanent discontinuation related to toxicity are provided in Section 6.4.1.3. Details of required carboplatin-pemetrexed dose interruptions and permanent discontinuation related to toxicity are provided in Section 6.4.1.4. Details of required carboplatin–nab-paclitaxel dose interruptions and permanent discontinuation related to toxicity are provided in Section 6.4.1.5. Details of required bevacizumab dose interruptions and permanent discontinuation related to toxicity are provided in Section 6.4.1.6.

If a patient must stop a study drug other than TRS-042 or TSR-022 due to toxicity after Cycle 1 (see Section 6.4.1), the patient will be allowed to continue TSR-042 or TSR-022 if the criteria listed below are met:

1. The patient is receiving clinical benefit from study treatment.
2. The AE that led to discontinuation of a study drug is not related to TSR-042 or TSR-022 in the judgement of the investigator.

Patients who discontinue from all study treatments will continue to receive follow-up assessments [see Table 18 (Part A), Table 20 (Part B), Table 22 (Part C), Table 24 (Part D), Table 26 (Part E), Table 28 (Part F), Table 30 (Part G), Table 32 (Part H), and Table 34 (Part I)], as part of the study unless they are discontinued from the study (Section 7.3.2).

7.3.2. Discontinuation from the Study

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

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

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

7.3.3. Replacement of Patients

After consultation between the Sponsor and the Investigator, enrollment may be extended to replace patient(s) who become non-evaluable for safety during Parts A, B, C, D, E, F, G, H, or I.

7.4. Patient Identification and Randomization

7.4.1. Patient Identification

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

7.4.2. Randomization Scheme

Not applicable.

8. TREATMENT OF PATIENTS

8.1. Description of Study Drug

Table 15: Investigational Product

Parameter	**Investigational Product**							
Product name	TSR-042	Niraparib	Carboplatin[a]	Paclitaxel	Pemetrexed	Nab-Paclitaxel	Bevacizumab	TSR-022[b]
Dosage form	Infusion	Capsule	Infusion	Infusion	Infusion	Infusion	Infusion	Infusion
Duration of infusion	30 minutes	NA	30 or 60 minutes (30 minutes preferred)	3 hours	10 minutes	30 minutes	Based on local approved product label	30 minutes
Unit dose	• 500 mg on Day 1 of every cycle Q3W (first 4 cycles), followed by 1,000 mg on Day 1 of every other cycle (Q6W) beginning on Day 1/Cycle 5 for Parts A, B, C, and D. • 500 mg on Day 1 of every cycle Q3W for Parts E, F, G, H, and I	Dose level 1: 200 mg on Days 1 to 21 Q3W thereafter Dose level 2: 300 mg on Days 1 to 21 Q3W thereafter	AUC of 5 or 6 on Day 1 Q3W administered for 4 to 6 cycles as clinically indicated	175 mg/m^2 on Day 1 Q3W administered for 4 to 6 cycles as clinically indicated	500 mg/m^2 Day 1 Q3W (with vitamin supplementation)	100 mg/m^2 on Days 1, 8, and 15 (Q1W) of every 3-week cycle, administered for 4 to 6 cycles as clinically indicated	15 mg/kg on Day 1 Q3W for up to 15 months	Dose Level 1: 900 mg Day 1 Q3W Dose level -1: 300 mg Day 1 Q3W
Route of administration	IV	PO	IV	IV	IV	IV	IV	IV

Abbreviations: AUC = area under the plasma or serum concentration-time curve; IV = intravenous; NA = not applicable; PO = orally; Q1W = every week; Q3W = every 3 weeks; Q6W = every 6 weeks.

[a] The carboplatin dose will be determined by the Investigator, taking into consideration the patient's prior anticancer therapies and pre-existing medical conditions.

[b] 900 mg of TSR-022 is the highest dose tested in dose escalation in combination with TSR-042 that provides maximal pharmacodynamic effect; this dose may be lowered to dose level -1 if needed. Based on available safety information, the Sponsor may decide to test additional dose levels of TSR-022.

9. STUDY DRUG MATERIALS AND MANAGEMENT

9.1. Identity

9.1.1. Niraparib

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

9.1.2. TSR-042

TSR-042 is an IgG4-κ humanized monoclonal antibody and will be supplied as a solution in vials containing 160 mg or 500 mg (20 mg/mL or 50 mg/mL, respectively).

9.1.3. TSR-022

TSR-022 is a humanized monoclonal IgG4 antibody and will be supplied as a solution in vials containing 160 mg (20 mg/mL).

9.1.4. Carboplatin-Paclitaxel

9.1.4.1. Carboplatin

Carboplatin (platinum, diamine [1,1-cyclobutanedicarboxylato(2-)-*O,O'*]-,(*SP*-4-2)) is a platinum coordination compound and will be supplied as a sterile, pyrogen-free, 10 mg/mL aqueous solution for infusion.

9.1.4.2. Paclitaxel

Paclitaxel (5β,20-Epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4,10-diacetate 2-benzoate 13-ester with (2*R*,3*S*)-*N*-benzoyl-3-phenylisoserine) is a natural product with antitumor activity, derived from *Taxus baccata.*

Paclitaxel for injection is a clear, colorless to slightly yellow viscous solution. It is supplied as a nonaqueous solution intended for dilution prior to IV infusion.

9.1.5. Pemetrexed

Pemetrexed will be supplied as a single vial (Pemetrexed [pemetrexed disodium] 500 mg/vial, lyophilized powder for infusion).

9.1.6. Nab-Paclitaxel

Nab-paclitaxel will be supplied as a single vial of lyophilized powder containing 100 mg of paclitaxel in a single-use vial for reconstitution.

9.1.7. Bevacizumab

Bevacizumab (Avastin) is a clear to slightly opalescent, colorless to pale brown, sterile, pH 6.2 solution for IV infusion.[110] 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.

9.2. Administration

9.2.1. Niraparib

Niraparib will be supplied as 100-mg capsules and will be administered orally QD continuously at the assigned dose (see Table 48 for Part A and Table 50 for Part C). On Day 1 of each cycle, a niraparib dose will be administered upon completion of all infusions. Depending on the dose regimen, 2 or 3 capsules of 100-mg strength niraparib will be taken at each dose administration (total dose of 200 or 300 mg per dose regimen, respectively). Subsequent to Amendment 1, only patients with a screening actual body weight ≥ 77 kg **and** screening platelet count ≥ 150,000 µL will be eligible to receive niraparib 300 mg as a stating dose. Patients will be instructed to take their niraparib dose 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 21-day cycle for up to 2 years or until disease progression, unacceptable toxicity, patient withdrawal, Investigator's decision, or death. Continued treatment with niraparib beyond 2 years may be considered following discussion between the Sponsor and Investigator.

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

9.2.2. TSR-042

TSR-042 will be administered at the study site by a 30-minute IV infusion on Day 1 of every 21-day cycle (Q3W) at 500 mg for the first 4 cycles. Beginning on Day 1 of Cycle 5, TSR-042 will be administered at 1,000 mg on Day 1 of every other cycle (Q6W) to patients in Parts A, B, C, and D for up to 2 years or until disease progression, unacceptable toxicity, patient withdrawal, Investigator's decision, or death. Patients in Parts E, F, G, H, and I will continue to receive 500 mg on Day 1 of every cycle (Q3W) throughout the study. Continued treatment with TSR-042 beyond 2 years may be considered following discussion between the Sponsor and Investigator. The Pharmacy Manual contains descriptions of the packaging of TSR-042 and instructions for the preparation and administration of TSR-042. (See Table 48 for Part A, Table 49 for Part B, Table 50 for Part C, Table 51 for Part D, Table 52 for Part E, Table 53 for Part F, Table 54 for Part G, Table 55 for Part H, and Table 56 for Part I.)

9.2.3. TSR-022

TSR-022 will be administered at the study site by a 30-minute IV infusion on Day 1 of every 21-day Cycle (Q3W) at 900 mg (or 300 mg if lowered to dose level -1 for reasons of safety) for up to 2 years or until disease progression, unacceptable toxicity, patient withdrawal, Investigator's decision, or death. All patients should be monitored on site for AEs for at least 4 hours after the completion of infusion for the first and second doses. Continued treatment with TSR-022 beyond 2 years may be considered following discussion between the Sponsor and Investigator.

The Pharmacy Manual contains descriptions of the packaging of TSR-022 and instructions for the preparation and administration of TSR-022.

9.2.4. Carboplatin-Paclitaxel

Paclitaxel will be administered at the study site by a 3-hour IV infusion on Day 1 of every 21-day cycle (Q3W) at 175 mg/m^2 for 4 to 6 cycles or until disease progression, unacceptable toxicity, patient withdrawal, Investigator's decision, or death. The paclitaxel package insert contains descriptions of the packaging of paclitaxel and instructions for preparation and administration of paclitaxel.

Carboplatin will be administered at the study site by a 30- or 60-minute IV infusion (30 minutes preferred) on Day 1 of every 21-day cycle (Q3W) at an area under the plasma or serum concentration-time curve (AUC) of 5 or 6, and will be administered for 4 to 6 cycles as clinically indicated. The carboplatin dose will be determined by the Investigator, taking into consideration the patient's prior anticancer therapies and pre-existing medical conditions. The carboplatin package insert contains descriptions of the packaging of carboplatin and instructions for preparation and administration of carboplatin.

The order of administration of both agents is as follows: TSR-042 (followed by TSR-022 in Part I only) followed by paclitaxel (see Table 49 for Part B, Table 51 for Part D, and Table 56 for Part I).

9.2.5. Carboplatin-Pemetrexed

Pemetrexed will be administered at the study site by a 10-minute IV infusion on Day 1 of every 21-day cycle (Q3W) at 500 mg/m^2 for up to 2 years or until progression, unacceptable toxicity, patient withdrawal, Investigator's decision, or death. The pemetrexed package insert contains descriptions of the packaging of pemetrexed and instructions for preparation and administration of pemetrexed. Continued treatment with pemetrexed beyond 2 years may be considered following discussion between the Sponsor and Investigator.

All patients should receive the appropriate supplementation of vitamin B12 and folic acid as listed below:

- Folic acid 350 to 1,000 µg oral: At least 5 doses of folic acid must be taken during the 7 days preceding the first dose of pemetrexed, and folic acid dosing must continue during the full course of therapy and for 21 days after the last dose of pemetrexed.

- Vitamin B12 1,000 µg intramuscular injection will be administered in the week preceding the first dose of pemetrexed and once every 3 cycles thereafter. Subsequent vitamin B12 injections may be given the same day as pemetrexed administration.

Carboplatin will be administered at the study site by a 30- or 60-minute IV infusion (30 minutes preferred) on Day 1 of every 21-day cycle (Q3W) at an area under the plasma or serum concentration-time curve (AUC) of 5 or 6, and will be administered for 4 to 6 cycles as clinically indicated. The carboplatin dose will be determined by the Investigator, taking into consideration the patient's prior anticancer therapies and pre-existing medical conditions. The carboplatin package insert contains descriptions of the packaging of carboplatin and instructions for preparation and administration of carboplatin.

Both agents will be administered at the study site on Day 1 of every 21-day cycle (Q3W) after administration of TSR-042 and will be administered for 4 to 6 cycles as clinically indicated, and thereafter pemetrexed will be administered for up to 2 years or until progression, unacceptable toxicity, patient withdrawal, Investigator's decision, or death. (Order of administration: TSR-042 infusion [followed by TSR-022 in Part F only] followed by pemetrexed infusion followed by carboplatin infusion.) (See Table 52 for Part E and Table 53 for Part F.)

9.2.6. Carboplatin–Nab-Paclitaxel

Nab-paclitaxel will be administered at the study site by a 30-minute IV infusion on Days 1, 8, and 15 (Q1W) of every 21-day cycle at 100 mg/m^2 for 4 to 6 cycles as clinically indicated or until disease progression, unacceptable toxicity, patient withdrawal, Investigator's decision, or death, after administration of TSR-042 for Part G (see Table 54) and after administration of TSR-042 and TSR-022 for Part H (see Table 55).

The nab-paclitaxel package insert contains descriptions of the packaging of nab-paclitaxel and instructions for preparation and administration of nab-paclitaxel.

Carboplatin will be administered at the study site by a 30- or 60-minute IV infusion (30 minutes preferred) on Day 1 of every 21-day cycle (Q3W) an area under the plasma or serum concentration-time curve (AUC) of 5 or 6, and will be administered for 4 to 6 cycles as clinically indicated, after administration of TSR-042 and nab-paclitaxel for Part G (see Table 54) and after administration of TSR-042, TSR-022, and nab-paclitaxel for Part H (see Table 55). The carboplatin dose will be determined by the Investigator, taking into consideration the patient's prior anticancer therapies and pre-existing medical conditions.

The carboplatin package insert contains descriptions of the packaging of carboplatin and instructions for preparation and administration of carboplatin.

9.2.7. Bevacizumab

Bevacizumab will be administered at the study site by IV infusion based on local approved product label [111] on Day 1 of every 21-day cycle (Q3W) at 15 mg/kg for up to 15 months or until progression, unacceptable toxicity, patient withdrawal, Investigator's decision, or death.

This agent will be administered after administration of TSR-042 in Part C and after administration of TSR-042, paclitaxel, and carboplatin in Part D (See Table 50 for Part C and

Table 51 for Part D).The bevacizumab package insert contains descriptions of the packaging of bevacizumab and instructions for the preparation and administration of bevacizumab.

9.2.8. Order of Administration

The order of study drug administration for each part is listed below:

- Part A: TSR-042 followed by niraparib after completion of infusion
- Part B: TSR-042 followed by paclitaxel, then carboplatin
- Part C: TSR-042 followed by bevacizumab, then niraparib after completion of both infusions
- Part D: TSR-042 followed by paclitaxel, then carboplatin then bevacizumab
- Part E: TSR-042 followed by pemetrexed, then carboplatin
- Part F: TSR-042 followed by TSR-022, then pemetrexed, then carboplatin
- Part G: TSR-042 followed by nab-paclitaxel, then carboplatin
- Part H: TSR-042 followed by TSR-022, then nab-paclitaxel, then carboplatin
- Part I: TSR-042 followed by TSR-022, then paclitaxel, then carboplatin

9.3. Dose Modification

Dose modification of study treatment will be conducted as described in Section 6.4.1.

9.4. Study Drug Packaging, Labeling, and Storage

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

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

9.5. Study Drug Accountability

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

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

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

9.6. Study Drug Handling and Disposal

At the end of study, when all patients have stopped protocol treatment, complete drug reconciliation per batch should be available at the site for verification in order to allow drug destruction or return procedure. All dispensing and accountability records will be available for Sponsor review. After receiving Sponsor approval in writing, the investigational site is responsible for destruction of study treatment according to local regulations. If a site does not have the capability for on-site destruction, the Sponsor will provide a return for destruction service to a third party.

Both the unused and expired study treatment must be destroyed, upon authorization of the Sponsor, according to local regulations and procedures, and a copy of the destruction form must be filed in the study binder.

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

9.7. Previous and Concomitant Medications

9.7.1. Recording of Previous and Concomitant Medications

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

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

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

The metabolism of paclitaxel is catalyzed by CYP2C8 and CYP3A4. Investigators are advised to use caution when administering paclitaxel concomitantly with known substrates, inducers or inhibitors of CYP2C8 and CYP3A4 (see Table 57 in Appendix A).

9.7.2. Prohibited Medications

Known prior medications that exclude a patient from participating in the study are described in the exclusion criteria (see Section 7.2).

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

- Systemic anticancer or biological therapy. For patients with castration resistant prostate cancer, it is allowed to continue androgen deprivation therapy after cycle 1.
- Immunotherapy not specified in this protocol.

- Chemotherapy not specified in this protocol.
- Investigational agents other than niraparib, TSR-042, TSR-022, carboplatin-paclitaxel, bevacizumab, pemetrexed, and nab-paclitaxel.
- Radiation therapy is prohibited within 3 weeks prior to Day 1 and during study treatment. Note: Palliative radiation therapy to a small field >1 week prior to Day 1 of study treatment may be allowed. Palliative radiation therapy to a small field is allowed after Cycle 1 after consultation with the Sponsor.
- Any surgery that involves tumor lesions, except for diagnostic biopsy.
- 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 (e.g., acute asthma or chronic obstructive pulmonary disease exacerbation), 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 and/or TSR-022.
- Live vaccines within 14 days prior to the first dose of study treatment. Seasonal flu vaccines that do not contain live viruses are allowed. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, bacille Calmette-Guerin, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed. Intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines and are not allowed.
- Prophylactic cytokines (i.e., 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.[112]

In addition, niraparib has been shown to weakly induce cytochrome P450 (CYP) 1A2 in vitro and is an insensitive substrate for P-glycoprotein (P-gp). 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 (e.g., warfarin) and antiplatelet drugs (e.g., aspirin).

Physicians should follow the current versions of the niraparib Investigator's Brochure, the Zejula® package insert[113], the Avastin® [Genentech/Roche US] package insert[111], the TSR-042 Investigator's Brochure, the carboplatin package insert[114], the paclitaxel package insert[115], the pemetrexed package insert[116], and the nab-paclitaxel package insert[74] for information on the general management of the patients receiving these therapies.

Patients in Parts B, D, E, F, G, H, and I are additionally prohibited from receiving the following therapies during the screening and treatment phase of this study:

- Aminoglycocides

- Known ototoxic agents

9.7.3. Contraception

TSR-042, TSR-022, and niraparib are known to have properties that require the patient to use contraception. For details on niraparib, refer to the Investigator's Brochure.

It is not known if TSR-042 or TSR-022 may have adverse effects on a fetus in utero. However, blockade of PD-L1 and TIM-3 signaling in murine models of allogeneic pregnancy can eliminate fetomaternal tolerance and cause spontaneous abortion as indicated by increase in embryo resorption and a reduction in litter size and TIM-3 down-regulation has been correlated with human miscarriage.[117-119] Therefore, female patients of childbearing potential may only be enrolled if they have a negative serum pregnancy test within 72 hours prior to taking study treatment. Female patients must agree to abstain from activities that could result in pregnancy from screening through 180 days after the last dose of study treatment, be willing to use 2 adequate barrier methods or a barrier method plus a hormonal method throughout the study, or be of nonchildbearing potential, as defined in Section 7.1.

Male patients are required to use an adequate method of contraception starting with the first dose of study treatment through 90 days after the last dose of study treatment.

The following are considered highly effective methods of contraception: combined (estrogen and progesterone containing) hormonal contraception associated with inhibition of ovulation (including oral, intravaginal, or transdermal agents); progesterone-only hormonal contraception associated with inhibition of ovulation (including oral, injectable, or implantable agents); intrauterine device (IUD); intrauterine hormone-releasing system (IUS); bilateral tubal occlusion; vasectomized partner; or sexual abstinence.

Patients should be informed that taking the study treatment may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. To participate in the study they must adhere to the contraception requirement (described above) for the duration of the study and through 180 days after the last study treatment. If there is any question that a patient will not reliably comply with the requirements for contraception, that patient should not be enrolled into the study.

9.7.4. Rescue Medications and Supportive Care Guidelines

Supportive care measures for AEs during treatment with niraparib, carboplatin, paclitaxel, bevacizumab, pemetrexed, and nab-paclitaxel 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 and/or TSR-022, 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 (e.g., GCSF) should be administered according to current ASCO guidelines.[112] 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.

9.7.4.1. Pneumonitis

- Treat with systemic corticosteroids, oral for Grade 2 (e.g., 0.5 to 1 mg/kg/day of prednisone or equivalent) and IV for Grade 3 or 4 (e.g., 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 or less over no less than 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.

9.7.4.2. 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 (e.g., 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 (e.g., 1 to 2 mg/kg/day of prednisone or equivalent) followed by high-dose oral steroids.
- Taper corticosteroids when symptoms improve to Grade 1 or less over no less than 4 weeks.

9.7.4.3. 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.

9.7.4.4. Hypophysitis

- Treat with systemic corticosteroids, oral for Grade 2 (e.g., 0.5 to 1 mg/kg/day of prednisone or equivalent) and IV for Grade 3 or 4 (e.g., 1 to 2 mg/kg/day of prednisone or equivalent).
- Taper corticosteroids when symptoms improve to Grade 1 or less over no less than 4 weeks.
- Replacement of appropriate hormones may be required as the steroid dose is tapered.

9.7.4.5. 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 non-selective beta-blockers (e.g., propranolol) as initial therapy.
- Grade 3 or 4 HYPERthyroidism: Treat with an initial dose of IV corticosteroids followed by oral corticosteroids (e.g., 0.5 to 1 mg/kg/day of prednisone or equivalent). Taper corticosteroids when symptoms improve to Grade 1 or less over no less than 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.

9.7.4.6. 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 or less over no less than 4 weeks.

9.7.4.7. 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 or less over no less than 4 weeks.

9.7.4.8. 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 16 shows treatment guidelines for patients who experience an infusion-related reaction associated with administration of TSR-042 and/or TSR-022.

Table 16: TSR-042 and TSR-022 Infusion Reaction Treatment Guidelines

CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the Investigator.	None.

CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, or IV fluids); prophylactic medications indicated for ≤24 h	Stop infusion and monitor symptoms. Additional appropriate medical therapy may include but is not limited to: • IV fluids • Antihistamines • NSAIDs • Acetaminophen • Narcotics Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the Investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/h to 50 mL/h). Otherwise, dosing will be withheld until symptoms resolve, and the patient should be premedicated for the next scheduled dose. Patients who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study treatment administration.	Patient may be premedicated 1.5 h (±30 min) prior to infusion of TSR-042 and/or TSR-022 with: • Diphenhydramine 50 mg PO (or equivalent dose of antihistamine) • Acetaminophen 500 to 1,000 mg PO (or equivalent dose of antipyretic)
Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) **Grade 4:** Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: • IV fluids • Antihistamines • NSAIDs • Acetaminophen • Narcotics • Oxygen • Pressors • Corticosteroids • Epinephrine Increase monitoring of vital signs as medically indicated until the patient is	No subsequent dosing.

CTCAE Grade	Treatment	Premedication at Subsequent Dosing
	deemed medically stable in the opinion of the Investigator. Hospitalization may be indicated. **Patient is permanently discontinued from further study treatment administration.**	

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

9.7.5. Other Study Restrictions

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

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

For Parts E and F, use caution in patients with mild to moderate renal insufficiency (creatinine clearance of 45 to 79 mL/min). Caution should be used when administering ibuprofen concurrently with pemetrexed to patients with mild to moderate renal insufficiency (creatinine clearance from 45 to 79 mL/min). Other NSAIDs should also be used with caution.

9.8. Treatment Compliance

Compliance with inclusion and exclusion criteria will be assessed as outlined in Section 7.1 and Section 7.2.

Carboplatin-paclitaxel, carboplatin-pemetrexed, carboplatin–nab-paclitaxel, TSR-042, TSR-022, and bevacizumab will be administered by site personnel at study sites as detailed in Section 9.2.

Study drug accountability will be monitored as detailed in Section 9.5.

10. ENDPOINTS AND METHODS OF ASSESSMENT

10.1. Efficacy Endpoints

10.1.1. Evaluation of Tumor Response

10.1.1.1. Overview

The efficacy of TSR-042 with niraparib combination treatment (Part A), TSR-042 with niraparib and bevacizumab combination treatment (Part C), TSR-042 and carboplatin-paclitaxel combination treatment (Part B), TSR-042 with carboplatin-paclitaxel and bevacizumab combination treatment (Part D), TSR-042 with carboplatin-pemetrexed combination treatment (Part E), and TSR-042 with TSR-022 and carboplatin-pemetrexed combination treatment (Part F), TSR-042 with carboplatin–nab-paclitaxel combination treatment (Part G), TSR-042 with TSR-022 and carboplatin–nab-paclitaxel combination treatment (Part H), and TSR-042 with TSR-022 and carboplatin-paclitaxel combination treatment (Part I) will be evaluated by assessment of tumor response to treatment according to RECIST v1.1[120] per Investigator assessment. Serum tumor marker data 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.

Tumor imaging (chest, abdomen, and pelvis [plus head if clinically indicated]) should be performed by CT (preferred). MRI should only be used 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. An MRI can be utilized if clinically appropriate. Positron emission tomography (PET)/CT may be used according to RECIST v1.1 guidelines. If the chest and/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.

10.1.1.2. Timing of Radiographic Evaluations

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

The first on-study imaging assessment will be performed at 12 weeks (84 ± 10 days) from the date of the first dose of study treatment. Subsequent tumor imaging should be performed every 12 weeks (84 ± 10 days) thereafter until progression while on study treatment, independent of cycle delays or dose interruptions, or at any time when progression of disease is suspected. CT or MRI of the head will be conducted if clinically indicated; bone scans will be conducted per standard of care. Imaging should not be delayed for delays in cycle starts or extension of combination treatment cycle intervals.

Per RECIST v1.1 (see Appendix B), CR or PR should be confirmed, and 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 (i.e., 12 weeks later), whichever is clinically indicated. Imaging should be continued until whichever of the following occurs:

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

There is accumulating evidence indicating clinical benefit in a subset of patients treated with immunotherapy despite initial evidence of progressive disease (PD).[121] Therefore, patients with initial radiologic evidence of PD who are clinically stable may continue study treatment at the Investigator's discretion while awaiting confirmatory tumor imaging. Confirmatory imaging of PD must be performed after initial evidence of PD. Patients with confirmed PD may continue study treatment at the Investigator's discretion 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 (e.g., every 12 weeks [84 ± 10 days]) until disease progression, start of a non–study anticancer treatment, withdrawal of consent to study participation, becoming lost to follow-up, death, or end of the study.

10.1.1.3. Assessment of Response by RECIST v1.1

RECIST v1.1 will be used by the Investigator as the primary measure for assessment of tumor response, date of disease progression, and as a basis for all protocol guidelines related to disease status.

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

10.1.2. Secondary Endpoints

10.1.2.1. Objective Response Rate

ORR will be evaluated as a secondary endpoint and is defined as the proportion of patients who have achieved confirmed CR or PR, evaluated using RECIST v1.1 (Appendix B) based on Investigator assessment. Tumor assessments after the initiation of further anticancer therapy are excluded for the assessment of best overall response.

10.1.2.2. Duration of Response

DOR will be evaluated as a secondary endpoint and is defined as the time from first documentation of response (CR or PR) until the time of first documentation of disease progression by RECIST v1.1 (Appendix B) or death by any cause.

10.1.2.3. Disease Control Rate

DCR will be assessed as a secondary endpoint and is defined as the percentage of patients who have achieved CR, PR, or stable disease (SD) per RECIST v1.1 (Appendix B).

10.1.2.4. Progression-Free Survival

PFS will be assessed as a secondary endpoint and is defined as the time from the date of the first dose of study treatment to the earlier date of assessment of progression, or death by any cause in the absence of progression by RECIST v1.1 (Appendix B).

10.2. Pharmacokinetic Assessments

Plasma and serum samples for PK determination will be collected from all patients enrolled in all parts of the study. All sampling times are relative to the start dose of the corresponding agent.

For Part A (TSR-042 and niraparib combination treatment) and Part C (TSR-042, niraparib, and bevacizumab combination treatment), plasma will be analyzed using liquid chromatography with mass spectrometry detection for niraparib and its major metabolite M1. The serum will be analyzed for TSR-042 using enzyme-linked immunosorbent assay (ELISA).

For Part B (TSR-042 and carboplatin-paclitaxel combination treatment), Part D (TSR-042, carboplatin-paclitaxel, and bevacizumab combination treatment), Part E (TSR-042 and carboplatin-pemetrexed combination treatment), Part F (TSR-042, TSR-022, and carboplatin-pemetrexed combination treatment), Part G (TSR-042 and carboplatin–nab-paclitaxel combination treatment), Part H (TSR-042, TSR-022, and carboplatin–nab-paclitaxel), and Part I (TSR-042, TSR-022, and carboplatin-paclitaxel), serum samples will be analyzed for TSR-042 and TSR-022 using ELISA. The plasma samples will be analyzed for carboplatin using inductively coupled plasma mass spectrometry, and for paclitaxel, pemetrexed, and nab-paclitaxel using liquid chromatography tandem-mass spectrometry, if appropriate.

10.3. Immunogenicity Assessments

Serum samples for the determination of TSR-042 and TSR-022 ADAs will be the same samples collected for TSR-042 and TSR-022 PK assessments. ADAs will be analyzed in a tiered approach using electrochemiluminescence (i.e., screening, confirmation, titer, and neutralizing antibody assay). Minimally, ADAs will be analyzed in predose samples from all cycles collected; additional samples for ADA determination will be collected upon treatment discontinuation at a safety follow-up visit (i.e., approximately 90 days after the last dose of TSR-042 and TSR-022).

10.4. Biomarker Assessments

FFPE tumor archival tissue samples (mandatory [if available] for Parts F, H, and I; optional for Parts A, B, C, D, E, and G) and blood samples will be assessed for biomarkers that may correlate with clinical benefit from TSR-042 and niraparib combination treatment (Part A); TSR-042 and carboplatin-paclitaxel combination treatment (Part B); TSR-042, niraparib, and bevacizumab combination treatment (Part C); TSR-042, carboplatin-paclitaxel, and bevacizumab combination treatment (Part D); TSR-042 and carboplatin-pemetrexed combination treatment (Part E); TSR-042, TSR-022, and carboplatin-pemetrexed combination treatment (Part F); TSR-042 and carboplatin–nab-paclitaxel combination treatment (Part G); TSR-042, TSR-022, and carboplatin–nab-paclitaxel combination treatment (Part H); and TSR-042, TSR-022, and carboplatin-paclitaxel combination treatment (Part I), including, but not limited to, g*BRCA*mut, HRD status, the phenotype and molecular profile of immune cells, expression of PD-L1 on tumor cells, and cytokines or chemokines prior to and during treatment. To enable these evaluations, blood samples for biomarker analysis will be obtained in Parts A, B, C, and D at the time of screening, at predose on Day 1 of Cycles 1 and 2, and at EOT or time of disease progression. Blood samples for biomarker analysis will be obtained in Parts E, F, G, H, and I at the screening visit, predose on Days 1 and 15 of Cycle 1 and predose on Day 1 of Cycles 2, 4, and 6, and at EOT or time of disease progression.

Biopsies are an integral component of this study to enable an assessment of the pharmacodynamic effects of TSR-042 in combination with niraparib, carboplatin-paclitaxel, bevacizumab, carboplatin-pemetrexed, and TSR-022, as well as to develop an understanding of the tumor micro-environment, including but not limited to immune cells, tumor characteristics, and immune-related gene and protein expression and how they relate to clinical response.

On-treatment and progression (EOT visit) biopsies are optional for patients in Parts E, F, G, H, and I. In the subset of patients who undergo serial biopsies, biomarkers will be evaluated in new tumor samples obtained at approximately 4 to 6 weeks after initiating study treatment and at time of disease progression (EOT visit). Evaluation of these tumor tissue samples may include but not be limited to analyses of immune cells, gene-expression profiling for immune-related and tumor-related proteins, and assessment of tumor genome for mutations and/or alterations. In addition to monitoring of the immune response, tumor cell characteristics may be correlated with other immune-related biomarkers and with clinical activity. Therefore, all patients should be considered for research tumor tissue biopsies, if it is deemed safe and clinically appropriate.

During screening, the Investigator will assess the feasibility of obtaining tumor tissue biopsies from each patient. Typically, this will require that the tumor lesions be superficially accessible, as occurs with some subcutaneous and lymph node metastases, or that the lesions can be safely biopsied under CT scan or ultrasound guidance. It is preferred that for tumor biopsies that are not simply incisional or excisional, a 16-gauge core biopsy needle is used; however, a smaller bore needle may be used if considered necessary for the patient's safety. Several core biopsies with the same smaller (than 16 gauge) needle need to be obtained. Fine needle biopsies are not recommended for this study. Pleural effusions or lung aspirate samples cannot be substituted for tumor biopsies. Patients undergoing tumor biopsy must have PT/aPTT $\leq 1.5 \times$ ULN. Details on sample collection and management are provided in the Study Laboratory Manual.

10.5. Use of Remaining Study Patient Specimens/Samples

Following the conclusion of the study, patient samples that have not been depleted may be stored and used for future additional research. This research will help understand disease subtypes, drug response, and toxicity, and possibly to identify new biomarkers that predict subject response to treatment. This use of the samples for internal research will be done in accordance with the guidelines defined by the FDA document "Guidance on Informed Consent for In Vitro Diagnostic Device Studies Using Leftover Human Specimens that are Not Individual Identifiable"[122] and European Medicines Agency's (EMEA's) Reflection Paper on Pharmacogenetic Samples, Testing, and Data Handling.[123] If a patient requests destruction of their tissue and blood samples and the samples have not yet been de-identified, the sponsor (or central laboratory) will destroy the samples as described in this FDA guidance. The sponsor (or central laboratory) will notify the investigator in writing that the samples have been destroyed.

10.6. Safety Endpoints

Safety parameters evaluated during the conduct of the study include TEAEs, clinical laboratory values (hematology, serum chemistry, coagulation, thyroid function, and urinalysis), vital signs, ECGs, physical examination findings, and use of concomitant medications.

All safety parameters will be performed in accordance with the schedules of events (Section 11.1).

10.6.1. Definitions

10.6.1.1. Adverse Event (AE)

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

AEs may include the onset of new illness and the exacerbation of pre-existing medical conditions. An AE can include an undesirable medical condition occurring at any time after the time of randomization and/or treatment assignment, including baseline or washout periods, even if no study treatment has been administered. (See Section 10.6.3 for information about AE collecting and reporting.)

10.6.1.2. Serious Adverse Event (SAE)

Any untoward medical occurrence that, at any dose;

- Results in death;
- Is life threatening (i.e., an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe);
- Requires inpatient hospitalization* or prolongation of existing hospitalization;

- Results in persistent or significant disability/incapacity;
- Is a congenital anomaly/birth defect; or
- Is an important medical event**

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

**Medical and scientific judgment should be exercised in determining whether situations or events should be considered serious adverse events: an important medical event may not be immediately life-threatening or result in death or require hospitalization but may jeopardize the patient or require intervention to prevent one of the above outcomes. Examples of such events are allergic bronchospasm, blood dyscrasias, or convulsions that may require intensive treatment in an emergency room or at home but do not result in hospitalization, development of drug dependency or drug abuse, and transmission of disease associated with the administration of the study drug. (See Section 10.6.5 for information about SAE reporting.)

10.6.1.3. Treatment-Emergent Adverse Event (TEAE)

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

10.6.1.4. Adverse Event of Special Interest (AESI)

Any AE (serious or non-serious) that is of scientific and medical concern specific to the study treatment, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor is appropriate. AESIs are described in Section 10.6.7.

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

- **Abuse:** is the persistent or sporadic, intentional excessive use of the study treatment which is accompanied by harmful physical or psychological effects.
- **Misuse:** medicinal product is intentionally and inappropriately used not in accordance with the authorized/approved product information.
- **Medication error:** is any preventable incident that may cause or lead to inappropriate study treatment use or patient harm while the study treatment is in the control of the health care professionals or patients. Such incident may be due to health care professional practice, product labeling, packaging and preparation, procedures for administration, and systems, including the following: prescribing, order communication, nomenclature, compounding, dispensing, distribution, administration, education, monitoring, and use.
- **Overdose:** is a deliberate or accidental administration of study treatment to a study patient, at a dose greater than that which was assigned to that patient per the study

protocol and under the direction of the Investigator. If an overdose occurs, the Investigator and the Sponsor should be notified immediately, and the patient should be observed closely for AEs. Associated AEs should be treated and monitored by the Investigator. The dosage of study drug administered, any associated AEs, and/or treatment provided to the patient because of the overdose, should be documented on the applicable sections within the eCRF. An overdose (including an AE or SAE resulting from the overdose, if any) will be reported as described in Section 10.6.5.

- **Accidental /Occupational exposure:** is the unintentional exposure to a study treatment as a result of one's professional or non-professional occupation, or accidental exposure to a non-professional to whom exposure was not intended (i.e., study product given to wrong patient).

Reporting Special Situations: All occurrences of abuse, misuse, medication error, overdose, and accidental or occupational exposure with any study treatment must be reported on an SAE Report Form [or designated Special Form] to the Sponsor regardless of whether or not an AE or SAE has occurred. If the abuse, misuse, medication error, overdose, or accidental / occupational exposure is associated with an SAE, an SAE report form must be submitted to the Sponsor within 24 hours of awareness. If there is no AE or SAE, the occurrence must be submitted on the designated Special Form (indicate 'no AE has occurred') as soon as possible.

10.6.2. Assessment of Adverse Events

10.6.2.1. Severity Assessment

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

Please note that there is a distinction between **serious** and **severe** AEs: Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 10.6.1.2. For example, a mild degree of gastrointestinal bleeding requiring an overnight hospitalization for monitoring purposes may be considered an SAE but is not necessarily severe.

10.6.2.2. Relationship to Study Intervention

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

- Related: A causal relationship between the medicinal product (and/or study procedures) and AE is a reasonable possibility. For example, the occurrence of the AE cannot be explained by other causative factors. The AE, however, can be explained by pharmacological effect of the medicinal product such as a similar event having been reported previously, alteration of the dose effect, or the timing or seriousness of the AE, etc. Positive rechallenge/dechallenge is supportive.

- Not Related: A causal relationship between the medicinal product (and/or study procedures) and AE is not a reasonable possibility: there is no temporal relationship between the medicinal product and event, or an alternative etiology is more reasonable.

10.6.2.3. Expectedness

The Sponsor will be responsible for determining whether an adverse event is 'expected' or 'unexpected'. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information provided in the Reference Safety Information of the effective niraparib or TSR-042 Investigator Brochure (IB).

For carboplatin, paclitaxel, or bevacizumab, the local approved product label should be consulted.

10.6.3. Collection and Recording Adverse Events

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

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

All SAEs will be collected from the signing of the ICF for this study through 90 days after the last dose of study drug (or to a minimum of 30 days post-treatment if the patient starts alternate anticancer therapy) and recorded in the eCRF. SAEs will also be reported on an SAE form as described in Section 10.6.5 of this protocol. SAEs considered by the Investigator to be related to study medication are reported until study closeout.

All AEs, regardless of the source of identification (e.g., physical examination, laboratory assessment, ECG, or reported by patient), will be collected and recorded in the eCRF for each patient from the time of randomization and/or treatment assignment until 30 days after the last dose of study drug.

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

Disease progression is an efficacy criterion and is therefore not considered an AE or SAE (even if fatal). Disease progression should be reported within the eCRF. If AEs/SAEs occur in relation to disease progression that are not consistent with the natural progression of the patient's disease, these AEs/SAEs must be reported per AE/SAE reporting requirements described in Section 10.6.5.

10.6.4. Follow-Up of Adverse Events

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

If an Investigator becomes aware of an SAE after the specified follow-up period and considers the SAE related to the study drug, the Investigator should report the SAE to the Sponsor according to timelines for reporting SAEs described in Section 10.6.5.

10.6.5. Reporting

The Investigator or sub-investigator must report all SAEs, and all follow up information to the Sponsor on an SAE Report Form within 24 hours of becoming aware of the initial event or follow-up information. The Investigator must provide a causality assessment and must sign and date all SAE Report Forms.

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

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

10.6.6. Submission and Distribution of Serious Adverse Event Reports

Per regulatory requirements, if an event is assessed by the Sponsor as a Serious Unexpected Adverse Reaction (SUSAR), it is the responsibility of the Sponsor to submit the SUSAR Regulatory Authorities according to applicable regulations.

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

10.6.7. Adverse Events of Special Interest

10.6.7.1. Niraparib

Adverse Events of Special Interest (AESI) for niraparib are the following:

- Myelodysplastic Syndromes (MDS) and Acute Myeloid Leukemia (AML)
- Secondary cancers (new malignancies [other than MDS or AML])

- Pneumonitis
- Embryo-fetal toxicity

AESI should be collected and reported as follows:

- MDS and AML along with other secondary cancers should be reported to the Sponsor throughout the Follow-up Assessment Period
- Pneumonitis should be reported to the Sponsor through 90 days after the last dose of study drug (or until the start of alternate anticancer therapy, whichever occurs first).
- Embryo-fetal toxicity should be reported as outlined in Section 10.6.8

10.6.7.2. TSR-042

No AESIs have been reported to date, therefore all SAEs 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 Section 10.6.5.

10.6.7.3. TSR-022

No AESIs have been reported to date, therefore all SAEs assessed by the Investigator or Sponsor to be reasonably associated with the use of TSR-022 are considered to be unexpected and should be reported as described in Section 10.6.5.

10.6.8. Pregnancy

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

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

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

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

10.6.9. Special Situations

All occurrences of abuse, misuse, medication error, overdose, and accidental or occupational exposure with any study treatment must be reported on a Special Situations Report Form to the Sponsor within 5 calendar days of becoming aware of the occurrence, regardless of whether it is categorized as an AE. If the occurrence is associated with an SAE, an SAE Report Form, along with the Special Situations Report Form, must be submitted to the Sponsor within 24 hours of awareness.

10.6.10. Clinical Laboratory Assessments

The following laboratory variable will be determined in accordance with the schedule of events in (Section 11). These tests will be performed by the local laboratory at the clinical site. Details on sample collection, processing, and management for clinical laboratory assessments can be found in the Study Laboratory Manual.

Any laboratory values assessed as clinically significant should be recorded as an AE. If SAE criteria are met or the laboratory abnormality is an AESI (see Section 10.6.7), the AE should be recorded and reported according to the SAE reporting process (see Section 10.6.5).

Hematological testing may occur more frequently than is specified in Section 11.1 when additional testing is medically indicated per Investigator judgment or if the AE meets the criteria for niraparib dose modification (see Section 6.4.1.1). Additional tests may be performed at a laboratory facility other than the study site, but test results must be reported to the study site. The study site must keep a copy of test results with the patient's study file, and the results must be entered into the eCRF.

The following clinical laboratory assessments will be performed:

- **Complete blood count:**
  - Hemoglobin
  - Platelets
  - Mean corpuscular volume
  - White blood cell count
  - Differential white cell count
  - Mean platelet volume (optional; Note: Although mean platelet volume collection is optional, it is highly encouraged, especially for patients with high-grade thrombocytopenia.)
- **Coagulation factors:**
  - International normalized ratio
  - aPTT
- **Serum chemistry:**
  - Sodium
  - Amylase
  - Chloride
  - Glucose (fasting at baseline)

  - Potassium
  - Total bilirubin
  - Calcium
  - Alkaline phosphatase
  - Magnesium
  - AST
  - ALT
  - Total protein
  - Creatinine
  - Albumin
  - Urea or blood urea nitrogen
  - Lactate dehydrogenase
- **Urinalysis:**
  - Specific gravity
  - Protein
  - Leukocyte esterase
  - Glucose
  - Nitrite
  - Ketones
  - Blood
  - Specific gravity
  - Protein
- Thyroid panel: thyroid stimulating hormone (TSH), triiodothyronine (T3) or free triiodothyronine (FT3), and free thyroxine (FT4) or equivalent tests if TSH, T3 or FT3, or FT4 are not available
- Serum pregnancy testing/urine pregnancy testing
- HBsAg and HCV ribonucleic acid testing (performed at screening only when medically indicated based on history and physical examination)

10.6.11. Physical Examination and Vital Signs

Physical examinations, including height (screening only), weight, and vital signs (blood pressure [BP], pulse, and temperature), will be performed in accordance with the schedule of events (Section 11).

Any physical examination or vital signs assessed as clinically significant should be recorded as an AE or SAE. If SAE criteria are met or the abnormality is an AESI (see Section 10.6.7), the event should be recorded and reported according to the SAE reporting process (see Section 10.6.5).

Vital signs will be measured in all patients and include BP, pulse rate, and temperature. Height and weight will be measured in all patients. Height will be measured at screening only.

10.6.12. Eastern Cooperative Oncology Group Performance Status

Performance status will be assessed using the ECOG scale (see Appendix C) in accordance with the schedule of events (Section 11). The same observer should assess performance status each time.

10.6.13. Additional Safety Assessments

All patients will undergo ECGs in accordance with the schedule of events (Section 11). ECGs should be performed prior to any blood draws. Patients will be supine or in a semi-recumbent position (about 30 degrees of elevation) and rested for approximately 2 minutes before ECGs are recorded.

Any ECG findings assessed as clinically significant should be recorded as an AE. If SAE criteria are met or the abnormality is an AESI (see Section 10.6.7), the AE should be recorded and reported according to the SAE reporting process (see Section 10.6.5).

10.7. Demographics and Baseline Characteristics

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

10.7.1. Patient Eligibility

Compliance with inclusion and exclusion criteria will be assessed as outlined in Section 7.1 and Section 7.2.

10.7.2. Patient Demography

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

10.7.3. Disease History

For disease history the following will be documented:

- Date of first diagnosis
- Tumor type
- Stage at time of initial diagnosis
- Histology and grade of disease at diagnosis and most recent biopsy if additional biopsy performed
- Information on first anticancer treatment:
  - Intent (adjuvant, neoadjuvant, curative, and palliative)
  - Date of start of first treatment
  - Agents used in first treatment
  - Date of last dose of first treatment
- Information on second and subsequent anticancer treatments:
  - Intent (adjuvant, neoadjuvant, curative, and palliative)
  - Dates of start of all subsequent treatments
  - Agents in all subsequent treatments
  - Dates of last dose of all subsequent treatments

- Best response and toxicities (including hematologic AEs) for each prior anticancer treatment
- Date of recurrence for each prior anticancer treatment

10.7.4. Medical and Surgical History

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

10.7.5. Previous and Concomitant Medications

Previous and concomitant medication will be documented as described in Section 9.7. Medications will be coded using WHO Anatomical Therapeutic Chemical classification.

11. STUDY CONDUCT

11.1. Schedule of Events

The schedule of study procedures is provided in Table 17 and Table 18 for Part A, in Table 19 and Table 20 for Part B, in Table 21 and Table 22 for Part C, in Table 23 and Table 24 for Part D, in Table 25 and Table 26 for Part E, in Table 27 and Table 28 for Part F, in Table 29 and Table 30 for Part G, in Table 31 and Table 32 for Part H, and in Table 33 and Table 34 for Part I.

The detailed schedule for PK and ADA sampling and ECG assessments is provided in Table 35 and Table 36 for Part A, in Table 37 and Table 38 for Part B, in Table 39 and Table 40 for Part C, in Table 41 and Table 42 for Part D, in Table 43 for Part E, in Table 44 for Part F, in Table 45 for Part G, in Table 46 for Part H, and in Table 47 for Part I.

The detailed schedules of administration are provided for TSR-042 and niraparib combination treatment in Part A (Table 48); for TSR-042 and carboplatin-paclitaxel combination treatment in Part B (Table 49); for TSR-042, niraparib, and bevacizumab combination treatment in Part C (Table 50); for TSR-042, carboplatin-paclitaxel, and bevacizumab combination treatment in Part D (Table 51); for TSR-042 and carboplatin-pemetrexed combination treatment in Part E (Table 52); for TSR-042, TSR-022, and carboplatin-pemetrexed combination treatment in Part F (Table 53); for TSR-042 and carboplatin–nab-paclitaxel in Part G (Table 54); for TSR-042, TSR-022, and carboplatin–nab-paclitaxel in Part H (Table 55); and for TSR-042, TSR-022, and carboplatin-paclitaxel in Part I (Table 56).

Table 17: Schedule of Events - Part A - TSR-042 + Niraparib- Screening and Cycle 1 Through Cycle 4

Cycle/Visit[a]	**Screening**	**Cycle 1**			**Cycle 2**	**Cycle 3**	**Cycle 4**
Day: **Procedure**	**-28 to -1**	**1**	**8**	**15**	**1**	**1**	**1**
Informed consent	X						
Inclusion/exclusion criteria review	X	X					
Demographics	X						
Medical, surgical, cancer, and medication history	X						
Archival FFPE tumor tissue sample (optional)[b]	X						
Blood sample for exploratory biomarkers	X	X[c]			X[c]		
Blood sample for PK and ADAs[d]		X	X	X	X		X
Tumor assessment (RECIST v1.1)[e]	X[f]						
Laboratory assessments	X[f]	X[g]	X	X	X[h]	X[h]	X[h]
CBC[i]	X	X	X	X	X	X	X
Serum chemistry	X	X		X	X	X	X
Coagulation	X			X	X	X	
Pregnancy test	X[j]						X[k]
Serum tumor markers (if indicated)[e]	X	X					X
Urinalysis	X	X			X	X	X
TSH, T3 or FT3, and FT4 or equivalent[l]	X				X		X
ECG[d]	X[f]	X			X		
Physical examination	X[f]						
Symptom-directed physical examination		X		X	X	X	X
Vital signs, height, and weight[m]	X[f]	X	X	X	X	X	X

Table 17: Schedule of Events - Part A - TSR-042 + Niraparib- Screening and Cycle 1 Through Cycle 4 (Continued)

Cycle/Visit[a]	Screening	Cycle 1			Cycle 2	Cycle 3	Cycle 4
Day: Procedure	-28 to -1	1	8	15	1	1	1
ECOG performance status	X				X	X	X
Concomitant medications	X	X	X	X	X	X	X
AE monitoring[n]	X	X	X	X	X	X	X
TSR-042 study treatment administered[o]		X			X	X	X
Niraparib study treatment dispensed/collected[o]		X			X	X	X

Abbreviations: ADA = anti-drug antibody; AE = adverse event; CBC = complete blood count; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; FFPE = formalin-fixed paraffin embedded; FT3 = free triiodothyronine; FT4 = free thyroxine; PK = pharmacokinetics; Q3W = every 3 weeks; Q6W = every 6 weeks; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1; 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.

[b] Archival FFPE tumor tissue sample should be submitted within 30 days of patient's first dose.

[c] Obtained predose.

[d] PK and ADA blood sampling and ECG assessment will be conducted on additional days during treatment cycles according to the cycle number and agent. Full details on PK and ADA blood sampling and ECG assessments are provided in Table 35. On Day 1 of Cycles 1 and 2, ECG monitoring is to be done 30 minutes prior to and 2 hours after the niraparib dose.

[e] Tumor assessment per RECIST v1.1 and appropriate testing of serum tumor markers will be performed as described in Section 11.2.1 and Section 11.2.3.

[f] Standard of care tests/procedures, including radiographic scans, laboratory assessments (fasting glucose at baseline), ECG, physical examination, vital signs, height, and weight, will be performed as described in Section 11.2.1.

[g] If screening laboratory testing (CBC, serum chemistry, serum tumor markers [if indicated], urinalysis, 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] May be done within 24 hours prior to the visit.

[i] If dose interruption or modification of niraparib is required at any point on study because of hematologic toxicity, CBCs will be performed as described in Section 6.4.1.1.

[j] For women of childbearing potential only. Serum pregnancy test must be performed within 72 hours of the first dose of study treatment (see Section 11.2.1).

[k] Performed as described in Section 11.2.3.

[l] If TSH, T3 or FT3, or FT4 are not available, equivalent tests should be performed.

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

[n] AEs are required to be captured through 30 days after cessation of study treatment, SAEs (see Section 10.6.5) 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), AESIs are required to be captured as described in Section 10.6.7, and any pregnancies that occur within 180 days post-treatment are to be captured.

[o] See Table 48 for details of TSR-042 and niraparib combination treatment administration in Part A. TSR-042 will be administered at a dose of 500 mg on Day 1 on Day 1 of every cycle (Q3W) for 4 cycles, followed by 1,000 mg beginning on Cycle 5 Day 1 and every other cycle (Q6W) thereafter for up to 2 years or until progression, unacceptable toxicity, patient withdrawal, Investigator's decision, or death.. Niraparib will be dispensed/collected on Day 1 of every 21-day cycle (Q3W).

Table 18: Schedule of Events - Part A - TSR-042 + Niraparib - Cycle 5 Through End of Study

Cycle/Visit[a]	**Cycle 5**	**Cycle 6**	**Subsequent Cycles**	**EOT**	**Safety Follow-Up**[b]		**Survival Assessment (Every 90 ± 14 Days)**
Day: **Procedure**	**1**	**1**	**1**	**+7 Days Post-treatment**	**30 ± 7 Days Post-treatment**	**90 ± 7 Days Post-treatment**	
Blood sample for exploratory biomarkers				X[c]			
Blood sample for PK and ADAs[d]	X	X	X	X[e]	X[e]	X[e]	
Tumor assessment (RECIST v1.1)[f,g]	X		X	X	X	X	X
Laboratory assessments	X[h]	X[h]	X[h]	X	X[i]	X[i]	X
CBC[j]	X	X	X	X			
Serum chemistry	X	X	X	X[k]	X	X	
Pregnancy test			X[k]		X[i]		
Serum tumor markers (if indicated)	X		X	X	X	X	X
Urinalysis	X	X	X	X	X		
TSH, T3 or FT3, and FT4 or equivalent[l]		X[k]	X[k]	X	X		
ECG[d]	X		X	X			
Physical examination				X			
Symptom-directed physical examination	X	X	X		X		
Vital signs and weight[m]	X	X	X	X	X		
ECOG performance status	X	X	X	X			
Concomitant medications	X	X	X	X	X		
AE monitoring[n]	X	X	X	X	X	X	X

Table 18: Schedule of Events - Part A - TSR-042 + Niraparib - Cycle 5 Through End of Study (Continued)

Cycle/Visit	Cycle 5	Cycle 6	Subsequent Cycles	EOT	Safety Follow-Up		Survival Assessment (Every 90 ± 14 Days)
Day: / Procedure	1	1	1	+7 Days Post-treatment	30 ± 7 Days Post-treatment	90 ± 7 Days Post-treatment	
TSR-042 study treatment administered[o]	X		X				
Niraparib study treatment dispensed/collected[o]	X	X	X	X			
Survival assessment							X

Abbreviations: ADA = anti-drug antibody; AE = adverse event; AESI = adverse event of special interest; CBC = complete blood count; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; FT3 = free triiodothyronine; FT4 = free thyroxine; EOT = end of treatment; PK = pharmacokinetics; Q3W = every 3 weeks; Q6W = every 6 weeks; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1; 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.

[b] Safety follow-up visits are required only for those patients who have not started an alternate anticancer therapy as described in Section 11.2.5.

[c] Obtained at End of Treatment visit. EOT visit will occur within 7 days of study treatment discontinuation or at the time of disease progression, whichever occurs first.

[d] PK and ADA blood sampling and ECG assessment will be conducted on additional days during treatment cycles according to the cycle number and agent. Full details on PK and ADA blood sampling and ECG assessments are provided in Table 36. On Day 1 of Cycles 5 and 11, ECG monitoring is to be done 30 minutes prior to the niraparib dose.

[e] Blood sample for ADAs only.

[f] Tumor assessment per RECIST v1.1 and appropriate testing of serum tumor markers will be performed as described in Section 11.2.3 . Tumor assessments are to be performed within 1 week prior to Day 1 of Cycle 5.

[,g] Upon study treatment discontinuation, tumor assessment and appropriate testing of serum tumor markers will be performed as described in Section 11.2.4. If a patient discontinued treatment for a reason other than progression or death, withdrawal of consent, or loss to follow-up, radiographic scans and appropriate testing of serum tumor markers testing should continue at the specified intervals as described in Section 11.2.5 and Section 11.2.6 for the safety follow-up visits and survival assessment, respectively.

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

[i] Performed as described in Section 11.2.5.

[j] If dose interruption and/or modification of niraparib is required at any point on study because of hematologic toxicity, CBCs will be performed as described in Section 6.4.1.1.

[k] Performed as described in Section 11.2.3.

[l] If TSH, T3 or FT3, or FT4 are not available, equivalent tests should be performed. TSH testing will be done at screening; Cycles 2, 4, and 6; and every other cycle thereafter.

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

[n] AEs are required to be captured through 30 days after cessation of study treatment, SAEs (see Section 10.6.5) 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), AESIs are required to be captured as described in Section 10.6.7, and any pregnancies that occur within 180 days post treatment are to be captured. In conjunction with the survival assessment, AESI (regardless of causality) and study-drug related SAEs will be collected every 90 ± 14 days after the last dose of study treatment.

[o] See Table 48 for details of TSR-042 and niraparib combination treatment administration in Part A. TSR-042 will be administered at a dose of 500 mg on Day 1 on Day 1 of every cycle (Q3W) for 4 cycles, followed by 1,000 mg beginning on Cycle 5 Day 1 and every other cycle (Q6W) thereafter for up to 2 years or until progression, unacceptable toxicity, patient withdrawal, Investigator's decision, or death. Niraparib will be dispensed/collected on Day 1 of every 21-day cycle (Q3W).

Table 19: Schedule of Events - Part B – TSR-042 + Carboplatin-Paclitaxel - Screening and Cycle 1 Through Cycle 4

Cycle/Visit[a]	**Screening**	**Cycle 1**			**Cycle 2**	**Cycle 3**	**Cycle 4**
Day: **Procedure**	**-28 to -1**	**1**	**8**	**15**	**1**	**1**	**1**
Informed consent	X						
Inclusion/exclusion criteria review	X	X					
Demographics	X						
Medical, surgical, cancer, and medication history	X						
Archival FFPE tumor tissue sample (optional)[b]	X						
Blood sample for exploratory biomarkers	X	X[c]			X[c]		
Blood sample for PK and ADAs[d]		X	X	X	X		X
Tumor assessment (RECIST v1.1)[e]	X[f]						
Laboratory assessments	X[f]	X[g]	X	X	X[h]	X[h]	X[h]
CBC	X	X	X	X	X	X	X
Serum chemistry	X	X		X	X	X	X
Coagulation	X			X	X	X	
Pregnancy test	X[i]						X[j]
Serum tumor markers (if indicated)[e]	X	X					X
Urinalysis	X	X			X	X	X
TSH, T3 or FT3, and FT4 or equivalent[k]	X				X		X
ECG[d]	X[f]						
Physical examination	X[f]						
Symptom-directed physical examination		X		X	X	X	X
Vital signs, height, and weight[l]	X[f]	X	X	X	X	X	X

Table 19: Schedule of Events - Part B – TSR-042 + Carboplatin-Paclitaxel - Screening and Cycle 1 Through Cycle 4 (Continued)

Cycle/Visit[a]	Screening	Cycle 1			Cycle 2	Cycle 3	Cycle 4
Day: / Procedure	-28 to -1	1	8	15	1	1	1
ECOG performance status	X				X	X	X
Concomitant medications	X	X	X	X	X	X	X
AE monitoring[m]	X	X	X	X	X	X	X
TSR-042 study treatment administered[n]		X			X	X	X
Carboplatin-paclitaxel study treatment administered[n]		X			X	X	X

Abbreviations: ADA = anti-drug antibody; AE = adverse event; CBC = complete blood count; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; FFPE = formalin-fixed paraffin embedded; FT3 = free triiodothyronine; FT4 = free thyroxine; PK = pharmacokinetics; Q3W = every 3 weeks; Q6W = every 6 weeks; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1; 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.

[b] Archival FFPE tumor tissue sample should be submitted within 30 days of patient's first dose.

[c] Obtained predose.

[d] PK and ADA blood sampling will be conducted on additional days during treatment cycles according to the cycle number and agent. Full details on PK and ADA blood sampling and ECG assessments are provided in Table 37 for Part B.

[e] Tumor assessment per RECIST v1.1 and appropriate testing of serum tumor markers will be performed as described in Section 11.2.1 and Section 11.2.3.

[f] Standard of care tests/procedures, including radiographic scans, laboratory assessments (fasting glucose at baseline), ECG, physical examination, vital signs, weight, and height, will be performed as described in Section 11.2.1.

[g] If screening laboratory testing (CBC, serum chemistry, serum tumor markers [if indicated], urinalysis, 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] May be done within 24 hours prior to the visit.

[i] For women of childbearing potential only. Serum pregnancy test must be performed within 72 hours of the first dose of study treatment (see Section 11.2.1).

[j] Performed as described in Section 11.2.3.

[k] If TSH, T3 or FT3, or FT4 are not available, equivalent tests should be performed. TSH testing will be done at screening; Cycles 2, 4, and 6; and every other cycle thereafter.

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

[m] AEs are required to be captured through 30 days after cessation of study treatment, SAEs (see Section 10.6.5) 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), AESIs are required to be captured as described in Section 10.6.7, and any pregnancies that occur within 180 days post-treatment are to be captured.

[n] See Table 49 for details of TSR-042 and carboplatin-paclitaxel combination treatment administration in Part B. TSR-042 will be administered at a dose of 500 mg on Day 1 of every cycle (Q3W) for 4 cycles, followed by 1,000 mg beginning on Cycle 5 Day 1 and every other cycle (Q6W) thereafter for up to 2 years or until progression, unacceptable toxicity, patient withdrawal, Investigator's decision, or death. Carboplatin and paclitaxel will be administered for 4 to 6 cycles as clinically indicated.

Table 20: Schedule of Events - Part B – TSR-042 + Carboplatin-Paclitaxel - Cycle 5 Through End of Study

Cycle/Visit[a]	**Cycle 5**	**Cycle 6**	**Subsequent Cycles**	**EOT**	**Safety Follow-Up**[b]		**Survival Assessment (Every 90 ± 14 Days)**
Day: **Procedure**	**1**	**1**	**1**	**+7 Days Post-treatment**	**30 ± 7 Days Post-treatment**	**90 ± 7 Days Post-treatment**	
Blood sample for exploratory biomarkers				X[c]			
Blood sample for PK and ADAs[d]	X	X	X	X[e]	X[e]	X[e]	
Tumor assessment (RECIST v1.1)[f]	X		X	X[g]	X[g]	X[g]	X[g]
Laboratory assessments	X[h]	X[h]	X[h]	X	X[i]	X[i]	X
CBC	X	X	X	X			
Serum chemistry	X	X	X	X[j]	X	X	
Pregnancy test			X		X[i]		
Serum tumor markers (if indicated)[f]	X		X	X	X	X	X
Urinalysis	X	X	X	X	X		
TSH, T3 or FT3, and FT4 or equivalent[k]		X[j]	X[j]	X	X		
ECG[d]				X			
Physical examination				X			
Symptom-directed physical examination	X	X	X		X		
Vital signs and weight[l]	X	X	X	X	X		
ECOG performance status	X	X	X	X			
Concomitant medications	X	X	X	X	X		

Table 20: Schedule of Events - Part B – TSR-042 + Carboplatin-Paclitaxel - Cycle 5 Through End of Study (Continued)

Cycle/Visit	Cycle 5	Cycle 6	Subsequent Cycles	EOT	Safety Follow-Up		Survival Assessment (Every 90 ± 14 Days)	
Day: / Procedure	1	1	1	+7 Days Post-treatment	30 ± 7 Days Post-treatment	90 ± 7 Days Post-treatment		
AE monitoring[m]	X	X	X	X	X	X	X	
TSR-042 study treatment administered[n]	X		X					
Carboplatin-paclitaxel study treatment administered[n]	X	X						
Survival assessment							X	

Abbreviations: ADA = anti-drug antibody; AE = adverse event; AESI = adverse event of special interest; CBC = complete blood count; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; FT3 = free triiodothyronine; FT4 = free thyroxine; EOT = end of treatment; PK = pharmacokinetics; Q3W = every 3 weeks; Q6W = every 6 weeks; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1; 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.

[b] Safety follow-up visits are required only for those patients who have not started an alternate anticancer therapy as described in Section 11.2.5.

[c] Obtained at EOT visit. EOT visit will occur within 7 days of study treatment discontinuation or at the time of disease progression, whichever occurs first.

[d] PK and ADA blood sampling will be conducted on additional days during treatment cycles according to the cycle number and agent. Full details on PK and ADA blood sampling and ECG assessments are provided in Table 38 for Part B.

[e] Blood sample for ADAs only.

[f] Tumor assessment per RECIST v1.1 and appropriate testing of serum tumor markers will be performed as described in Section 11.2.3. Tumor assessments are to be performed within 1 week prior to Day 1 of Cycle 5 and every 12 weeks (84 ± 10 days) thereafter until progression while on study treatment, independent of cycle delays or dose interruptions, or at any time when progression of disease is suspected.

[g] Upon study treatment discontinuation, tumor assessment and appropriate testing of serum tumor markers will be performed as described in Section 11.2.4. If a patient discontinued treatment for a reason other than progression or death, withdrawal of consent, or loss to follow-up, radiographic scans and appropriate testing of serum tumor markers testing should continue at the specified intervals as described in Section 11.2.5 and Section 11.2.6for the safety follow-up visits and survival assessment, respectively.

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

[i] Performed as described in Section 11.2.5.

[j] Performed as described in Section 11.2.3.

[k] If TSH, T3 or FT3, or FT4 are not available, equivalent tests should be performed. TSH testing will be done at screening; Cycles 2, 4, and 6; and every other cycle thereafter.

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

[m] AEs are required to be captured through 30 days after cessation of study treatment, SAEs (see Section 10.6.5) 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), AESIs are required to be captured as

described in Section 10.6.7, and any pregnancies that occur within 180 days post treatment are to be captured. In conjunction with the survival assessment, AESI (regardless of causality) and study-drug related SAEs will be collected every 90 ± 14 days after the last dose of study treatment.

[n] See Table 49 for details of TSR-042 and carboplatin-paclitaxel combination treatment administration in Part B. TSR-042 will be administered at a dose of 500 mg on Day 1 of every cycle (Q3W) for 4 cycles, followed by 1,000 mg beginning on Cycle 5 Day 1 and every other cycle (Q6W) thereafter for up to 2 years or until progression, unacceptable toxicity, patient withdrawal, Investigator's decision, or death. Carboplatin and paclitaxel will be administered for 4 to 6 cycles as clinically indicated.

Table 21: Schedule of Events - Part C - TSR-042 + Niraparib + Bevacizumab - Screening and Cycle 1 Through Cycle 4

Cycle/Visit[a]	Screening	Cycle 1			Cycle 2	Cycle 3	Cycle 4
Day: Procedure	-28 to -1	1	8	15	1	1	1
Informed consent	X						
Inclusion/exclusion criteria review	X	X					
Demographics	X						
Medical, surgical, cancer, and medication history	X						
Archival FFPE tumor tissue sample (optional)[b]	X						
Blood sample for exploratory biomarkers	X	X[c]			X[c]		
Blood sample for PK and ADAs[d]		X	X	X	X		X
Tumor assessment (RECIST v1.1)[e]	X[f]						
Laboratory assessments	X[f]	X[g]	X	X	X[h]	X[h]	X[h]
CBC[i]	X	X	X	X	X	X	X
Serum chemistry	X	X		X	X	X	X
Coagulation	X			X	X	X	
Pregnancy test	X[j]						X[k]
Serum tumor markers (if indicated)[e]	X	X					X
Urinalysis	X	X			X	X	X
TSH, T3 or FT3, and FT4 or equivalent[l]	X				X		X
ECG[d]	X[f]	X			X		
Physical examination	X[f]						
Symptom-directed physical examination		X		X	X	X	X
Vital signs, height, and weight[m]	X[f]	X	X	X	X	X	X

Table 21: Schedule of Events - Part C - TSR-042 + Niraparib + Bevacizumab - Screening and Cycle 1 Through Cycle 4 (Continued)

Cycle/Visit[a]	Screening	Cycle 1			Cycle 2	Cycle 3	Cycle 4
Day: / Procedure	-28 to -1	1	8	15	1	1	1
ECOG performance status	X				X	X	X
Concomitant medications	X	X	X	X	X	X	X
AE monitoring[n]	X	X	X	X	X	X	X
TSR-042 study treatment administered[o]		X			X	X	X
Niraparib study treatment dispensed/collected[o]		X			X	X	X
Bevacizumab[o]		X			X	X	X

Abbreviations: ADA = anti-drug antibody; AE = adverse event; CBC = complete blood count; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; FFPE = formalin-fixed paraffin embedded; FT3 = free triiodothyronine; FT4 = free thyroxine; PK = pharmacokinetics; Q3W = every 3 weeks; Q6W = every 6 weeks; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1; 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.

[b] Archival FFPE tumor tissue sample should be submitted within 30 days of patient's first dose.

[c] Obtained predose.

[d] PK and ADA blood sampling and ECG assessment will be conducted on additional days during treatment cycles according to the cycle number and agent. Full details on PK and ADA blood sampling and ECG assessments are provided in Table 39 for Part C. On Day 1 of Cycles 1 and 2, ECG monitoring is to be done 30 minutes prior to and 2 hours after the niraparib dose.

[e] Tumor assessment per RECIST v1.1 and appropriate testing of serum tumor markers will be performed as described in Section 11.2.1 and Section 11.2.3.

[f] Standard of care tests/procedures, including radiographic scans, laboratory assessments (fasting glucose at baseline), ECG, physical examination, vital signs, height, and weight, will be performed as described in Section 11.2.1.

[g] If screening laboratory testing (CBC, serum chemistry, serum tumor markers [if indicated], urinalysis, 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] May be done within 24 hours prior to the visit.

[i] If dose interruption or modification of niraparib is required at any point on study because of hematologic toxicity, CBCs will be performed as described in Section 6.4.1.1.

[j] For women of childbearing potential only. Serum pregnancy test must be performed within 72 hours of the first dose of study treatment (see Section 11.2.1).

[k] Performed as described in Section 11.2.3.

[l] If TSH, T3 or FT3, or FT4 are not available, equivalent tests should be performed. TSH testing will be done at screening; Cycles 2, 4, and 6; and every other cycle thereafter.

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

[n] AEs are required to be captured through 30 days after cessation of study treatment, SAEs (see Section 10.6.3) 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), AESIs are required to be captured as described in Section 10.6.7, and any pregnancies that occur within 180 days post-treatment are to be captured.

- See Table 50 for details of TSR‑042, niraparib, and bevacizumab combination treatment administration in Part C. TSR-042 will be administered at a dose of 500 mg on Day 1 of every cycle (Q3W) for 4 cycles, followed by 1,000 mg beginning on Cycle 5 Day 1 and every other cycle (Q6W) thereafter for up to 2 years or until disease progression, unacceptable toxicity, patient withdrawal, Investigator's decision, or death. Niraparib will be dispensed/collected on Day 1 of every 21-day cycle (Q3W). Bevacizumab will be administered at a dose of 15 mg/kg on Day 1 of every 21-day cycle (Q3W) for up to 15 months.

Table 22: Schedule of Events - Part C – TSR-042 + Niraparib + Bevacizumab - Cycle 5 Through End of Study

Cycle/Visit[a]	Cycle 5	Cycle 6	Subsequent Cycles	EOT	Safety Follow-Up[b]		Survival Assessment (Every 90 ± 14 Days)
Day: Procedure	1	1	1	+7 Days Post-treatment	30 ± 7 Days Post-treatment	90 ± 7 Days Post-treatment	
Blood sample for exploratory biomarkers				X[c]			
Blood sample for PK and ADAs[d]	X	X	X	X[e]	X[e]	X[e]	
Tumor assessment (RECIST v1.1)[f,g]	X		X	X	X	X	X
Laboratory assessments	X[h]	X[h]	X[h]	X[i]	X[i]	X[i]	X[i]
CBC[j]	X	X	X	X			
Serum chemistry	X	X	X	X[k]	X[c]	X	
Pregnancy test			X[k]		X[i]		
Serum tumor markers (if indicated)	X		X	X	X	X	X
Urinalysis	X	X	X	X	X		
TSH, T3 or FT3, and FT4 or equivalent[l]		X[k]	X[k]	X	X		
ECG[d]	X		X	X			
Physical examination				X			
Symptom-directed physical examination	X	X	X		X		
Vital signs and weight[m]	X	X	X	X	X		
ECOG performance status	X	X	X	X			
Concomitant medications	X	X	X	X	X		
AE monitoring[n]	X	X	X	X	X	X	X

Table 22: Schedule of Events - Part C – TSR-042 + Niraparib + Bevacizumab - Cycle 5 Through End of Study (Continued)

Cycle/Visit[a]	Cycle 5	Cycle 6	Subsequent Cycles	EOT	Safety Follow-Up[b]		Survival Assessment (Every 90 ± 14 Days)
Day: / Procedure	1	1	1	+7 Days Post-treatment	30 ± 7 Days Post-treatment	90 ± 7 Days Post-treatment	
TSR-042 study treatment administered[o]	X		X				
Niraparib study treatment dispensed/collected[o]	X	X	X	X			
Bevacizumab study treatment administered[o]	X	X	X				
Survival assessment							X

Abbreviations: ADA = anti-drug antibody; AE = adverse event; AESI = adverse event of special interest; CBC = complete blood count; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; FT3 = free triiodothyronine; FT4 = free thyroxine; EOT = end of treatment; PK = pharmacokinetics; Q3W = every 3 weeks; Q6W = every 6 weeks; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1; 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.

[b] Safety follow-up visits are required only for those patients who have not started an alternate anticancer therapy as described in Section 11.2.5.

[c] Obtained at EOT visit. EOT visit will occur within 7 days of study treatment discontinuation or at the time of disease progression, whichever occurs first.

[d] PK and ADA blood sampling and ECG assessment will be conducted on additional days during treatment cycles according to the cycle number and agent. Full details on PK and ADA blood sampling and ECG assessments are provided in Table 40 for Part C. On Day 1 of Cycles 5 and 11, ECG monitoring is to be done 30 minutes prior to the niraparib dose.

[e] Blood sample for ADAs only.

[f] Tumor assessment per RECIST v1.1 and appropriate testing of serum tumor markers will be performed as described in Section 11.2.3. Tumor assessments are to be performed within 1 week prior to Day 1 of Cycle 5.

[g] Upon study treatment discontinuation, tumor assessment and appropriate testing of serum tumor markers will be performed as described in Section 11.2.4. If a patient discontinued treatment for a reason other than progression or death, withdrawal of consent, or loss to follow-up, radiographic scans and appropriate testing of serum tumor markers testing should continue at the specified intervals as described in Section 11.2.5 and Section 11.2.6 for the safety follow-up visits and survival assessment, respectively.

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

[i] Performed as described in Section 11.2.5.

[j] If dose interruption and/or modification of niraparib is required at any point on study because of hematologic toxicity, CBCs will be performed as described in Section 6.4.1.1.

[k] Performed as described in Section 11.2.3.

[l] If TSH, T3 or FT3, or FT4 are not available, equivalent tests should be performed. TSH testing will be done at screening; Cycles 2, 4, and 6; and every other cycle thereafter.

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

[n] AEs are required to be captured through 30 days after cessation of study treatment, SAEs (see Section 10.6.5) 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), AESIs are required to be captured as described in Section 10.6.7, and any pregnancies that occur within 180 days post treatment are to be captured. In conjunction with the survival assessment, AESI (regardless of causality) and study-drug related SAEs will be collected every 90 ± 14 days after the last dose of study treatment.

- See Table 50 for details of TSR-042, niraparib, and bevacizumab combination treatment administration in Part C. TSR-042 will be administered at a dose of 500 mg on Day 1 of every cycle (Q3W) for 4 cycles, followed by 1,000 mg beginning on Cycle 5 Day 1 and every other cycle (Q6W) thereafter for up to 2 years or until progression, unacceptable toxicity, patient withdrawal, Investigator's decision, or death. Niraparib will be dispensed/collected on Day 1 of every 21-day cycle (Q3W). Bevacizumab will be administered at a dose of 15 mg/kg on Day 1 of every 21-day cycle (Q3W) for up to 15 months.

Table 23: Schedule of Events - Part D – TSR-042 + Carboplatin-Paclitaxel + Bevacizumab - Screening and Cycle 1 Through Cycle 4

Cycle/Visit[a]	**Screening**	**Cycle 1**			**Cycle 2**	**Cycle 3**	**Cycle 4**
Day: **Procedure**	**-28 to -1**	**1**	**8**	**15**	**1**	**1**	**1**
Informed consent	X						
Inclusion/exclusion criteria review	X	X					
Demographics	X						
Medical, surgical, cancer, and medication history	X						
Archival FFPE tumor tissue sample (optional)[b]	X						
Blood sample for exploratory biomarkers	X	X[c]			X[c]		
Blood sample for PK and ADAs[d]		X	X	X	X		X
Tumor assessment (RECIST v1.1)[e]	X[f]						
Laboratory assessments	X[f]	X[g]	X	X	X[h]	X[h]	X[h]
CBC	X	X	X	X	X	X	X
Serum chemistry	X	X		X	X	X	X
Coagulation	X			X	X	X	
Pregnancy test	X[i]						X[j]
Serum tumor markers (if indicated)[e]	X	X					X
Urinalysis	X	X			X	X	X
TSH, T3 or FT3, and FT4 or equivalent[k]	X				X		X
ECG[d]	X[f]						
Physical examination	X[f]						
Symptom-directed physical examination		X		X	X	X	X

Table 23: Schedule of Events - Part D – TSR-042 + Carboplatin-Paclitaxel + Bevacizumab - Screening and Cycle 1 Through Cycle 4 (Continued)

Cycle/Visit[a]	Screening	Cycle 1			Cycle 2	Cycle 3	Cycle 4
Day: / Procedure	-28 to -1	1	8	15	1	1	1
Vital signs, height, and weight[l]	X[f]	X	X	X	X	X	X
ECOG performance status	X				X	X	X
Concomitant medications	X	X	X	X	X	X	X
AE monitoring[m]	X	X	X	X	X	X	X
TSR-042 study treatment administered[n]		X			X	X	X
Carboplatin-paclitaxel study treatment administered[n]		X			X	X	X
Bevacizumab study treatment administered[n]		X			X	X	X

Abbreviations: ADA = anti-drug antibody; AE = adverse event; CBC = complete blood count; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; FFPE = formalin-fixed paraffin embedded; FT3 = free triiodothyronine; FT4 = free thyroxine; PK = pharmacokinetics; Q3W = every 3 weeks; Q6W = every 6 weeks; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1; 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.

[b] Archival FFPE tumor tissue sample should be submitted within 30 days of patient's first dose.

[c] Obtained predose.

[d] PK and ADA blood sampling will be conducted on additional days during treatment cycles according to the cycle number and agent. Full details on PK and ADA blood sampling and ECG assessments are provided in Table 41 for Part D.

[e] Tumor assessment per RECIST v1.1 and appropriate testing of serum tumor markers will be performed as described in Section 11.2.1 and Section 11.2.3.

[f] Standard of care tests/procedures, including radiographic scans, laboratory assessments (fasting glucose at baseline), ECG, physical examination, vital signs, weight, and height, will be performed as described in Section 11.2.1.

[g] If screening laboratory testing (CBC, serum chemistry, serum tumor markers [if indicated], urinalysis, 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] May be done within 24 hours prior to the visit.

[i] For women of childbearing potential only. Serum pregnancy test must be performed within 72 hours of the first dose of study treatment (see Section 11.2.1).

[j] Performed as described in Section 11.2.3.

[k] If TSH, T3 or FT3, or FT4 are not available, equivalent tests should be performed. TSH testing will be done at screening; Cycles 2, 4, and 6; and every other cycle thereafter.

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

[m] AEs are required to be captured through 30 days after cessation of study treatment, SAEs (see Section 10.6.5) 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), AESIs are required to be captured as described in Section 10.6.7, and any pregnancies that occur within 180 days post-treatment are to be captured.

[n] See Table 51 for details of TSR-042, carboplatin-paclitaxel, and bevacizumab combination treatment administration in Part D. TSR-042 will be administered at a dose of 500 mg on Day 1 of every cycle (Q3W) for 4 cycles, followed by 1,000 mg beginning on Cycle 5 Day 1 and every other cycle (Q6W) thereafter for up to 2 years or until disease progression, unacceptable toxicity, patient withdrawal, Investigator's decision, or death. Carboplatin and paclitaxel will be administered on Day 1 of every 21-day cycle (Q3W) for 4 to 6 cycles as clinically indicated. Bevacizumab will be administered at a dose of 15 mg/kg on Day 1 of every 21-day cycle (Q3W) for up to 15 months.

Table 24: Schedule of Events - Part D – TSR-042 + Carboplatin-Paclitaxel + Bevacizumab -Cycle 5 Through End of Study

Cycle/Visit[a]	**Cycle 5**	**Cycle 6**	**Subsequent Cycles**	**EOT**	**Safety Follow-Up**[b]		**Survival Assessment (Every 90 ± 14 Days)**
Day: **Procedure**	**1**	**1**	**1**	**+7 Days Post-treatment**	**30 ± 7 Days Post-treatment**	**90 ± 7 Days Post-treatment**	
Blood sample for exploratory biomarkers				X[c]			
Blood sample for PK and ADAs[d]	X	X	X	X[e]	X[e]	X[e]	
Tumor assessment (RECIST v1.1)[f]	X		X	X[g]	X[g]	X[g]	X[g]
Laboratory assessments	X[h]	X[h]	X[h]	X	X[i]	X[i]	X
CBC	X	X	X	X			
Serum chemistry	X	X	X	X[j]	X	X	
Pregnancy test			X[j]		X[i]		
Serum tumor markers (if indicated)[f]	X		X	X	X	X	X
Urinalysis	X	X	X	X	X		
TSH, T3 or FT3, and FT4 or equivalent[k]		X[j]	X[j]	X	X		
ECG[d]				X			
Physical examination				X			
Symptom-directed physical examination	X	X	X		X		
Vital signs and weight[l]	X	X	X	X	X		
ECOG performance status	X	X	X	X			
Concomitant medications	X	X	X	X	X		
AE monitoring[m]	X	X	X	X	X	X	X
TSR-042 study treatment administered[n]	X		X				

Table 24: Schedule of Events - Part D – TSR-042 + Carboplatin-Paclitaxel + Bevacizumab -Cycle 5 Through End of Study (Continued)

Cycle/Visit	Cycle 5	Cycle 6	Subsequent Cycles	EOT	Safety Follow-Up		Survival Assessment (Every 90 ± 14 Days)
Day: Procedure	1	1	1	+7 Days Post-treatment	30 ± 7 Days Post-treatment	90 ± 7 Days Post-treatment	
Carboplatin-paclitaxel study treatment administered[n]	X	X					
Bevacizumab study treatment administered[n]	X	X	X				
Survival assessment							X

Abbreviations: ADA = anti-drug antibody; AE = adverse event; AESI = adverse event of special interest; CBC = complete blood count; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; FT3 = free triiodothyronine; FT4 = free thyroxine; EOT = end of treatment; PK = pharmacokinetics; Q3W = every 3 weeks; Q6W = every 6 weeks; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1; 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.

[b] Safety follow-up visits are required only for those patients who have not started an alternate anticancer therapy as described in Section 11.2.5.

[c] Obtained at End of Treatment visit. EOT visit will occur within 7 days of study treatment discontinuation or at the time of disease progression, whichever occurs first.

[d] PK and ADA blood sampling will be conducted on additional days during treatment cycles according to the cycle number and agent. Full details on PK and ADA blood sampling and ECG assessments are provided in Table 42 for Part D.

[e] Blood sample for ADAs only.

[f] Tumor assessment per RECIST v1.1 and appropriate testing of serum tumor markers will be performed as described in Section 11.2.3. Tumor assessments are to be performed within 1 week prior to Day 1 of Cycle 5.

[g] Upon study treatment discontinuation, tumor assessment and appropriate testing of serum tumor markers will be performed as described in Section 11.2.4. If a patient discontinued treatment for a reason other than progression or death, withdrawal of consent, or loss to follow-up, radiographic scans and appropriate testing of serum tumor markers testing should continue at the specified intervals as described in Section 11.2.5 and Section 11.2.6 for the safety follow-up visits and survival assessment, respectively.

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

[i] Performed as described in Section 11.2.5.

[j] Performed as described in Section 11.2.3.

[k] If TSH, T3 or FT3, or FT4 are not available, equivalent tests should be performed. TSH testing will be done at screening; Cycles 2, 4, and 6; and every other cycle thereafter.

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

[m] AEs are required to be captured through 30 days after cessation of study treatment, SAEs (see Section 10.6.5) 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), AESIs are required to be captured as described in Section 10.6.7, and any pregnancies that occur within 180 days post‑treatment are to be captured.. In conjunction with the survival assessment, AESI (regardless of causality) and study-drug related SAEs will be collected every 90 ± 14 days after the last dose of study treatment.

[n] See Table 51 for details of TSR-042, carboplatin-paclitaxel, and bevacizumab combination treatment administration in Part D. TSR-042 will be administered at a dose of 500 mg on Day 1 of every cycle (Q3W) for 4 cycles, followed by 1,000 mg beginning on Cycle 5 Day 1 and every other cycle (Q6W) thereafter for up to 2 years or until progression, unacceptable toxicity, patient withdrawal, Investigator's decision, or death. Carboplatin and paclitaxel will be administered for 4 to 6 cycles as clinically indicated. Bevacizumab will be administered at a dose of 15 mg/kg on Day 1 of every 21-day cycle (Q3W) for up to 15 months.

Table 25: Schedule of Events - Part E – TSR-042 + Carboplatin-Pemetrexed - Screening and Cycle 1 Through Cycle 4

Cycle/Visit[a]	**Screening**	**Cycle 1**			**Cycle 2**	**Cycle 3**	**Cycle 4**
Day: **Procedure**	**-28 to -1**	**1**	**8**	**15**	**1**	**1**	**1**
Informed consent	X						
Inclusion/exclusion criteria review	X	X					
Demographics	X						
Medical, surgical, cancer, and medication history	X						
Archival FFPE tumor tissue sample (optional)[b]	X						
Serial tumor tissue biopsy (optional)[c]					4 to 6 weeks following Dose 1		
Blood sample for exploratory biomarkers	X	X[d]		X[d]	X[d]		X[d]
Blood sample for PK and ADAs[e]		X	X	X	X		
Tumor assessment (RECIST v1.1)[f]	X[g]						
Laboratory assessments	X[g]	X[h]	X	X	X[i]	X[i]	X[i]
CBC	X	X	X	X	X	X	X
Serum chemistry	X	X		X	X	X	X
Coagulation	X			X	X	X	
Pregnancy test	X[j]						X[k]
Serum tumor markers (if indicated)[f]	X	X					X
Urinalysis	X	X			X	X	X
TSH, T3 or FT3, and FT4 or equivalent[l]	X				X		X
ECG[e]	X[g]						
Physical examination	X[g]						
Symptom-directed physical examination		X		X	X	X	X
Vital signs, height, and weight[m]	X[g]	X	X	X	X	X	X
ECOG performance status	X				X	X	X
Concomitant medications	X	X	X	X	X	X	X
AE monitoring[n]	X	X	X	X	X	X	X
TSR-042 study treatment administered[o]		X			X	X	X

Table 25: Schedule of Events - Part E – TSR-042 + Carboplatin-Pemetrexed - Screening and Cycle 1 Through Cycle 4 (Continued)

Cycle/Visit[a]	Screening	Cycle 1			Cycle 2	Cycle 3	Cycle 4
Day: / Procedure	-28 to -1	1	8	15	1	1	1
Pemetrexed study treatment administered[o]		X			X	X	X
Carboplatin study treatment administered[o]		X			X	X	X

Abbreviations: ADA = anti-drug antibody; AE = adverse event; AESI = adverse event of special interest; CBC = complete blood count; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; FFPE = formalin-fixed paraffin embedded; FT3 = free triiodothyronine; FT4 = free thyroxine; PK = pharmacokinetics; Q3W = every 3 weeks; Q6W = every 6 weeks; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1; 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.

[b] The archival FFPE tumor tissue sample (optional) should be submitted within 30 days of patient's first dose.

[c] For patients who consent to optional serial biopsies, the biopsies will be obtained approximately 4 to 6 weeks after initiating study treatment and, whenever possible, at the time of disease progression (EOT visit) (note: while the biopsy is voluntary, it is highly encouraged). A core biopsy is recommended (details are provided in the Study Laboratory Manual).

[d] Obtained predose.

[e] PK and ADA blood sampling will be conducted on additional days during treatment cycles according to the cycle number and agent. Full details on PK and ADA blood sampling and ECG assessments are provided in Table 43 for Part E.

[f] Tumor assessment per RECIST v1.1 and appropriate testing of serum tumor markers will be performed as described in Section 11.2.1 and Section 11.2.3.

[g] Standard of care tests/procedures, including radiographic scans, laboratory assessments (fasting glucose at baseline), ECG, physical examination, vital signs, weight, and height, will be performed as described in Section 11.2.1.

[h] If screening laboratory testing (CBC, serum chemistry, serum tumor markers [if indicated], urinalysis, 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.

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

[j] For women of childbearing potential only. Serum pregnancy test must be performed within 72 hours of the first dose of study treatment (see Section 11.2.1).

[k] Performed as described in Section 11.2.3.

[l] If TSH, T3 or FT3, or FT4 are not available, equivalent tests should be performed. TSH testing will be done at screening; Cycles 2, 4, and 6; and every other cycle thereafter.

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

[n] AEs are required to be captured through 30 days after cessation of study treatment, SAEs (see Section 10.6.5) 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), AESIs are required to be captured as described in Section 10.6.7, and any pregnancies that occur within 180 days post-treatment are to be captured.

[o] See Table 52 for details of TSR-042 and carboplatin-pemetrexed combination treatment administration in Part E. TSR-042 will be administered at a dose of 500 mg on Day 1 of every cycle (Q3W) for up to 2 years or until disease progression, unacceptable toxicity, patient withdrawal, Investigator's decision, or death. Pemetrexed will be administered on Day 1 Q3W for up to 2 years or until progression, unacceptable toxicity, patient withdrawal, Investigator's decision, or death. Carboplatin will be administered on Day 1 of every 21-day cycle (Q3W) for 4 to 6 cycles as clinically indicated.

Table 26: Schedule of Events - Part E – TSR-042 + Carboplatin-Pemetrexed - Cycle 5 Through End of Study

Cycle/Visit[a]	Cycle 5	Cycle 6	Subsequent Cycles	EOT	Safety Follow-Up[b]		Survival Assessment (Every 90 ± 14 Days)
Day: / Procedure	1	1	1	+7 Days Post-treatment	30 ± 7 Days Post-treatment	90 ± 7 Days Post-treatment	
Serial tumor tissue biopsy (optional)[c]				X[d]			
Blood sample for exploratory biomarkers		X[e]		X[d]			
Blood sample for PK and ADAs[f]	X	X		X[g]	X[g]	X[g]	
Tumor assessment (RECIST v1.1)[h]	X		X	X[i]	X[i]	X[i]	X[i]
Laboratory assessments	X[j]	X[j]	X[j]	X	X[k]	X[k]	X
CBC	X	X	X	X			
Serum chemistry	X	X	X	X	X	X	
Pregnancy test			X[l]		X[k]		
Serum tumor markers (if indicated)[h]	X		X	X	X	X	X
Urinalysis	X	X	X	X	X		
TSH, T3 or FT3, and FT4 or equivalent[m]		X[l]	X[l]	X	X		
ECG[f]				X			
Physical examination				X			
Symptom-directed physical examination	X	X	X		X		
Vital signs and weight[n]	X	X	X	X	X		
ECOG performance status	X	X	X	X			
Concomitant medications	X	X	X	X	X		
AE monitoring[o]	X	X	X	X	X	X	X
TSR-042 study treatment administered[p]	X	X	X				
Pemetrexed study treatment administered[p]	X	X	X				
Carboplatin study treatment administered[p]	X	X					
Survival assessment							X

Abbreviations: ADA = anti-drug antibody; AE = adverse event; CBC = complete blood count; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; FFPE = formalin-fixed paraffin embedded; FT3 = free triiodothyronine; FT4 = free thyroxine; PK = pharmacokinetics; Q3W = every 3 weeks; Q6W = every 6 weeks; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1; 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.

[b] Safety follow-up visits are required only for those patients who have not started an alternate anticancer therapy as described in Section 11.2.5.
[c] For patients who consent to optional serial biopsies, the biopsies will be obtained approximately 4 to 6 weeks after initiating study treatment and, whenever possible, at the time of disease progression (EOT visit) as described in Section 10.4 (note: while the biopsy is voluntary, it is highly encouraged). A core biopsy is recommended (details are provided in the Study Laboratory Manual).
[d] Obtained at EOT visit. EOT visit will occur within 7 days of study treatment discontinuation or at the time of disease progression, whichever occurs first.
[e] Obtained predose.
[f] PK and ADA blood sampling will be conducted on additional days during treatment cycles according to the cycle number and agent. Full details on PK and ADA blood sampling and ECG assessments are provided in Table 43 for Part E.
[g] Blood sample for ADAs only.
[h] Tumor assessment per RECIST v1.1 and appropriate testing of serum tumor markers will be performed as described in Section 11.2.3. Tumor assessments are to be performed within 1 week prior to Day 1 of Cycle 5.
[i] Upon study treatment discontinuation, tumor assessment and appropriate testing of serum tumor markers will be performed as described in Section 11.2.4. If a patient discontinued treatment for a reason other than progression or death, withdrawal of consent, or loss to follow-up, radiographic scans and appropriate testing of serum tumor markers testing should continue at the specified intervals as described in Section 11.2.5and Section 11.2.6 for the safety follow-up visits and survival assessment, respectively.
[j] May be done within 24 hours prior to the visit.
[k] Performed as described in Section 11.2.5.
[l] Performed as described in Section 11.2.3.
[m] If TSH, T3 or FT3, or FT4 are not available, equivalent tests should be performed. TSH testing will be done at screening; Cycles 2, 4, and 6; and every other cycle thereafter.
[n] Vital signs include blood pressure, pulse, and temperature. Height obtained at screening only.
[o] AEs are required to be captured through 30 days after cessation of study treatment, SAEs (see Section 10.6.5) 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), AESIs are required to be captured as described in Section 10.6.7, and any pregnancies that occur within 180 days post-treatment are to be captured. In conjunction with the survival assessment, AESI (regardless of causality) and study-drug related SAEs will be collected every 90 ± 14 days after the last dose of study treatment.
[p] See Table 52 for details of TSR-042 and carboplatin-pemetrexed combination treatment administration in Part E. TSR-042 will be administered at a dose of 500 mg on Day 1 of every cycle (Q3W) for up to 2 years or until disease progression, unacceptable toxicity, patient withdrawal, Investigator's decision, or death. Pemetrexed will be administered on Day 1 Q3W for up to 2 years or until disease progression, unacceptable toxicity, patient withdrawal, Investigator's decision, or death. Carboplatin will be administered on Day 1 of every 21-day cycle (Q3W) for 4 to 6 cycles as clinically indicated.

Table 27: Schedule of Events - Part F – TSR-042 + TSR-022 + Carboplatin-Pemetrexed - Screening and Cycle 1 Through Cycle 4

Cycle/Visit[a]	**Screening**	**Cycle 1**			**Cycle 2**	**Cycle 3**	**Cycle 4**
Day: **Procedure**	**-28 to -1**	**1**	**8**	**15**	**1**	**1**	**1**
Informed consent	X						
Inclusion/exclusion criteria review	X	X					
Demographics	X						
Medical, surgical, cancer, and medication history	X						
Archival FFPE tumor tissue sample (mandatory, if available)[b]	X						
Serial tumor tissue biopsy (optional)[c]					4 to 6 weeks following Dose 1		
Blood sample for exploratory biomarkers	X	X[d]		X[d]	X[d]		X[d]
Blood sample for PK and ADAs[e]		X	X	X	X		
Tumor assessment (RECIST v1.1)[f]	X						
Laboratory assessments	X[g]	X[h]	X	X	X[i]	X[i]	X[i]
CBC	X	X	X	X	X	X	X
Serum chemistry	X	X		X	X	X	X
Coagulation	X			X	X	X	
Pregnancy test	X[j]						X[k]
Serum tumor markers (if indicated)[f]	X	X					X
Urinalysis	X	X			X	X	X
TSH, T3 or FT3, and FT4 or equivalent[l]	X				X		X
ECG[e]	X[g]						
Physical examination	X[g]						
Symptom-directed physical examination		X		X	X	X	X

Table 27: Schedule of Events - Part F – TSR-042 + TSR-022 + Carboplatin-Pemetrexed - Screening and Cycle 1 Through Cycle 4 (Continued)

Cycle/Visit[a]	Screening	Cycle 1			Cycle 2	Cycle 3	Cycle 4
Day: / Procedure	-28 to -1	1	8	15	1	1	1
Vital signs, height, and weight[m]	X[g]	X	X	X	X	X	X
ECOG performance status	X				X	X	X
Concomitant medications	X	X	X	X	X	X	X
AE monitoring[n]	X	X	X	X	X	X	X
TSR-042 study treatment administered[o]		X			X	X	X
TSR-022 study treatment administered[o]		X			X	X	X
Pemetrexed study treatment administered[o]		X			X	X	X
Carboplatin study treatment administered[o]		X			X	X	X

Abbreviations: ADA = anti-drug antibody; AE = adverse event; AESI = adverse event of special interest; CBC = complete blood count; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; FFPE = formalin-fixed paraffin embedded; FT3 = free triiodothyronine; FT4 = free thyroxine; PK = pharmacokinetics; Q3W = every 3 weeks; Q6W = every 6 weeks; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1; 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.

[b] Mandatory submission of archival FFPE tumor tissue sample, if available, should be within 30 days of patient's first dose.

[c] For patients who consent to optional serial biopsies, the biopsies will be obtained approximately 4 to 6 weeks after initiating study treatment and, whenever possible, at the time of disease progression (EOT visit) (note: while the biopsy is voluntary, it is highly encouraged). A core biopsy is recommended (details are provided in the Study Laboratory Manual).

[d] Obtained predose.

[e] PK and ADA blood sampling will be conducted on additional days during treatment cycles according to the cycle number and agent. Full details on PK and ADA blood sampling and ECG assessments are provided in Table 44 for Part F.

[f] Tumor assessment per RECIST v1.1 and appropriate testing of serum tumor markers will be performed as described in Section 11.2.1 and Section 11.2.3.

[g] Standard of care tests/procedures, including radiographic scans, laboratory assessments (fasting glucose at baseline), ECG, physical examination, vital signs, weight, and height, will be performed as described in Section 11.2.1.

[h] If screening laboratory testing (CBC, serum chemistry, serum tumor markers [if indicated], urinalysis, 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.

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

[j] For women of childbearing potential only. Serum pregnancy test must be performed within 72 hours of the first dose of study treatment (see Section 11.2.1).

[k] Performed as described in Section 11.2.3.

[l] If TSH, T3 or FT3, or FT4 are not available, equivalent tests should be performed. TSH testing will be done at screening; Cycles 2, 4, and 6; and every other cycle thereafter.

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

[n] AEs are required to be captured through 30 days after cessation of study treatment, SAEs (see Section 10.6.5) 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), AESIs are required to be captured as described in Section 10.6.7, and any pregnancies that occur within 180 days post‑treatment are to be captured.

[o] See Table 53 for details of TSR-042, TSR-022, and carboplatin-pemetrexed combination treatment administration in Part F. TSR-042 will be administered at a dose of 500 mg on Day 1 of every cycle (Q3W) for up to 2 years or until disease progression, unacceptable toxicity, patient withdrawal, Investigator's decision, or death. TSR-022 will be administered at a dose of 900 mg on Day 1 Q3W for up to 2 years or until disease progression, unacceptable toxicity, patient withdrawal, Investigator's decision, or death. Pemetrexed will be administered on Day 1 Q3W for up to 2 years or until progression, unacceptable toxicity, patient withdrawal, Investigator's decision, or death. Carboplatin will be administered on Day 1 of every 21-day cycle (Q3W) for 4 to 6 cycles as clinically indicated.

Table 28: Schedule of Events - Part F – TSR-042 + TSR-022 + Carboplatin-Pemetrexed - Cycle 5 Through End of Study

Cycle/Visit[a]	**Cycle 5**	**Cycle 6**	**Subsequent Cycles**	**EOT**	**Safety Follow-Up**[b]		**Survival Assessment (Every 90 ± 14 Days)**
Day: **Procedure**	**1**	**1**	**1**	**+7 Days Post-treatment**	**30 ± 7 Days Post-treatment**	**90 ± 7 Days Post-treatment**	
Serial tumor tissue biopsy (optional)[c]				X[d]			
Blood sample for exploratory biomarkers		X[e]		X[d]			
Blood sample for PK and ADAs[e,f]	X			X[g]	X[g]	X[g]	
Tumor assessment (RECIST v1.1)[h,i]	X		X	X	X	X	X
Laboratory assessments	X[j]	X[j]	X[j]	X	X[k]	X[k]	X
CBC	X	X	X	X			
Serum chemistry	X	X	X	X	X	X	
Pregnancy test			X[l]		X[k]	X[k]	
Serum tumor markers (if indicated)	X		X	X	X	X	X
Urinalysis	X	X	X	X	X		
TSH, T3 or FT3, and FT4 or equivalent[m]		X[l]	X[l]	X	X		
ECG[f]				X			
Physical examination				X			
Symptom-directed physical examination	X	X	X		X		
Vital signs and weight[n]	X	X	X	X	X		
ECOG performance status	X	X	X	X			
Concomitant medications	X	X	X	X	X		
AE monitoring[o]	X	X	X	X	X	X	X

Table 28: Schedule of Events - Part F – TSR-042 + TSR-022 + Carboplatin-Pemetrexed - Cycle 5 Through End of Study (Continued)

Cycle/Visit[a]	Cycle 5	Cycle 6	Subsequent Cycles	EOT	Safety Follow-Up[b]		Survival Assessment (Every 90 ± 14 Days)
Day: / Procedure	1	1	1	+7 Days Post-treatment	30 ± 7 Days Post-treatment	90 ± 7 Days Post-treatment	
TSR-042 study treatment administered[p]	X	X	X				
TSR-022 study treatment administered[p]	X	X	X				
Pemetrexed study treatment administered[p]	X	X	X				
Carboplatin study treatment administered[p]	X	X					
Survival assessment							X

Abbreviations: ADA = anti-drug antibody; AE = adverse event; AESI = adverse event of special interest; CBC = complete blood count; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; FT3 = free triiodothyronine; FT4 = free thyroxine; EOT = end of treatment; PK = pharmacokinetics; Q3W = every 3 weeks; Q6W = every 6 weeks; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1; 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.

[b] Safety follow-up visits are required only for those patients who have not started an alternate anticancer therapy as described in Section 11.2.5.

[c] For patients who consent to optional serial biopsies, the biopsies will be obtained approximately 4 to 6 weeks after initiating study treatment and, whenever possible, at the time of disease progression (EOT visit) (note: while the biopsy is voluntary, it is highly encouraged). A core biopsy is recommended (details are provided in the Study Laboratory Manual).

[d] Obtained at End of Treatment visit. EOT visit will occur within 7 days of study treatment discontinuation or at the time of disease progression, whichever occurs first.

[e] Obtained predose.

[f] PK and ADA blood sampling will be conducted on additional days during treatment cycles according to the cycle number and agent. Full details on PK and ADA blood sampling and ECG assessments are provided in Table 44 for Part F.

[g] Blood sample for ADAs only.

[h] Tumor assessment per RECIST v1.1 and appropriate testing of serum tumor markers will be performed as described in Section 11.2.3. Tumor assessments are to be performed within 1 week prior to Day 1 of Cycle 5.

[i] Upon study treatment discontinuation, tumor assessment and appropriate testing of serum tumor markers will be performed as described in Section 11.2.4. If a patient discontinued treatment for a reason other than progression or death, withdrawal of consent, or loss to follow-up, radiographic scans and appropriate

testing of serum tumor markers testing should continue at the specified intervals as described in Section 11.2.5 and Section 11.2.6 for the safety follow-up visits and survival assessment, respectively.

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

[k] Performed as described in Section 11.2.5.

[l] Performed as described in Section 11.2.3.

[m] If TSH, T3 or FT3, or FT4 are not available, equivalent tests should be performed. TSH testing will be done at screening; Cycles 2, 4, and 6; and every other cycle thereafter.

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

[o] AEs are required to be captured through 30 days after cessation of study treatment, SAEs (see Section 10.6.5) 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), AESIs are required to be captured as described in Section 10.6.7, and any pregnancies that occur within 180 days post treatment are to be captured. In conjunction with the survival assessment, AESI (regardless of causality) and study-drug related SAEs will be collected every 90 ± 14 days after the last dose of study treatment.

[p] See Table 53 for details of TSR-042, TSR-022, and carboplatin-pemetrexed combination treatment administration in Part F. TSR-042 will be administered at a dose of 500 mg on Day 1 of every cycle (Q3W) for up to 2 years or until disease progression, unacceptable toxicity, patient withdrawal, Investigator's decision, or death. TSR-022 will be administered at a dose of 900 mg on Day 1 Q3W for up to 2 years or until disease progression, unacceptable toxicity, patient withdrawal, Investigator's decision, or death. Pemetrexed will be administered on Day 1 Q3W for up to 2 years or until progression or toxicity. Carboplatin will be administered on Day 1 of every 21-day cycle (Q3W) for 4 to 6 cycles as clinically indicated.

Table 29: Schedule of Events - Part G – TSR-042 + Carboplatin–Nab-Paclitaxel - Screening and Cycle 1 Through Cycle 4

Cycle/Visit[a]	**Screening**	**Cycle 1**			**Cycle 2**	**Cycle 3**	**Cycle 4**
Day: **Procedure**	**-28 to -1**	**1**	**8**	**15**	**1**	**1**	**1**
Informed consent	X						
Inclusion/exclusion criteria review	X	X					
Demographics	X						
Medical, surgical, cancer, and medication history	X						
Archival FFPE tumor tissue sample (optional)[b]	X						
Serial tumor tissue biopsy (optional)[c]					4 to 6 weeks following Dose 1		
Blood sample for exploratory biomarkers	X	X[d]		X[d]	X[d]		X[d]
Blood sample for PK and ADAs[e]		X	X	X	X		
Tumor assessment (RECIST v1.1)[f]	X						
Laboratory assessments	X[g]	X[h]	X	X	X[i]	X[i]	X[i]
CBC	X	X	X	X	X	X	X
Serum chemistry	X	X		X	X	X	X
Coagulation	X			X	X	X	
Pregnancy test	X[j]						X[k]
Serum tumor markers (if indicated)[f]	X	X					X
Urinalysis	X	X			X	X	X
TSH, T3 or FT3, and FT4 or equivalent[l]	X				X		X
ECG[e]	X[g]						
Physical examination	X[g]						
Symptom-directed physical examination		X		X	X	X	X
Vital signs, height, and weight[m]	X[g]	X	X	X	X	X	X
ECOG performance status	X				X	X	X
Concomitant medications	X	X	X	X	X	X	X
AE monitoring[n]	X	X	X	X	X	X	X
TSR-042 study treatment administered[o]		X			X	X	X

Table 29: Schedule of Events - Part G – TSR-042 + Carboplatin–Nab-Paclitaxel - Screening and Cycle 1 Through Cycle 4 (Continued)

Cycle/Visit[a]	Screening	Cycle 1			Cycle 2	Cycle 3	Cycle 4
Day: / Procedure	-28 to -1	1	8	15	1	1	1
Nab-paclitaxel study treatment - administered on Day 1 of each week[o]		X	X	X	X	X	X
Carboplatin study treatment administered[o]		X			X	X	X

Abbreviations: ADA = anti-drug antibody; AE = adverse event; AESI = adverse event of special interest; CBC = complete blood count; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; FFPE = formalin-fixed paraffin embedded; FT3 = free triiodothyronine; FT4 = free thyroxine; PK = pharmacokinetics; Q3W = every 3 weeks; Q6W = every 6 weeks; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1; 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. Visits for subsequent cycles continue every 21 days (±3 days) until study treatment discontinuation. Nab‑paclitaxel will also be administered on Day 1 of each week (Q1W).

[b] The archival FFPE tumor tissue sample (optional) should be submitted within 30 days of patient's first dose.

[c] For patients who consent to optional serial biopsies, the biopsies will be obtained approximately 4 to 6 weeks after initiating study treatment and, whenever possible, at the time of disease progression (EOT visit) (note: while the biopsy is voluntary, it is highly encouraged). A core biopsy is recommended (details are provided in the Study Laboratory Manual).

[d] Obtained predose.

[e] PK and ADA blood sampling will be conducted on additional days during treatment cycles according to the cycle number and agent. Full details on PK and ADA blood sampling and ECG assessments are provided in Table 45 for Part G.

[f] Tumor assessment per RECIST v1.1 and appropriate testing of serum tumor markers will be performed as described in Section 11.2.1 and Section 11.2.3.

[g] Standard of care tests/procedures, including radiographic scans, laboratory assessments (fasting glucose at baseline), ECG, physical examination, vital signs, weight, and height, will be performed as described in Section 11.2.1.

[h] If screening laboratory testing (CBC, serum chemistry, serum tumor markers [if indicated], urinalysis, 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.

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

[j] For women of childbearing potential only. Serum pregnancy test must be performed within 72 hours of the first dose of study treatment (see Section 11.2.1).

[k] Performed as described in Section 11.2.3.

[l] If TSH, T3 or FT3, or FT4 are not available, equivalent tests should be performed. TSH testing will be done at screening; Cycles 2, 4, and 6; and every other cycle thereafter.

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

[n] AEs are required to be captured through 30 days after cessation of study treatment, SAEs (see Section 10.6.5) 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), AESIs are required to be captured as described in Section 10.6.7, and any pregnancies that occur within 180 days post‑treatment are to be captured.

[o] See Table 54 for details of TSR-042 and carboplatin–nab‑paclitaxel combination treatment administration in Part G. TSR-042 will be administered at a dose of 500 mg on Day 1 of every cycle (Q3W) for up to 2 years or until disease progression, unacceptable toxicity, patient withdrawal, Investigator's decision, or death. Nab-paclitaxel will be administered on Days 1, 8, and 15 (Q1W) of every 3-week cycle for 4 to 6 cycles as clinically indicated. Carboplatin will be administered on Day 1 of every 21-day cycle (Q3W) for 4 to 6 cycles as clinically indicated.

Table 30: Schedule of Events - Part G – TSR-042 + Carboplatin–Nab-Paclitaxel - Cycle 5 Through End of Study

Cycle/Visit[a]	Cycle 5	Cycle 6	Subsequent Cycles	EOT	Safety Follow-Up[b]		Survival Assessment (Every 90 ± 14 Days)
Day: Procedure	1	1	1	+7 Days Post-treatment	30 ± 7 Days Post-treatment	90 ± 7 Days Post-treatment	
Serial tumor tissue biopsy (optional)[c]				X[d]			
Blood sample for exploratory biomarkers		X[e]		X[d]			
Blood sample for PK and ADAs[f]	X	X		X[g]	X[g]	X[g]	
Tumor assessment (RECIST v1.1)[h]	X		X	X[i]	X[i]	X[i]	X[i]
Laboratory assessments	X[j]	X[j]	X[j]	X	X[k]	X[k]	X
CBC	X	X	X	X			
Serum chemistry	X	X	X	X	X	X	
Pregnancy test			X[l]		X[k]		
Serum tumor markers (if indicated)[h]	X		X	X	X	X	X
Urinalysis	X	X	X	X	X		
TSH, T3 or FT3, and FT4 or equivalent[m]		X[l]	X[l]	X	X		
ECG[f]				X			
Physical examination				X			
Symptom-directed physical examination	X	X	X		X		
Vital signs and weight[n]	X	X	X	X	X		
ECOG performance status	X	X	X	X			
Concomitant medications	X	X	X	X	X		
AE monitoring[o]	X	X	X	X	X	X	X
TSR-042 study treatment administered[p]	X	X	X				
Nab-paclitaxel study treatment - administered on Day 1 of each week[p]	X	X	X				
Carboplatin study treatment administered[p]	X	X					

Table 30: Schedule of Events - Part G – TSR-042 + Carboplatin–Nab-Paclitaxel - Cycle 5 Through End of Study (Continued)

Cycle/Visit	Cycle 5	Cycle 6	Subsequent Cycles	EOT	Safety Follow-Up		Survival Assessment (Every 90 ± 14 Days)
Day: / Procedure	1	1	1	+7 Days Post-treatment	30 ± 7 Days Post-treatment	90 ± 7 Days Post-treatment	
Survival assessment							X

Abbreviations: ADA = anti-drug antibody; AE = adverse event; CBC = complete blood count; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; FFPE = formalin-fixed paraffin embedded; FT3 = free triiodothyronine; FT4 = free thyroxine; PK = pharmacokinetics; Q3W = every 3 weeks; Q6W = every 6 weeks; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1; T3 = triiodothyronine; TSH = thyroid-stimulating hormone.

[a] Treatment cycles are 21 days long, with visits on Day 1 of each cycle beyond Cycle 1. Visits for subsequent cycles continue every 21 days (±3 days) until study treatment discontinuation.
[b] Safety follow-up visits are required only for those patients who have not started an alternate anticancer therapy as described in Section 11.2.5.
[c] For patients who consent to optional serial biopsies, the biopsies will be obtained approximately 4 to 6 weeks after initiating study treatment and, whenever possible, at the time of disease progression (EOT visit) (note: while the biopsy is voluntary, it is highly encouraged). A core biopsy is recommended (details are provided in the Study Laboratory Manual).
[d] Obtained at EOT visit. EOT visit will occur within 7 days of study treatment discontinuation or at the time of disease progression, whichever occurs first.
[e] Obtained predose.
[f] PK and ADA blood sampling will be conducted on additional days during treatment cycles according to the cycle number and agent. Full details on PK and ADA blood sampling and ECG assessments are provided in Table 45 for Part G.
[g] Blood sample for ADAs only.
[h] Tumor assessment per RECIST v1.1 and appropriate testing of serum tumor markers will be performed as described in Section 11.2.3. Tumor assessments are to be performed within 1 week prior to Day 1 of Cycle 5.
[i] Upon study treatment discontinuation, tumor assessment and appropriate testing of serum tumor markers will be performed as described in Section 11.2.4. If a patient discontinued treatment for a reason other than progression or death, withdrawal of consent, or loss to follow-up, radiographic scans and appropriate testing of serum tumor markers testing should continue at the specified intervals as described in Section 11.2.5 and Section 11.2.6 for the safety follow-up visits and survival assessment, respectively.
[j] May be done within 24 hours prior to the visit.
[k] Performed as described in Section 11.2.5.
[l] Performed as described in Section 11.2.3.
[m] If TSH, T3 or FT3, or FT4 are not available, equivalent tests should be performed. TSH testing will be done at screening; Cycles 2, 4, and 6; and every other cycle thereafter.
[n] Vital signs include blood pressure, pulse, and temperature. Height obtained at screening only.
[o] AEs are required to be captured through 30 days after cessation of study treatment, SAEs (see Section 10.6.5) 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), AESIs are required to be captured as

described in Section 10.6.7, 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.

[p] See Table 54 for details of TSR-042 and nab-paclitaxel combination treatment administration in Part G. TSR-042 will be administered at a dose of 500 mg on Day 1 of every cycle (Q3W) for up to 2 years or until disease progression, unacceptable toxicity, patient withdrawal, Investigator's decision, or death. Nab-paclitaxel will be administered on Days 1, 8, and 15 (Q1W) of every 3-week cycle for 4 to 6 cycles as clinically indicated. Carboplatin will be administered on Day 1 of every 21-day cycle (Q3W) for 4 to 6 cycles as clinically indicated.

Table 31: Schedule of Events - Part H – TSR-042 + TSR-022 + Carboplatin–Nab-Paclitaxel - Screening and Cycle 1 Through Cycle 4

Cycle/Visit[a]	Screening	Cycle 1			Cycle 2	Cycle 3	Cycle 4
Day: Procedure	-28 to -1	1	8	15	1	1	1
Informed consent	X						
Inclusion/exclusion criteria review	X	X					
Demographics	X						
Medical, surgical, cancer, and medication history	X						
Archival FFPE tumor tissue (mandatory, if available)[b]	X						
Serial tumor tissue biopsy (optional)[c]					4 to 6 weeks following Dose 1		
Blood sample for exploratory biomarkers	X	X[d]		X[d]	X[d]		X[d]
Blood sample for PK and ADAs[e]		X	X	X	X		
Tumor assessment (RECIST v1.1)[f]	X						
Laboratory assessments	X[g]	X[h]	X	X	X[i]	X[i]	X[i]
CBC	X	X	X	X	X	X	X
Serum chemistry	X	X		X	X	X	X
Coagulation	X			X	X	X	
Pregnancy test	X[j]						X[k]
Serum tumor markers (if indicated)[f]	X	X					X
Urinalysis	X	X			X	X	X
TSH, T3 or FT3, and FT4 or equivalent[l]	X				X		X
ECG[e]	X[g]						
Physical examination	X[g]						
Symptom-directed physical examination		X		X	X	X	X

Table 31: Schedule of Events - Part H – TSR-042 + TSR-022 + Carboplatin–Nab-Paclitaxel - Screening and Cycle 1 Through Cycle 4 (Continued)

Cycle/Visit[a]	Screening	Cycle 1			Cycle 2	Cycle 3	Cycle 4
Day: / Procedure	-28 to -1	1	8	15	1	1	1
Vital signs, height, and weight[m]	X[g]	X	X	X	X	X	X
ECOG performance status	X				X	X	X
Concomitant medications	X	X	X	X	X	X	X
AE monitoring[n]	X	X	X	X	X	X	X
TSR-042 study treatment administered[o]		X			X	X	X
TSR-022 study treatment administered[o]		X			X	X	X
Nab-paclitaxel study treatment - administered on Day 1 of each week[o]		X	X	X	X	X	X
Carboplatin study treatment administered[o]		X			X	X	X

Abbreviations: ADA = anti-drug antibody; AE = adverse event; AESI = adverse event of special interest; CBC = complete blood count; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; FFPE = formalin-fixed paraffin embedded; FT3 = free triiodothyronine; FT4 = free thyroxine; PK = pharmacokinetics; Q1W = every week; Q3W = every 3 weeks; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1; 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. Visits for subsequent cycles continue every 21 days (±3 days) until study treatment discontinuation. Nab-paclitaxel will also be administered on Day 1 of each week (Q1W).

[b] Mandatory submission of archival FFPE tumor tissue sample, if available, should be within 30 days of patient's first dose.

[c] For patients who consent to optional serial biopsies, the biopsies will be obtained approximately 4 to 6 weeks after initiating study treatment and, whenever possible, at the time of disease progression (EOT visit) (note: while the biopsy is voluntary, it is highly encouraged). A core biopsy is recommended (details are provided in the Study Laboratory Manual).

[d] Obtained predose.

[e] PK and ADA blood sampling will be conducted on additional days during treatment cycles according to the cycle number and agent. Full details on PK and ADA blood sampling and ECG assessments are provided in Table 46 for Part H.

[f] Tumor assessment per RECIST v1.1 and appropriate testing of serum tumor markers will be performed as described in Section 11.2.1 and Section 11.2.3.

[g] Standard of care tests/procedures, including radiographic scans, laboratory assessments (fasting glucose at baseline), ECG, physical examination, vital signs, weight, and height, will be performed as described in Section 11.2.1.

[h] If screening laboratory testing (CBC, serum chemistry, serum tumor markers [if indicated], urinalysis, 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.

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

[j] For women of childbearing potential only. Serum pregnancy test must be performed within 72 hours of the first dose of study treatment (see Section 11.2.1).

[k] Performed as described in Section 11.2.3.

[l] If TSH, T3 or FT3, or FT4 are not available, equivalent tests should be performed. TSH testing will be done at screening; Cycles 2, 4, and 6; and every other cycle thereafter.

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

[n] AEs are required to be captured through 30 days after cessation of study treatment, SAEs (see Section 10.6.5) 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), AESIs are required to be captured as described in Section 10.6.7, and any pregnancies that occur within 180 days post‑treatment are to be captured.

[o] See Table 55 for details of TSR-042, TSR-022, and carboplatin–nab-paclitaxel combination treatment administration in Part H. TSR-042 will be administered at a dose of 500 mg on Day 1 of every cycle (Q3W) for up to 2 years or until disease progression, unacceptable toxicity, patient withdrawal, Investigator's decision, or death. TSR-022 will be administered at a dose of 900 mg on Day 1 Q3W for up to 2 years or until disease progression, unacceptable toxicity, patient withdrawal, Investigator's decision, or death. Nab-paclitaxel will be administered on Days 1, 8, and 15 (Q1W) of every 3-week cycle for 4 to 6 cycles as clinically indicated. Carboplatin will be administered on Day 1 of every 21-day cycle (Q3W) for 4 to 6 cycles as clinically indicated.

Table 32: Schedule of Events - Part H – TSR-042 + TSR-022 + Carboplatin–Nab-Paclitaxel - Cycle 5 Through End of Study

Cycle/Visit[a]	**Cycle 5**	**Cycle 6**	**Subsequent Cycles**	**EOT**	**Safety Follow-Up**[b]		**Survival Assessment (Every 90 ± 14 Days)**
Day: **Procedure**	**1**	**1**	**1**	**+7 Days Post-treatment**	**30 ± 7 Days Post-treatment**	**90 ± 7 Days Post-treatment**	
Serial tumor tissue biopsy (optional)[c]				X[d]			
Blood sample for exploratory biomarkers		X[e]		X[d]			
Blood sample for PK and ADAs[f]	X	X		X[g]	X[g]	X[g]	
Tumor assessment (RECIST v1.1)[h]	X		X	X[i]	X[i]	X[i]	X[i]
Laboratory assessments	X[j]	X[j]	X[j]	X	X[k]	X[k]	X
CBC	X	X	X	X			
Serum chemistry	X	X	X	X	X	X	
Pregnancy test			X[l]		X[k]		
Serum tumor markers (if indicated)[h]	X		X	X	X	X	X
Urinalysis	X	X	X	X	X		
TSH, T3 or FT3, and FT4 or equivalent[m]		X[l]	X[l]	X	X		
ECG[f]				X			
Physical examination				X			
Symptom-directed physical examination	X	X	X		X		
Vital signs and weight[n]	X	X	X	X	X		
ECOG performance status	X	X	X	X			
Concomitant medications	X	X	X	X	X		
AE monitoring[o]	X	X	X	X	X	X	X
TSR-042 study treatment administered[p]	X	X	X				

Table 32: Schedule of Events - Part H – TSR-042 + TSR-022 + Carboplatin–Nab-Paclitaxel - Cycle 5 Through End of Study (Continued)

Cycle/Visit[a]	Cycle 5	Cycle 6	Subsequent Cycles	EOT	Safety Follow-Up[b]		Survival Assessment (Every 90 ± 14 Days)
Day: Procedure	1	1	1	+7 Days Post-treatment	30 ± 7 Days Post-treatment	90 ± 7 Days Post-treatment	
TSR-022 study treatment administered[p]	X	X	X				
Nab-paclitaxel study treatment - administered on Day 1 of each week[p]	X	X	X				
Carboplatin study treatment administered[p]	X	X					
Survival assessment							X

Abbreviations: ADA = anti-drug antibody; AE = adverse event; AESI = adverse event of special interest; CBC = complete blood count; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; FT3 = free triiodothyronine; FT4 = free thyroxine; EOT = end of treatment; PK = pharmacokinetics; Q3W = every 3 weeks; Q6W = every 6 weeks; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1; 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. Visits for subsequent cycles continue every 21 days (±3 days) until study treatment discontinuation. Nab-paclitaxel will also be administered on Day 1 of each week (Q1W).

[b] Safety follow-up visits are required only for those patients who have not started an alternate anticancer therapy as described in Section 11.2.5.

[c] For patients who consent to optional serial biopsies, the biopsies will be obtained approximately 4 to 6 weeks after initiating study treatment and, whenever possible, at the time of disease progression (EOT visit) (note: while the biopsy is voluntary, it is highly encouraged). A core biopsy is recommended (details are provided in the Study Laboratory Manual).

[d] Obtained at End of Treatment visit. EOT visit will occur within 7 days of study treatment discontinuation or at the time of disease progression, whichever occurs first.

[e] Obtained predose

[f] PK and ADA blood sampling will be conducted on additional days during treatment cycles according to the cycle number and agent. Full details on PK and ADA blood sampling and ECG assessments are provided in Table 46 for Part H.

[g] Blood sample for ADAs only.

[h] Tumor assessment per RECIST v1.1 and appropriate testing of serum tumor markers will be performed as described in Section 11.2.3. Tumor assessments are to be performed within 1 week prior to Day 1 of Cycle 5.

[i] Upon study treatment discontinuation, tumor assessment and appropriate testing of serum tumor markers will be performed as described in Section 11.2.4. If a patient discontinued treatment for a reason other than progression or death, withdrawal of consent, or loss to follow-up, radiographic scans and appropriate testing of serum tumor markers testing should continue at the specified intervals as described in Section 11.2.5 and Section 11.2.6 for the safety follow-up visits and survival assessment, respectively.

[j] May be done within 24 hours prior to the visit.
[k] Performed as described in Section 11.2.5.
[l] Performed as described in Section 11.2.3.
[m] If TSH, T3 or FT3, or FT4 are not available, equivalent tests should be performed. TSH testing will be done at screening; Cycles 2, 4, and 6; and every other cycle thereafter.
[n] Vital signs include blood pressure, pulse, and temperature. Height obtained at screening only.
[o] AEs are required to be captured through 30 days after cessation of study treatment, SAEs (see Section 10.6.5) 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), AESIs are required to be captured as described in Section 10.6.7, 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.
[p] See Table 55 for details of TSR-042, TSR-022, and carboplatin–nab-paclitaxel combination treatment administration in Part H. TSR-042 will be administered at a dose of 500 mg on Day 1 of every cycle (Q3W) for up to 2 years or until disease progression, unacceptable toxicity, patient withdrawal, Investigator's decision, or death. TSR-022 will be administered at a dose of 900 mg on Day 1 Q3W for up to 2 years or until disease progression, unacceptable toxicity, patient withdrawal, Investigator's decision, or death. Nab-paclitaxel will be administered on Day 1 of every week (Q1W) for 4 to 6 cycles as clinically indicated. Carboplatin will be administered on Day 1 of every 21-day cycle (Q3W) for 4 to 6 cycles as clinically indicated.

Table 33: Schedule of Events - Part I – TSR-042 + TSR-022 + Carboplatin-Paclitaxel - Screening and Cycle 1 Through Cycle 4

Cycle/Visit[a]	**Screening**	**Cycle 1**			**Cycle 2**	**Cycle 3**	**Cycle 4**
Day: **Procedure**	**-28 to -1**	**1**	**8**	**15**	**1**	**1**	**1**
Informed consent	X						
Inclusion/exclusion criteria review	X	X					
Demographics	X						
Medical, surgical, cancer, and medication history	X						
Archival FFPE tumor tissue sample (mandatory, if available)[b]	X						
Serial tumor tissue biopsy (optional)[c]					4 to 6 weeks following Dose 1		
Blood sample for exploratory biomarkers	X	X[d]		X[d]	X[d]		X[d]
Blood sample for PK and ADAs[e]		X	X	X	X		
Tumor assessment (RECIST v1.1)[f]	X						
Laboratory assessments	X[g]	X[h]	X	X	X[i]	X[i]	X[i]
CBC	X	X	X	X	X	X	X
Serum chemistry	X	X		X	X	X	X
Coagulation	X			X	X	X	
Pregnancy test	X[j]						X[k]
Serum tumor markers (if indicated)[f]	X	X					X
Urinalysis	X	X			X	X	X
TSH, T3 or FT3, and FT4 or equivalent[l]	X				X		X
ECG[e]	X[g]						
Physical examination	X[g]						
Symptom-directed physical examination		X		X	X	X	X
Vital signs, height, and weight[m]	X[g]	X	X	X	X	X	X
ECOG performance status	X				X	X	X
Concomitant medications	X	X	X	X	X	X	X
AE monitoring[n]	X	X	X	X	X	X	X

Table 33: Schedule of Events - Part I – TSR-042 + TSR-022 + Carboplatin-Paclitaxel - Screening and Cycle 1 Through Cycle 4 (Continued)

Cycle/Visit[a]	Screening	Cycle 1			Cycle 2	Cycle 3	Cycle 4
Day: / Procedure	-28 to -1	1	8	15	1	1	1
TSR-042 study treatment administered[o]		X			X	X	X
TSR-022 study treatment administered[o]		X			X	X	X
Paclitaxel study treatment administered[o]		X			X	X	X
Carboplatin study treatment administered[o]		X			X	X	X

Abbreviations: ADA = anti-drug antibody; AE = adverse event; AESI = adverse event of special interest; CBC = complete blood count; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; FFPE = formalin-fixed paraffin embedded; FT3 = free triiodothyronine; FT4 = free thyroxine; PK = pharmacokinetics; Q3W = every 3 weeks; Q6W = every 6 weeks; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1; 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.

[b] Mandatory submission of archival FFPE tumor tissue sample, if available, should be submitted within 30 days of patient's first dose.

[c] For patients who consent to optional serial biopsies, the biopsies will be obtained approximately 4 to 6 weeks after initiating study treatment and, whenever possible, at the time of disease progression (EOT visit) (note: while the biopsy is voluntary, it is highly encouraged). A core biopsy is recommended (details are provided in the Study Laboratory Manual).

[d] Obtained predose.

[e] PK and ADA blood sampling will be conducted on additional days during treatment cycles according to the cycle number and agent. Full details on PK and ADA blood sampling and ECG assessments are provided in Table 47 for Part I.

[f] Tumor assessment per RECIST v1.1 and appropriate testing of serum tumor markers will be performed as described in Section 11.2.1 and Section 11.2.3.

[g] Standard of care tests/procedures, including radiographic scans, laboratory assessments (fasting glucose at baseline), ECG, physical examination, vital signs, weight, and height, will be performed as described in Section 11.2.1.

[h] If screening laboratory testing (CBC, serum chemistry, serum tumor markers [if indicated], urinalysis, 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.

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

[j] For women of childbearing potential only. Serum pregnancy test must be performed within 72 hours of the first dose of study treatment (see Section 11.2.1).

[k] Performed as described in Section 11.2.3.

[l] If TSH, T3 or FT3, or FT4 are not available, equivalent tests should be performed. TSH testing will be done at screening; Cycles 2, 4, and 6; and every other cycle thereafter.

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

[n] AEs are required to be captured through 30 days after cessation of study treatment, SAEs (see Section 10.6.5) 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), AESIs are required to be captured as described in Section 10.6.7, and any pregnancies that occur within 180 days post-treatment are to be captured.

[o] See Table 56 for details of TSR-042, TSR-022, and carboplatin-paclitaxel combination treatment administration in Part I. TSR-042 will be administered at a dose of 500 mg on Day 1 of every cycle (Q3W) for up to 2 years or until disease progression, unacceptable toxicity, patient withdrawal, Investigator's decision, or death. TSR-022 will be administered at a dose of 900 mg on Day 1 Q3W for up to 2 years or or until disease progression, unacceptable toxicity, patient withdrawal, Investigator's decision, or death.

Paclitaxel will be administered on Day 1 Q3W for 4 to 6 cycles as clinically indicated. Carboplatin will be administered on Day 1 every 3 weeks (Q3W) for 4 to 6 cycles as clinically indicated.

Table 34: Schedule of Events - Part I – TSR-042 + TSR-022 + Carboplatin-Paclitaxel - Cycle 5 Through End of Study

Cycle/Visit[a]	**Cycle 5**	**Cycle 6**	**Subsequent Cycles**	**EOT**	**Safety Follow-Up**[b]		**Survival Assessment (Every 90 ± 14 Days)**
Day: **Procedure**	**1**	**1**	**1**	**+7 Days Post-treatment**	**30 ± 7 Days Post-treatment**	**90 ± 7 Days Post-treatment**	
Serial tumor tissue biopsy (optional)[c]				X[d]			
Blood sample for exploratory biomarkers		X[e]		X[d]			
Blood sample for PK and ADAs[f]	X	X		X[g]	X[g]	X[g]	
Tumor assessment (RECIST v1.1)[h]	X		X	X[i]	X[i]	X[i]	X[i]
Laboratory assessments	X[j]	X[j]	X[j]	X	X[k]	X[k]	X
CBC	X	X	X	X			
Serum chemistry	X	X	X	X	X	X	
Pregnancy test			X[l]		X[k]		
Serum tumor markers (if indicated)	X		X	X	X	X	X
Urinalysis	X	X	X	X	X		
TSH, T3 or FT3, and FT4 or equivalent[m]		X[l]	X[l]	X	X		
ECG[f]				X			
Physical examination				X			
Symptom-directed physical examination	X	X	X		X		
Vital signs and weight[n]	X	X	X	X	X		
ECOG performance status	X	X	X	X			
Concomitant medications	X	X	X	X	X		
AE monitoring[o]	X	X	X	X	X	X	X
TSR-042 study treatment administered[p]	X	X	X				
TSR-022 study treatment administered[p]	X	X	X				
Paclitaxel study treatment administered[p]	X	X	X				

Table 34: Schedule of Events - Part I – TSR-042 + TSR-022 + Carboplatin-Paclitaxel - Cycle 5 Through End of Study (Continued)

Cycle/Visit	Cycle 5	Cycle 6	Subsequent Cycles	EOT	Safety Follow-Up		Survival Assessment (Every 90 ± 14 Days)
Day: / Procedure	1	1	1	+7 Days Post-treatment	30 ± 7 Days Post-treatment	90 ± 7 Days Post-treatment	
Carboplatin study treatment administered[p]	X	X					
Survival assessment							X

Abbreviations: ADA = anti-drug antibody; AE = adverse event; AESI = adverse event of special interest; CBC = complete blood count; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; FT3 = free triiodothyronine; FT4 = free thyroxine; EOT = end of treatment; PK = pharmacokinetics; Q3W = every 3 weeks; Q6W = every 6 weeks; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1; 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.

[b] Safety follow-up visits are required only for those patients who have not started an alternate anticancer therapy as described in Section 11.2.5.

[c] For patients who consent to optional serial biopsies, the biopsies will be obtained approximately 4 to 6 weeks after initiating study treatment and, whenever possible, at the time of disease progression (EOT visit) (note: while the biopsy is voluntary, it is highly encouraged). A core biopsy is recommended (details are provided in the Study Laboratory Manual).

[d] Obtained at End of Treatment visit. EOT visit will occur within 7 days of study treatment discontinuation or at the time of disease progression, whichever occurs first.

[e] Obtained predose.

[f] PK and ADA blood sampling will be conducted on additional days during treatment cycles according to the cycle number and agent. Full details on PK and ADA blood sampling and ECG assessments are provided in Table 47 for Part I.

[g] Blood sample for ADAs only.

[h] Tumor assessment per RECIST v1.1 and appropriate testing of serum tumor markers will be performed as described in Section 11.2.3. Tumor assessments are to be performed within 1 week prior to Day 1 of Cycle 5.

[i] Upon study treatment discontinuation, tumor assessment and appropriate testing of serum tumor markers will be performed as described in Section 11.2.4. If a patient discontinued treatment for a reason other than progression or death, withdrawal of consent, or loss to follow-up, radiographic scans and appropriate testing of serum tumor markers testing should continue at the specified intervals as described in Section 11.2.5 and Section 11.2.6 for the safety follow-up visits and survival assessment, respectively.

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

[k] Performed as described in Section 11.2.5.

[l] Performed as described in Section 11.2.3.

[m] If TSH, T3 or FT3, or FT4 are not available, equivalent tests should be performed. TSH testing will be done at screening; Cycles 2, 4, and 6; and every other cycle thereafter.

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

[o] AEs are required to be captured through 30 days after cessation of study treatment, SAEs (see Section 10.6.5) 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), AESIs are required to be captured as described in Section 10.6.7, 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.

[p] See Table 56 for details of TSR-042, TSR-022, and carboplatin-paclitaxel combination treatment administration in Part I. TSR-042 will be administered at a dose of 500 mg on Day 1 of every cycle (Q3W) for up to 2 years or until disease progression, unacceptable toxicity, patient withdrawal, Investigator's decision, or death. TSR-022 will be administered at a dose of 900 mg on Day 1 Q3W for up to 2 years or until disease progression, unacceptable toxicity, patient withdrawal, Investigator's decision, or death. Paclitaxel will be administered on Day 1 Q3W for 4 to 6 cycles as clinically indicated. Carboplatin will be administered on Day 1 every 3 weeks (Q3W) for 4 to 6 cycles as clinically indicated.

Table 35: PK and ADA Blood Sampling and ECG Schedule - Part A - TSR-042 + Niraparib- Screening and Cycle 1 Through Cycle 4

Cycle/Visit	Screening	Cycle 1						Cycle 2			Cycle 4				
Day	-28 to -1	1	1	2	5	8	15	1	1	2	1	2	5	8	15
Time Point/Assessment	ECG	ECG	Blood					ECG	Blood		Blood				
Anytime	X														
Pre-TSR-042 infusion[a]			X								X				
Post-TSR-042 infusion															
0.5 h (±5 min)			X								X				
2 h (±30 min)			X								X				
24 h (±4 h)				X								X			
96 h (±12 h)					X								X		
168 h (±24 h)						X								X	
336 h (±24 h)							X								X
504 h (±24 h)									X[b]						
1008 h (±24 h)															
Pre-niraparib dose[a]		X	X					X	X						
Post-niraparib dose															
1 h (±15 min)			X						X						
2 h (±15 min)		X	X					X	X						
4 h (±15 min)			X						X						
6 h (±30 min)			X						X						
8 h (±1 h)			X						X						
24 h (±2 h)				X[c]						X[c]					

Abbreviations: ADA = anti-drug antibody; ECG = electrocardiogram; PK = pharmacokinetic.
Note: All sampling times are relative to the start dosing of the specified study treatment. ECG should be conducted 30 minutes prior to PK blood draws for niraparib.
[a] To be obtained within 30 minutes prior to the administration of the dose of the corresponding agent for the cycle.
[b] The 504-hour sample is the postdose sample from the prior cycle (Cycle 1) and the predose sample for this cycle (Cycle 2). It must be collected within 30 minutes of the dose given at this study visit.
[c] The 24-hour sample is the postdose sample from the prior day (Day 1) and must be collected within 30 minutes of the dose given at this study visit (Day 2).

Table 36: PK and ADA Blood Sampling and ECG Schedule - Part A - TSR-042 + Niraparib- Cycle 5 Through End of Treatment

Cycle/Visit	Cycle 5						Cycle 6	Cycle 7	Cycle 11						Cycle 12	Cycle 13	EOT		Safety Follow-up (Post-treatment)	
Day	1	1	2	5	8	15	1	1	1	1	2	5	8	15	1	1	+7 Days Post-treatment		30 ± 7 Days	90 ± 7 Days
Time Point/ Assessment	ECG	Blood					Blood	Blood	ECG	Blood					Blood	Blood	ECG	Blood	Blood	Blood
Anytime																	X	X[a]	X[a]	X[a]
Pre-TSR-042 infusion[b]		X								X										
Post-TSR-042 infusion																				
0.5 h (±5 min)		X								X										
2 h (±30 min)		X								X										
24 h (±4 h)			X								X									
96 h (±12 h)				X								X								
168 h (±24 h)					X								X							
336 h (±24 h)						X								X						
504 h (±24 h)[c]							X								X					
1008 h (±24 h)[d]								X								X				
Pre-niraparib dose[b]	X	X							X	X										
Post-niraparib dose																				
2 h (±15 min)		X								X										

Abbreviations: ADA = anti-drug antibody; ECG = electrocardiogram; EOT = end of treatment; PK = pharmacokinetic. Note: All sampling times are relative to the start dosing of the specified study treatment. ECG should be conducted 30 minutes prior to PK blood draws for niraparib.

[a] Sample collected for TSR-042 ADA assessment only.

[b] To be obtained within 30 minutes prior to the administration of the dose of the corresponding agent for the cycle.

[c] The 504-hour sample is the postdose sample from the prior cycle (i.e., Cycle 5 or Cycle 11). It is collected during this cycle visit (i.e., Cycle 6 or Cycle 12).

[d] The 1008-hour sample is the postdose sample from the prior dose (dose given on D1 Cycle 5 or D1 Cycle 11) and the predose sample from this cycle (i.e., Cycle 7 or Cycle 13). It must be collected within 30 minutes of the dose given at this study visit.

Table 37: PK and ADA Blood Sampling and ECG Schedule - Part B – TSR-042 + Carboplatin-Paclitaxel - Screening and Cycle 1 through Cycle 4

Cycle/Visit	Screening	Cycle 1							Cycle 2	Cycle 4				
Day	-28 to -1	1	2	3	4	5	8	15	1	1	2	5	8	15
Time Point/Assessment	ECG	Blood							Blood	Blood				
Anytime	X													
Pre-TSR-042 infusion[a]		X								X				
Post-TSR-042 infusion														
0.5 h (±5 min)		X								X				
2 h (±30 min)		X								X				
24 h (±4 h)			X								X			
96 h (±12 h)						X						X		
168 h (±24 h)							X						X	
336 h (±24 h)								X						X
504 h (±24 h)									X[b]					
Pre-carboplatin infusion[a]		X							X					
Post-carboplatin infusion														
0.5 h (±5 min)[c]		X												
1 h (±15 min)[d]		X							X					
4 h (±15 min)		X												
6 h (±30 min)		X												
8 h (±1 h)		X												
24 h (±2 h)			X											

Table 37: PK and ADA Blood Sampling and ECG Schedule - Part B – TSR-042 + Carboplatin-Paclitaxel - Screening and Cycle 1 through Cycle 4 (Continued)

Cycle/Visit	Screening	Cycle 1							Cycle 2	Cycle 4				
Day	-28 to -1	1	2	3	4	5	8	15	1	1	2	5	8	15
Time Point/Assessment	ECG	Blood							Blood	Blood				
Pre-paclitaxel infusion[a]		X												
Post-paclitaxel infusion														
1.5 h (±15 min)[c]		X												
3 h (±15 min)[d]		X												
6 h (±30 min)		X												
8 h (±1 h)		X												
24 h (±2 h)			X											
48 h (±4 h)				X										
72 h (±8 h)					X									
96 h (±12 h)						X								

Abbreviations: ADA = anti-drug antibody; ECG = electrocardiogram; PK = pharmacokinetic.
Note: All sampling times are relative to the start dosing of the specified study treatment.
[a] To be obtained within 30 minutes prior to the administration of the dose of the corresponding agent for the cycle.
[b] The 504-hour sample is the postdose sample from the prior cycle (Cycle 1) and the predose sample for this cycle (Cycle 2). It must be collected within 30 minutes of the dose given at this study visit.
[c] Obtained during infusion of the specified study treatment.
[d] Obtained at the end of infusion of the specified study treatment.

Table 38: PK and ADA Blood Sampling and ECG Schedule - Part B – TSR-042 + Carboplatin-Paclitaxel - Cycle 5 Through End of Treatment

Cycle/Visit	Cycle 5					Cycle 6	Cycle 7	Cycle 11					Cycle 12	Cycle 13	EOT		Safety Follow-up (Post-treatment)	
Day	1	2	5	8	15	1	1	1	2	5	8	15	1	1	+7 Days Post-treatment		30 ± 7 Days	90 ± 7 Days
Time Point/Assessment	Blood					Blood	Blood	Blood					Blood	Blood	ECG	Blood	Blood	Blood
Anytime															X	X[a]	X[a]	X[a]
Pre-TSR-042 infusion[b]	X							X										
Post-TSR-042 infusion																		
0.5 h (±5 min)	X							X										
2 h (±30 min)	X							X										
24 h (±4 h)		X							X									
96 h (±12 h)			X							X								
168 h (±24 h)				X							X							
336 h (±24 h)					X							X						
504 h (±24 h)[c]						X							X					
1008 h (±24 h)[d]							X							X				
Pre-carboplatin infusion[b]	X[e]																	
1 h (±15 min)[f]	X[e]																	
Pre-paclitaxel infusion[b]	X[e]																	

Abbreviations: ADA = anti-drug antibody; ECG = electrocardiogram; EOT = end of treatment; PK = pharmacokinetic. Note: All sampling times are relative to the start dosing of the specified study treatment.

[a] Sample collected for TSR-042 ADA assessment only.

[b] To be obtained within 30 minutes prior to the administration of the dose of the corresponding agent for the cycle.

[c] The 504-hour sample is the postdose sample from the prior cycle (i.e., Cycle 5 or Cycle 11). It is collected during this cycle visit (i.e., Cycle 6 or Cycle 12).

[d] The 1008-hour sample is the postdose sample from the prior dose (dose given on D1 Cycle 5 or D1 Cycle 11) and the predose sample from this cycle (i.e., Cycle 7 or Cycle 13). It must be collected within 30 minutes of the dose given at this study visit.

[e] Collect only if there is dose of paclitaxel and carboplatin for Cycle 5.

[f] Obtained at the end of infusion of the specified study treatment.

Table 39: PK and ADA Blood Sampling and ECG Schedule - Part C - TSR-042 + Niraparib + Bevacizumab - Screening and Cycle 1 Through Cycle 4

Cycle/Visit	Screening	Cycle 1						Cycle 2			Cycle 4				
Day	-28 to -1	1	1	2	5	8	15	1	1	2	1	2	5	8	15
Time Point/Assessment	ECG	ECG	Blood					ECG	Blood		Blood				
Anytime	X														
Pre-TSR-042 infusion[a]			X								X				
Post-TSR-042 infusion															
0.5 h (±5 min)			X								X				
2 h (±30 min)			X								X				
24 h (±4 h)				X								X			
96 h (±12 h)					X								X		
168 h (±24 h)						X								X	
336 h (±24 h)							X								X
504 h (±24 h)									X[b]						
1008 h (±24 h)															
Pre-niraparib dose[a]		X	X					X	X						
Post-niraparib dose															
1 h (±15 min)			X						X						
2 h (±15 min)		X	X					X	X						
4 h (±15 min)			X						X						
6 h (±30 min)			X						X						
8 h (±1 h)			X						X						
24 h (±2 h)				X[c]						X[c]					

Abbreviations: ADA = anti-drug antibody; ECG = electrocardiogram; PK = pharmacokinetic.
Note: All sampling times are relative to the start dosing of the specified study treatment. ECG should be conducted 30 minutes prior to PK blood draws for niraparib.
[a] To be obtained within 30 minutes prior to the administration of the dose of the corresponding agent for the cycle.
[b] The 504-hour sample is the postdose sample from the prior cycle (Cycle 1) and the predose sample for this cycle (Cycle 2). It must be collected within 30 minutes of the dose given at this study visit.
[c] The 24-hour sample is the postdose sample from the prior day (Day 1) and must be collected within 30 minutes of the dose given at this study visit (Day 2).

Table 40: PK and ADA Blood Sampling and ECG Schedule - Part C - TSR-042 + Niraparib + Bevacizumab - Cycle 5 Through End of Treatment

Cycle/Visit	Cycle 5						Cycle 6	Cycle 7	Cycle 11						Cycle 12	Cycle 13	EOT		Safety Follow-up (Post-treatment)	
Day	1	1	2	5	8	15	1	1	1	1	2	5	8	15	1	1	+7 Days Post-treatment		30 ± 7 Days	90 ± 7 Days
Time Point/ Assessment	ECG	Blood					Blood	Blood	ECG	Blood					Blood	Blood	ECG	Blood	Blood	Blood
Anytime																	X	X[a]	X[a]	X[a]
Pre-TSR-042 infusion[b]		X								X										
Post-TSR-042 infusion																				
0.5 h (±5 min)		X								X										
2 h (±30 min)		X								X										
24 h (±4 h)			X								X									
96 h (±12 h)				X								X								
168 h (±24 h)					X								X							
336 h (±24 h)						X								X						
504 h (±24 h)[c]							X								X					
1008 h (±24 h)[d]								X								X				
Pre-niraparib dose[b]	X	X							X	X										
Post-niraparib dose																				
2 h (±15 min)		X								X										

Abbreviations: ADA = anti-drug antibody; ECG = electrocardiogram; EOT = end of treatment; PK = pharmacokinetic. Note: All sampling times are relative to the start dosing of the specified study treatment. ECG should be conducted 30 minutes prior to PK blood draws for niraparib.

[a] Sample collected for TSR-042 ADA assessment only.

[b] To be obtained within 30 minutes prior to the administration of the dose of the corresponding agent for the cycle.

[c] The 504-hour sample is the postdose sample from the prior cycle (i.e., Cycle 5 or Cycle 11). It is collected during this cycle visit (i.e., Cycle 6 or Cycle 12).

[d] The 1008-hour sample is the postdose sample from the prior dose (dose given on D1 Cycle 5 or D1 Cycle 11) and the predose sample from this cycle (i.e., Cycle 7 or Cycle 13). It must be collected within 30 minutes of the dose given at this study visit.

Table 41: PK and ADA Blood Sampling and ECG Schedule - Part D – TSR-042 + Carboplatin-Paclitaxel + Bevacizumab - Screening and Cycle 1 through Cycle 4

Cycle/Visit	Screening	Cycle 1							Cycle 2	Cycle 4				
Day	-28 to -1	1	2	3	4	5	8	15	1	1	2	5	8	15
Time Point/Assessment	ECG	Blood							Blood	Blood				
Anytime	X													
Pre-TSR-042 infusion[a]		X								X				
Post-TSR-042 infusion														
0.5 h (±5 min)		X								X				
2 h (±30 min)		X								X				
24 h (±4 h)			X								X			
96 h (±12 h)						X						X		
168 h (±24 h)							X						X	
336 h (±24 h)								X						X
504 h (±24 h)									X[b]					
Pre-carboplatin infusion[a]		X							X					
Post-carboplatin infusion														
0.5 h (±5 min)[c]		X												
1 h (±15 min)[d]		X							X					
4 h (±15 min)		X												
6 h (±30 min)		X												
8 h (±1 h)		X												
24 h (±2 h)			X											

Table 41: PK and ADA Blood Sampling and ECG Schedule - Part D – TSR-042 + Carboplatin-Paclitaxel + Bevacizumab - Screening and Cycle 1 through Cycle 4 (Continued)

Cycle/Visit	Screening	Cycle 1							Cycle 2	Cycle 4				
Day	-28 to -1	1	2	3	4	5	8	15	1	1	2	5	8	15
Time Point/Assessment	ECG	Blood							Blood	Blood				
Pre-paclitaxel infusion[a]		X												
Post-paclitaxel infusion														
1.5 h (±15 min)[c]		X												
3 h (±15 min)[d]		X												
6 h (±30 min)		X												
8 h (±1 h)		X												
24 h (±2 h)			X											
48 h (±4 h)				X										
72 h (±8 h)					X									
96 h (±12 h)						X								

Abbreviations: ADA = anti-drug antibody; ECG = electrocardiogram; PK = pharmacokinetic.
Note: All sampling times are relative to the start dosing of the specified study treatment.
[a] To be obtained within 30 minutes prior to the administration of the dose of the corresponding agent for the cycle.
[b] The 504-hour sample is the postdose sample from the prior cycle (Cycle 1) and the predose sample for this cycle (Cycle 2). It must be collected within 30 minutes of the dose given at this study visit.
[c] Obtained during infusion of the specified study treatment.
[d] Obtained at the end of infusion of the specified study treatment.

Table 42: PK and ADA Blood Sampling and ECG Schedule - Part D – TSR-042 + Carboplatin-Paclitaxel + Bevacizumab - Cycle 5 Through End of Treatment

Cycle/Visit	Cycle 5					Cycle 6	Cycle 7	Cycle 11					Cycle 12	Cycle 13	EOT		Safety Follow-up (Post-treatment)	
Day	1	2	5	8	15	1	1	1	2	5	8	15	1	1	+7 Days Post-treatment		30 ± 7 Days	90 ± 7 Days
Time Point/Assessment	Blood					Blood	Blood	Blood					Blood	Blood	ECG	Blood	Blood	Blood
Anytime															X	X[a]	X[a]	X[a]
Pre-TSR-042 infusion[b]	X							X										
Post-TSR-042 infusion																		
0.5 h (±5 min)	X							X										
2 h (±30 min)	X							X										
24 h (±4 h)		X							X									
96 h (±12 h)			X							X								
168 h (±24 h)				X							X							
336 h (±24 h)					X							X						
504 h (±24 h)[c]						X							X					
1008 h (±24 h)[d]							X							X				
Pre-carboplatin infusion[b]	X[e]																	
1 h (±15 min)[f]	X[e]																	
Pre-paclitaxel infusion[b]	X[e]																	

Abbreviations: ADA = anti-drug antibody; ECG = electrocardiogram; EOT = end of treatment; PK = pharmacokinetic. Note: All sampling times are relative to the start dosing of the specified study treatment.

[a] Sample collected for TSR-042 ADA assessment only.

[b] To be obtained within 30 minutes prior to the administration of the dose of the corresponding agent for the cycle.

[c] The 504-hour sample is the postdose sample from the prior cycle (i.e., Cycle 5 or Cycle 11). It is collected during this cycle visit (i.e., Cycle 6 or Cycle 12).

[d] The 1008-hour sample is the postdose sample from the prior dose (dose given on D1 Cycle 5 or D1 Cycle 11) and the predose sample from this cycle (i.e., Cycle 7 or Cycle 13). It must be collected within 30 minutes of the dose given at this study visit.

[e] Collect only if there is dose of paclitaxel and carboplatin for Cycle 5.

[f] Obtained at the end of infusion of the specified study treatment.

Table 43: PK and ADA Blood Sampling and ECG Schedule - Part E – TSR-042 + Carboplatin-Pemetrexed - Screening and Treatment Cycles

Cycle/Visit	Screening	Cycle 1						Cycle 2	Cycle 5						EOT		Safety follow-up (Post-treatment)	
Day	-21 to -1	1	2	3	5	8	15	1	1	2	3	5	8	15	7 days post-treatment		30 ± 7 Days	90 ± 7 Days
Time Point/Assessment	ECG	Blood						Blood	Blood						ECG	Blood	Blood	Blood
Anytime	X														X	X[a]	X[a]	X[a]
Pre-TSR-042 infusion[b]		X						X	X									
Post-TSR-042 infusion																		
0.5 h (±5 min)[c]		X							X									
2 h (±30 min)		X							X									
24 h (±4 h)			X							X								
48 h (±4 h)				X							X							
96 h (±12 h)					X							X						
168 h (±24 h)						X							X					
336 h (±24 h)							X							X				
Pre-pemetrexed infusion[b]		X						X										
Post-pemetrexed infusion																		
10 min (±2 min)[c]		X						X										
0.5 h (±5 min)		X																
1 h (±15 min)		X																
4 h (±15 min)		X																
6 h (±30 min)		X																
8 h (±1 h)		X																
24 h (±2 h)			X															

Table 43: PK and ADA Blood Sampling and ECG Schedule - Part E – TSR-042 + Carboplatin-Pemetrexed - Screening and Treatment Cycles (Continued)

Cycle/Visit	Screening	Cycle 1						Cycle 2	Cycle 5						EOT		Safety follow-up (Post-treatment)	
Day	-21 to -1	1	2	3	5	8	15	1	1	2	3	5	8	15	7 days post-treatment		30 ± 7 Days	90 ± 7 Days
Time Point/Assessment	ECG	Blood						Blood	Blood						ECG	Blood	Blood	Blood
Pre-carboplatin infusion[b]		X						X										
Post-carboplatin infusion																		
0.5 h (±5 min)[d]		X						X										
1 h (±15 min)[e]		X						X										
4 h (±15 min)		X																
6 h (±30 min)		X																
8 h (±1 h)		X																
24 h (±2 h)			X															

Abbreviations: ADA = anti-drug antibody; ECG = electrocardiogram; EOT = end of treatment; PK = pharmacokinetic.
Infusion order: 1) TSR-042 30 min; 2) pemetrexed 10 min; 3) carboplatin 30 min or 60 min
Note: All sampling times are relative to the start dosing of the specified study treatment.
Note: PK assessments will be performed for TSR-042, carboplatin, and pemetrexed. ADA assessments will be performed for TSR-042.
[a] Sample collected for TSR-042 ADA assessment only.
[b] To be obtained within 30 minutes prior to administration of the specified study treatment.
[c] Obtained at the end of infusion of the specified study treatment.
[d] For carboplatin, 0.5 h sample is collected during the infusion for 1 h insert and the end of infusion for 0.5 h insert.
[e] For carboplatin, 1 h sample is collected at the end of infusion for 1 h insert and as the postdose 1 h sample for 0.5 h insert.

Table 44: PK and ADA Blood Sampling and ECG Schedule - Part F – TSR-042 + TSR-022 + Carboplatin-Pemetrexed - Screening and Treatment Cycles

Cycle/Visit	**Screening**	**Cycle 1**							**Cycle 2**	**Cycle 5**						**EOT**		**Safety follow-up (Post treatment)**	
Day	**-21 to -1**	**1**	**2**	**3**	**4**	**5**	**8**	**15**	**1**	**1**	**2**	**3**	**5**	**8**	**15**	**7 days post-treatment**		**30±7 Days**	**90±7 Days**
Time Point/Assessment	**ECG**	**Blood**							**Blood**	**Blood**						**ECG**	**Blood**	**Blood**	**Blood**
Anytime	X															X	X[a]	X[a]	X[a]
Pre-TSR-042 and TSR-022 infusion[b]		X							X	X									
Post-TSR-042 infusion[c]																			
0.5 h (±5 min)[d]		X								X									
1 h (±15 min)[e]		X																	
2 h (±30 min)		X								X									
3 h (±30 min)		X																	
24 h (±4 h)			X								X								
48 h (±4 h)				X								X							
96 h (±12 h)						X							X						
168 h (±24 h)							X							X					
336 h (±24 h)								X							X				
Pre-pemetrexed infusion[b]		X							X										
Post-pemetrexed infusion																			
10 min (±2 min)[f]		X							X										
0.5 h (±5 min)		X																	
1 h (±15 min)		X																	
4 h (±15 min)		X																	
6 h (±30 min)		X																	
8 h (±1 h)		X																	
24 h (±2 h)			X																

Table 44: PK and ADA Blood Sampling and ECG Schedule - Part F – TSR-042 + TSR-022 + Carboplatin-Pemetrexed - Screening and Treatment Cycles (Continued)

Cycle/Visit	Screening	Cycle 1							Cycle 2	Cycle 5						EOT		Safety follow-up (Post-treatment)	
Day	-21 to -1	1	2	3	4	5	8	15	1	1	2	3	5	8	15	7 days post-treatment		30±7 Days	90±7 Days
Time Point/Assessment	ECG	Blood							Blood	Blood						ECG	Blood	Blood	Blood
Pre-carboplatin infusion[b]		X							X										
Post-carboplatin infusion																			
0.5 h (±5 min)[g]		X							X										
1 h (±15 min)[h]		X							X										
4 h (±15 min)		X																	
6 h (±30 min)		X																	
8 h (±1 h)		X																	
24 h (±2 h)			X																

Abbreviations: ADA = anti-drug antibody; ECG = electrocardiogram; EOT = end of treatment; PK = pharmacokinetic.
Infusion order: 1) TSR-042 30 min; 2) TSR-022 30 min; 3) pemetrexed 10 min; 4) carboplatin 30 or 60 min.
Note: All sampling times are relative to the start dosing of the specified study treatment.
Note: PK assessments will be performed for TSR-042, TSR-022, carboplatin, and pemetrexed. ADA assessments will be performed for TSR-042 and TSR-022.
[a] Sample collected for TSR-042 ADA assessment only.
[b] To be obtained within 30 minutes prior to administration of the specified study treatment. For both TSR-042 and TSR-022, it is obtained within 30 min prior to the administration of TSR-042.
[c] Samplings for both TSR-042 and TSR-022 use the same schedule and are relative to the start infusion of TSR-042.
[d] End of infusion for TSR-042.
[e] End of infusion for TSR-022.
[f] End of infusion for pemetrexed.
[g] For carboplatin, 0.5 h sample is collected during the infusion for 1 h insert and the end of infusion for 0.5 h insert.
[h] For carboplatin, 1 h sample is collected at the end of infusion for 1 h insert and as the postdose 1 h sample for 0.5 h insert.

Table 45: PK and ADA Blood Sampling and ECG Schedule - Part G – TSR-042 + Carboplatin–Nab-Paclitaxel - Screening and Treatment Cycles

Cycle/Visit	Screening	Cycle 1							Cycle 2	Cycle 5						EOT		Safety follow-up (Post-treatment)	
Day	-21 to -1	1	2	3	4	5	8	15	1	1	2	3	5	8	15	7 days post-treatment		30±7 days	90±7 days
Time Point/Assessment	ECG	Blood							Blood	Blood						ECG	Blood	Blood	Blood
Anytime	X															X	X[a]	X[a]	X[a]
Pre-TSR-042 infusion[b]		X							X	X									
Post-TSR-042 infusion																			
0.5 h (±5 min)[c]		X								X									
2 h (±30 min)		X								X									
24 h (±4 h)			X								X								
48 h (±4 h)				X								X							
96 h (±12 h)						X							X						
168 h (±24 h)							X							X					
336 h (±24 h)								X							X				
Pre-nab-paclitaxel infusion[b]		X							X										
Post-nab-paclitaxel infusion																			
30 min (±2 min)[c]		X							X										
1.0 h (±5 min)		X																	
1.5 h (±15 min)		X																	
3 h (±15 min)		X																	
6 h (±30 min)		X																	
8 h (±1 h)		X																	
24 h (±2 h)			X																
48 h (±4 h)				X															
72 h (±8 h)					X														
96 h (±12 h)						X													

Table 45: PK and ADA Blood Sampling and ECG Schedule - Part G – TSR-042 + Carboplatin–Nab-Paclitaxel - Screening and Treatment Cycles (Continued)

Cycle/Visit	Screening	Cycle 1							Cycle 2	Cycle 5						EOT		Safety follow-up (Post treatment)	
Day	-21 to -1	1	2	3	4	5	8	15	1	1	2	3	5	8	15	7 days post-treatment		30±7 days	90±7 days
Time Point/Assessment	ECG	Blood							Blood	Blood						ECG	Blood	Blood	Blood
Pre-carboplatin infusion[b]		X							X										
Post-carboplatin infusion																			
0.5 h (±5 min)[d]		X							X										
1 h (±15 min)[e]		X							X										
4 h (±15 min)		X																	
6 h (±30 min)		X																	
8 h (±1 h)		X																	
24 h (±2 h)			X																

Abbreviations: ADA = anti-drug antibody; ECG = electrocardiogram; EOT = end of treatment; PK = pharmacokinetic.
Infusion order: 1) TSR-042 30 min; 2) nab-paclitaxel 30 min; 3) carboplatin 30 min or 60 min.
Note: All sampling times are relative to the start dosing of the specified study treatment.
Note: PK assessments will be performed for TSR-042, carboplatin, and nab-paclitaxel. ADA assessments will be performed for TSR-042.
[a] Sample collected for TSR-042 ADA assessment only.
[b] To be obtained within 30 minutes prior to administration of the specified study treatment.
[c] Obtained at the end of infusion of the specified study treatment.
[d] For carboplatin, 0.5 h sample is collected during the infusion for 1 h insert and the end of infusion for 0.5 h insert.
[e] For carboplatin, 1 h sample is collected at the end of infusion for 1 h insert and as the postdose 1 h sample for 0.5 h insert.

Table 46: PK and ADA Blood Sampling and ECG Schedule - Part H – TSR-042 + TSR-022 + Carboplatin–Nab-Paclitaxel - Screening and Treatment Cycles

Cycle/Visit	Screening	Cycle 1							Cycle 2	Cycle 5						EOT		Safety follow-up (Post treatment)	
Day	-21 to -1	1	2	3	4	5	8	15	1	1	2	3	5	8	15	7 days post-treatment		30±7 days	90±7 days
Time Point/Assessment	ECG	Blood							Blood	Blood						ECG	Blood	Blood	Blood
Anytime	X															X	X[a]	X[a]	X[a]
Pre-TSR-042 and TSR-022 infusion[b]		X							X	X									
Post-TSR-042 infusion[c]																			
0.5 h (±5 min)[d]		X								X									
1 h (±15 min)[e]		X																	
2 h (±30 min)		X								X									
3 h (±30 min)		X																	
24 h (±4 h)			X								X								
48 h (±4 h)				X								X							
96 h (±12 h)						X							X						
168 h (±24 h)							X							X					
336 h (±24 h)								X							X				
Pre-nab-paclitaxel infusion[b]		X							X										
Post-nab-paclitaxel infusion																			
30 min (±2 min)[f]		X							X										
1.0 h (±5 min)		X																	
1.5 h (±15 min)		X																	
3 h (±15 min)		X																	
6 h (±30 min)		X																	
8 h (±1 h)		X																	
24 h (±2 h)			X																
48 h (±4 h)				X															
72 h (±8 h)					X														

Table 46: PK and ADA Blood Sampling and ECG Schedule - Part H – TSR-042 + TSR-022 + Carboplatin–Nab-Paclitaxel - Screening and Treatment Cycles (Continued)

Cycle/Visit	Screening	Cycle 1							Cycle 2	Cycle 5						EOT		Safety follow-up (Post treatment)	
Day	-21 to -1	1	2	3	4	5	8	15	1	1	2	3	5	8	15	7 days post-treatment		30±7 days	90±7 days
Time Point/Assessment	ECG	Blood							Blood	Blood						ECG	Blood	Blood	Blood
96 h (±12 h)						X													
Pre-carboplatin infusion[b]		X							X										
Post-carboplatin infusion																			
0.5 h (±5 min)[g]		X							X										
1 h (±15 min)[h]		X							X										
4 h (±15 min)		X																	
6 h (±30 min)		X																	
8 h (±1 h)		X																	
24 h (±2 h)			X																

Abbreviations: ADA = anti-drug antibody; ECG = electrocardiogram; EOT = end of treatment; PK = pharmacokinetic.
Infusion order: 1) TSR-042 30 min; 2) TSR-022 30 min; 3) nab-paclitaxel 30 min; 4) carboplatin 30 or 60 min.
Note: All sampling times are relative to the start dosing of the specified study treatment.
Note: PK assessments will be performed for TSR-042, TSR-022, carboplatin, and nab-paclitaxel. ADA assessments will be performed for TSR-042 and TSR-022.
[a] Sample collected for TSR-042 ADA assessment only.
[b] To be obtained within 30 minutes prior to administration of the specified study treatment. For both TSR-042 and TSR-022, it is obtained within 30 min prior to the administration of TSR-042.
[c] Samplings for both TSR-042 and TSR-022 use the same schedule and are relative to the start infusion of TSR-042.
[d] End of infusion for TSR-042.
[e] End of infusion for TSR-022.
[f] End of infusion for nab-paclitaxel.
[g] For carboplatin, 0.5 h sample is collected during the infusion for 1 h insert and the end of infusion for 0.5 h insert.
[h] For carboplatin, 1 h sample is collected at the end of infusion for 1 h insert and as the postdose 1 h sample for 0.5 h insert.

Table 47: PK and ADA Blood Sampling and ECG Schedule - Part I – TSR-042 + TSR-022 + Carboplatin-Paclitaxel - Screening and Treatment Cycles

Cycle/Visit	Screening	Cycle 1							Cycle 2	Cycle 5						EOT		Safety follow-up (Post treatment)	
Day	-21 to -1	1	2	3	4	5	8	15	1	1	2	3	5	8	15	7 days post-treatment		30±7 days	90±7 days
Time Point/Assessment	ECG	Blood							Blood	Blood						ECG	Blood	Blood	Blood
Anytime	X															X	X[a]	X[a]	X[a]
Pre-TSR-042 and TSR-022 infusion[b]		X							X	X									
Post-TSR-042 infusion[c]																			
0.5 h (±5 min)[d]		X								X									
1 h (±15 min)[e]		X																	
2 h (±30 min)		X								X									
3 h (±30 min)		X																	
24 h (±4 h)			X								X								
48 h (±4 h)				X								X							
96 h (±12 h)						X							X						
168 h (±24 h)							X							X					
336 h (±24 h)								X							X				
Pre-paclitaxel infusion[b]		X							X										
Post-paclitaxel infusion																			
1.5 h (±15 min)[f]		X																	
3 h (±15 min)[g]		X																	
6 h (±30 min)		X																	
8 h (±1 h)		X																	
24 h (±2 h)			X																
48 h (±4 h)				X															
72 h (±8 h)					X														
96 h (±12 h)						X													

Table 47: PK and ADA Blood Sampling and ECG Schedule - Part I – TSR-042 + TSR-022 + Carboplatin-Paclitaxel - Screening and Treatment Cycles (Continued)

Cycle/Visit	Screening	Cycle 1							Cycle 2	Cycle 5						EOT		Safety follow-up (Post treatment)	
Day	-21 to -1	1	2	3	4	5	8	15	1	1	2	3	5	8	15	7 days post-treatment		30±7 days	90±7 days
Time Point/Assessment	ECG	Blood							Blood	Blood						ECG	Blood	Blood	Blood
Pre-carboplatin infusion[b]	wp	X							X										
Post-carboplatin infusion																			
0.5 h (±5 min)[h]		X							X										
1 h (±15 min)[i]		X							X										
4 h (±15 min)		X																	
6 h (±30 min)		X																	
8 h (±1 h)		X																	
24 h (±2 h)			X																

Abbreviations: ADA = anti-drug antibody; ECG = electrocardiogram; EOT = end of treatment; PK = pharmacokinetic.
Infusion order: 1) TSR-042 30 min; 2) TSR-022 30 min; 3) paclitaxel 3 hours; 4) carboplatin 30 or 60 min.
Note: All sampling times are relative to the start dosing of the specified study treatment.
Note: PK assessments will be performed for TSR-042, TSR-022, carboplatin, and paclitaxel. ADA assessments will be performed for TSR-042 and TSR-022.
[a] Sample collected for TSR-042 ADA assessment only.
[b] To be obtained within 30 minutes prior to administration of the specified study treatment. For both TSR-042 and TSR-022, it is obtained within 30 min prior to the administration of TSR-042.
[c] Samplings for both TSR-042 and TSR-022 use the same schedule and are relative to the start infusion of TSR-042.
[d] End of infusion for TSR-042.
[e] End of infusion for TSR-022.
[f] During the infusion of paclitaxel.
[g] End of infusion of paclitaxel.
[h] For carboplatin, 0.5 h sample is collected during the infusion for 1 h insert and the end of infusion for 0.5 h insert.
[i] For carboplatin, 1 h sample is collected at the end of infusion for 1 h insert and as the postdose 1 h sample for 0.5 h insert.

Table 48: TSR-042 and Niraparib Combination Treatment Administration and Dispensation/Collection - Part A

Cycle/Visit	1	2	3	4	5	6	Subsequent Cycles
Day	**1**	**1**	**1**	**1**	**1**	**1**	**1**
Niraparib 200 mg PO on Days 1 to 21 Q3W (dose level 1)[a,b,c]	X	X	X	X	X	X	X
Niraparib 300 mg PO on Days 1 to 21 Q3W (dose level 2)[a,c]	X	X	X	X	X	X	X
TSR-042 IV on Day 1 Q3W for 4 cycles, then Day 1 Q6W	X[d]	X[d]	X[d]	X[d]	X[e]		X[e]

Abbreviations: IV = intravenous; PO = oral; Q3W = every 3 weeks; Q6W = every 6 weeks; QD = once daily.

[a] On Day 1 of each cycle conducted at the study site, the niraparib dose will be administered upon completion of TSR-042 infusion. After the Day 1 visit, patients will continue to take niraparib each day of every cycle thereafter (i.e., on Days 1 to 21) until treatment discontinuation.

[b] The dose of niraparib may be increased after Cycle 2 to a higher dose level that has been found to be safe during the dose-escalation phase following discussion with the Sponsor. Otherwise, niraparib will continue to be administered during each cycle at the same regimen as in Cycle 1.

[c] Niraparib will be dispensed/collected on Day 1 of every 21-day cycle (Q3W).

[d] TSR-042 administered at the study site IV at 500 mg on Day 1 of every 3-week cycle (Q3W) for 4 cycles.

[e] TSR-042 administered at the study site IV at 1,000 mg on Day 1 of every other cycle (Q6W) for up to 2 years or until progression, unacceptable toxicity, patient withdrawal, Investigator's decision, or death.

Table 49: TSR-042 and Carboplatin-Paclitaxel Combination Treatment Administration - Part B

Cycle/Visit	1	2	3	4	5	6	Subsequent Cycles
Day	**1**	**1**	**1**	**1**	**1**	**1**	**1**
Carboplatin AUC of 5 or 6 IV on Day 1[a,b,c]	X	X	X	X	X	X	
Paclitaxel 175 mg/m^2 IV on Day 1[b,c]	X	X	X	X	X	X	
TSR-042 on Day 1 Q3W for 4 cycles, then Day 1 Q6W[b]	X[d]	X[d]	X[d]	X[d]	X[e]		X[e]

Abbreviations: AUC = area under the plasma or serum concentration-time curve; IV = intravenous; Q3W = every 3 weeks; Q6W = every 6 weeks.

[a] The carboplatin dose will be determined by the Investigator, taking into consideration the patient's prior anticancer therapies and pre-existing medical conditions.

[b] The TSR-042 infusion is administered first, followed by the paclitaxel infusion and the carboplatin infusion.

[c] Carboplatin and paclitaxel will be administered for 4 to 6 cycles as clinically indicated.

[d] TSR-042 administered at the study site IV at 500 mg on Day 1 of every 3-week cycle (Q3W) for 4 cycles.

[e] TSR-042 administered at the study site IV at 1,000 mg on Day 1 of every other cycle (Q6W) for up to 2 years or until progression, unacceptable toxicity, patient withdrawal, Investigator's decision, or death.

Table 50: TSR-042, Niraparib, and Bevacizumab Combination Treatment Administration and Dispensation/Collection-Part C

Cycle/Visit	1	2	3	4	5	6	Subsequent Cycles
Day	**1**	**1**	**1**	**1**	**1**	**1**	**1**
Niraparib 200 mg PO on Days 1 to 21 Q3W (dose level 1)[a,b,c]	X	X	X	X	X	X	X
Niraparib 300 mg PO on Days 1 to 21 Q3W (dose level 2)[a,c]	X	X	X	X	X	X	X
TSR-042 IV on Day 1 Q3W for 4 cycles, then Day 1 Q6W	X[d]	X[d]	X[d]	X[d]	X[e]		X[e]
Bevacizumab IV on Day 1 Q3W for up to 15 months[f]	X	X	X	X	X	X	X

Abbreviations: IV = intravenous; PO = oral; Q3W = every 3 weeks; Q6W = every 6 weeks; QD = once daily.

[a] On Day 1 of each cycle conducted at the study site, the niraparib dose will be administered upon completion of TSR-042 infusion. After the Day 1 visit, patients will continue to take niraparib each day of every cycle thereafter (i.e., on Days 1 to 21) until treatment discontinuation.

[b] The dose of niraparib may be increased after Cycle 2 to a higher dose level that has been found to be safe during the dose-escalation phase following discussion with the Sponsor. Otherwise, niraparib will continue to be administered during each cycle at the same regimen as in Cycle 1.

[c] Niraparib will be dispensed/collected on Day 1 of every 21-day cycle (Q3W).

[d] TSR-042 administered at the study site IV at 500 mg on Day 1 of every 3-week cycle (Q3W) for 4 cycles.

[e] TSR-042 administered at the study site IV at 1,000 mg on Day 1 of every other cycle (Q6W) for up to 2 years or until progression, unacceptable toxicity, patient withdrawal, Investigator's decision, or death.

[f] Bevacizumab administered at the study site IV at 15mg/kg on Day 1 of every 21-day cycle (Q3W) for up to 15 months.

Table 51: TSR-042, Carboplatin-Paclitaxel, and Bevacizumab Combination Treatment Administration - Part D

Cycle/Visit	1	2	3	4	5	6	Subsequent Cycles
Day	**1**	**1**	**1**	**1**	**1**	**1**	**1**
Carboplatin AUC of 5 or 6 IV on Day 1[a,b,c]	X	X	X	X	X	X	
Paclitaxel 175 mg/m^2 IV on Day 1[b,c]	X	X	X	X	X	X	
TSR-042 on Day 1 Q3W for 4 cycles, then Day 1 Q6W[b]	X[d]	X[d]	X[d]	X[d]	X[e]		X[e]
Bevacizumab IV on Day 1 Q3W for up to 15 months[f]	X	X	X	X	X	X	X

Abbreviations: AUC = area under the plasma or serum concentration-time curve; IV = intravenous; Q3W = every 3 weeks; Q6W = every 6 weeks.

[a] The carboplatin dose will be determined by the Investigator, taking into consideration the patient's prior anticancer therapies and pre-existing medical conditions.

[b] The TSR-042 infusion is administered first, followed by the paclitaxel infusion, the carboplatin infusion, and lastly the bevacizumab infusion.

[c] Carboplatin and paclitaxel will be administered for 4 to 6 cycles as clinically indicated.

[d] TSR-042 administered at the study site IV at 500 mg on Day 1 of every 3-week cycle (Q3W) for 4 cycles.

[e] TSR-042 administered at the study site IV at 1,000 mg on Day 1 of every other cycle (Q6W) until disease progression, unacceptable toxicity, patient withdrawal, Investigator's decision, or death.

[f] Bevacizumab administered at the study site IV at 15mg/kg on Day 1 of every 21-day cycle (Q3W) for up to 15 months.

Table 52: TSR-042 and Carboplatin-Pemetrexed Combination Treatment Administration - Part E

Cycle/Visit	**1**	**2**	**3**	**4**	**5**	**6**	**Subsequent Cycles**
Day	**1**	**1**	**1**	**1**	**1**	**1**	**1**
TSR-042 on Day 1 Q3W[a]	X	X	X	X	X	X	X
Pemetrexed 500 mg/m^2 IV on Day 1 Q3W[b]	X	X	X	X	X	X	X
Carboplatin AUC of 5 or 6 IV on Day 1 Q3W[c]	X	X	X	X	X	X	

Abbreviations: AUC = area under the plasma or serum concentration-time curve; IV = intravenous; Q3W = every 3 weeks.
Infusion order: 1) TSR-042 30 min; 2) pemetrexed 10 min; 3) carboplatin 30 or 60 min.

[a] TSR-042 will be administered at the study site IV at 500 mg on Day 1 of every 21-day cycle (Q3W) for up to 2 years or until disease progression, unacceptable toxicity, patient withdrawal, Investigator's decision, or death.

[b] Pemetrexed 500 mg/m^2 will be administered by IV infusion over 10 minutes Q3W for up to 2 years or until progression, unacceptable toxicity, patient withdrawal, Investigator's decision, or death. All patients should receive the appropriate supplementation of vitamin B12, folic acid, and corticosteroid prophylaxis.

[c] The carboplatin dose will be determined by the Investigator, taking into consideration the patient's prior anticancer therapies and pre-existing medical conditions. Carboplatin will be administered on Day 1 of every 21-day cycle (Q3W) for 4 to 6 cycles as clinically indicated.

Table 53: TSR-042, TSR-022, and Carboplatin-Pemetrexed Combination Treatment Administration - Part F

Cycle/Visit	1	2	3	4	5	6	Subsequent Cycles
Day	**1**	**1**	**1**	**1**	**1**	**1**	**1**
TSR-042 on Day 1 Q3W[a]	X	X	X	X	X	X	X
TSR-022 on Day 1 Q3W[b]	X	X	X	X	X	X	X
Pemetrexed 500 mg/m^2 IV on Day 1 Q3W[c]	X	X	X	X	X	X	X
Carboplatin AUC of 5 or 6 IV on Day 1 Q3W[d]	X	X	X	X	X	X	

Abbreviations: AUC = area under the plasma or serum concentration-time curve; IV = intravenous; Q3W = every 3 weeks.
Infusion order: 1) TSR-042 30 min; TSR-022 30 min; 3) pemetrexed 10 min; 4) carboplatin 30 or 60 min.

[a] TSR-042 will be administered at the study site IV at 500 mg on Day 1 of every 21-day cycle (Q3W) for up to 2 years or until disease progression, unacceptable toxicity, patient withdrawal, Investigator's decision, or death.

[b] TSR-022 will be administered at the study site IV at 900 mg on Day 1 of every 21-day cycle (Q3W) for up to 2 years or until disease progression, unacceptable toxicity, patient withdrawal, Investigator's decision, or death. A dose of 900 mg of TSR-022 has been found to be the highest safest dose that provides maximal pharmacodynamic effect; this dose may be lowered to dose level -1 if needed. Based on available safety information, the Sponsor may decide to test additional dose levels of TSR-022.

[c] Pemetrexed 500 mg/m^2 will be administered by IV infusion over 10 minutes Q3W. All patients should receive the appropriate supplementation of vitamin B12, folic acid, and corticosteroid prophylaxis for up to 2 years or until disease progression, unacceptable toxicity, patient withdrawal, Investigator's decision, or death.

[d] The carboplatin dose will be determined by the Investigator, taking into consideration the patient's prior anticancer therapies and pre-existing medical conditions. Carboplatin will be administered on Day 1 of every 21-day cycle (Q3W) for 4 to 6 cycles as clinically indicated.

Table 54: TSR-042 and Carboplatin–Nab-Paclitaxel Combination Treatment Administration - Part G

Cycle/Visit	**1**	**2**	**3**	**4**	**5**	**6**	**Subsequent Cycles**
Day	**1**	**1**	**1**	**1**	**1**	**1**	**1**
TSR-042 on Day 1 Q3W[a]	X	X	X	X	X	X	X
Nab-paclitaxel 100 mg/m^2 IV on Day 1 Q1W[b]	X	X	X	X	X	X	X
Carboplatin AUC of 5 or 6 IV on Day 1 Q3W[c]	X	X	X	X	X	X	

Abbreviations: AUC = area under the plasma or serum concentration-time curve; IV = intravenous; Q3W = every 3 weeks.
Infusion order: 1) TSR-042 30 min; 2) nab-paclitaxel 30 min; 3) carboplatin 30 or 60 min.

[a] TSR-042 will be administered at the study site IV at 500 mg on Day 1 of every 21-day cycle (Q3W) for up to 2 years or until disease progression, unacceptable toxicity, patient withdrawal, Investigator's decision, or death.

[b] Nab-paclitaxel 100 mg/m^2 will be administered by IV infusion over 30 minutes on Days 1, 8, and 15 (Q1W) of every 3-week cycle for 4 to 6 cycles as clinically indicated.

[c] The carboplatin dose will be determined by the Investigator, taking into consideration the patient's prior anticancer therapies and pre-existing medical conditions. Carboplatin will be administered on Day 1 of every 21-day cycle (Q3W) for 4 to 6 cycles as clinically indicated.

Table 55: TSR-042, TSR-022, and Carboplatin–Nab-Paclitaxel Combination Treatment Administration - Part H

Cycle/Visit	1	2	3	4	5	6	Subsequent Cycles
Day	**1**	**1**	**1**	**1**	**1**	**1**	**1**
TSR-042 on Day 1 Q3W[a]	X	X	X	X	X	X	X
TSR-022 on Day 1 Q3W[b]	X	X	X	X	X	X	X
Nab-paclitaxel 100 mg/m^2 IV on Day 1 Q1W[c]	X	X	X	X	X	X	X
Carboplatin AUC of 5 or 6 IV on Day 1 Q3W[d]	X	X	X	X	X	X	

Abbreviations: AUC = area under the plasma or serum concentration-time curve; IV = intravenous; Q1W = every week; Q3W = every 3 weeks.
Infusion order: 1) TSR-042 30 min; TSR-022 30 min; 3) nab-paclitaxel 30 min; 4) carboplatin 30 or 60 min.

[a] TSR-042 will be administered at the study site IV at 500 mg on Day 1 of every 21-day cycle (Q3W) for up to 2 years or until disease progression, unacceptable toxicity, patient withdrawal, Investigator's decision, or death or until treatment discontinuation.

[b] TSR-022 will be administered at the study site IV at 900 mg on Day 1 of every 21-day cycle (Q3W) for up to 2 years or until disease progression, unacceptable toxicity, patient withdrawal, Investigator's decision, or death. 900 mg of TSR-022 is the highest dose tested in dose escalation in combination with TSR-042 that provides maximal pharmacodynamic effect; this dose may be lowered to dose level -1 if needed. Based on available safety information, the Sponsor may decide to test additional dose levels of TSR-022.

[c] Nab-paclitaxel 100 mg/m^2 will be administered by IV infusion over 30 minutes Q1W on Days 1, 8, and 15 (Q1W) of every 3-week cycle for 4 to 6 cycles as clinically indicated.

[d] The carboplatin dose will be determined by the Investigator, taking into consideration the patient's prior anticancer therapies and pre-existing medical conditions. Carboplatin will be administered on Day 1 of every 21-day cycle (Q3W) for 4 to 6 cycles as clinically indicated.

Table 56: TSR-042, TSR-022, and Carboplatin-Paclitaxel Combination Treatment Administration - Part I

Cycle/Visit	1	2	3	4	5	6	Subsequent Cycles
Day	**1**	**1**	**1**	**1**	**1**	**1**	**1**
TSR-042 on Day 1 Q3W[a]	X	X	X	X	X	X	X
TSR-022 on Day 1 Q3W[b]	X	X	X	X	X	X	X
Paclitaxel 175 mg/m^2 IV on Day 1 Q3W[c]	X	X	X	X	X	X	X
Carboplatin AUC of 5 or 6 IV on Day 1 Q3W[d]	X	X	X	X	X	X	

Abbreviations: AUC = area under the plasma or serum concentration-time curve; IV = intravenous; Q3W = every 3 weeks.
Infusion order: 1) TSR-042 30 min; 2) TSR-022 30 min; 3) paclitaxel 3 hours; 4) carboplatin 30 or 60 min.

[a] TSR-042 will be administered at the study site IV at 500 mg on Day 1 of every 3 weeks (Q3W) for up to 2 years or until disease progression, unacceptable toxicity, patient withdrawal, Investigator's decision, or death.

[b] TSR-022 will be administered at the study site IV at 900 mg on Day 1 of every 21-day cycle (Q3W) for up to 2 years or until disease progression, unacceptable toxicity, patient withdrawal, Investigator's decision, or death. 900 mg of TSR-022 is the highest dose tested in dose escalation in combination with TSR-042 that provides maximal pharmacodynamic effect; this dose may be lowered to dose level -1 if needed. Based on available safety information, the Sponsor may decide to test additional dose levels of TSR-022.

[c] Paclitaxel 175 mg/m^2 will be administered by IV infusion over 3 hours Q3W for 4 to 6 cycles as clinically indicated.

[d] The carboplatin dose will be determined by the Investigator, taking into consideration the patient's prior anticancer therapies and pre-existing medical conditions. Carboplatin will be administered on Day 1 of every 21-day cycle (Q3W) for 4 to 6 cycles as clinically indicated.

11.2. Procedures by Visit

11.2.1. Screening Visit

Standard of care tests or procedures, including radiographic scans, laboratory assessments (fasting glucose at baseline), ECG, physical examination, vital signs, height, and weight, performed prior to the patient signing the ICF can be used as part of the screening assessments as long as the tests or procedures meet the protocol-required timelines (i.e., within 28 days of first dose for these procedures with the exception of pregnancy testing, which must be conducted within 72 hours of first dose) and any relevant guidelines (e.g., diagnostic quality for radiographic scans). Note that source documents must clearly identify the standard of care tests or procedures that are used for screening, and the results of these tests or procedures must be entered in the eCRF.

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

- Obtain written informed consent
  - A single study ICF will be signed before any study procedures.
- Inclusion/exclusion criteria review
- Demographics
- Medical/surgical/cancer/medication history
- For patients in Parts A, B, C, D, E, and G:
  - Optional collection of archival FFPE tumor tissue sample (if available) for biomarker testing
- For patients in Parts F, H, and I:
  - Mandatory collection of archival FFPE tumor tissue sample (if available) prior to start of study treatment for assessment of the tumor microenvironment for exploratory biomarkers.
- Blood sample obtained for exploratory biomarkers
- Tumor assessment (CT/ MRI) for determination of measurable disease (RECIST v1.1)
  - Chest, abdomen, and pelvis (head, if clinically indicated) CT (preferred method) or MRI (if clinically indicated). If the chest and/or head CT/MRI is clear at screening, repeat imaging is not required in the absence of clinical indication requiring follow-up. PET/CT may be used according to RECIST v1.1 guidelines.
  - Scans performed prior to informed consent as part of routine clinical management are acceptable for use as initial tumor imaging if they are of diagnostic quality and are performed within 28 days prior to first dose date.
  - Bone scans performed per standard of care.
- Laboratory assessments:

  - CBC
  - Serum chemistry
  - Coagulation
  - Serum pregnancy test for women of childbearing potential only within 72 hours of first dose of study treatment
  - Serum tumor markers (if indicated)
  - Urinalysis
  - TSH, T3 or FT3, and FT4 or equivalent tests if TSH, T3 or FT3, or FT4 are not available
- ECG
- Physical examination
- Vital signs (BP, pulse, and temperature) and weight
- Height
- ECOG performance status
- Concomitant medications
- AE monitoring

11.2.2. Cycle 1

At Cycle 1, all patients will undergo the procedures as outlined in the following subsections.

Day 1

- Inclusion/exclusion criteria review
- Blood sample to be obtained predose for exploratory biomarkers
- Blood samples for PK and ADA assessment
- Laboratory assessments (if screening assessments were performed within 72 hours of Day 1, repeat testing is not required):
  - CBC
  - Serum chemistry
  - Serum tumor markers (if indicated)
  - Urinalysis
- ECG
  - **Parts A and C only:** ECG monitoring to be conducted 30 minutes prior to and 2 hours after the niraparib dose
- Symptom-directed physical examination

- Vital signs (BP, pulse, and temperature) and weight
- Concomitant medications
- AE monitoring
- TSR-042 study treatment administered at the study site after other visit procedures completed
- For patients in Parts G and H, nab-paclitaxel infusion will be administered after other visit procedures are completed on Day 1 of every week (Q1W).
- **Parts A and C only:** niraparib first dose administered at the study site after completion of all infusions
- **Parts B and D only:** carboplatin-paclitaxel infusion administered at the study site after completion of TSR-042 infusion (Order of administration: TSR-042 infusion followed by paclitaxel infusion followed by carboplatin infusion)
- **Parts C and D only:** bevacizumab infusion administered at the study site following carboplatin infusion
- **Part E only:** carboplatin-pemetrexed infusion administered at the study site after completion of TSR-042 infusion (Order of administration: TSR-042 infusion followed by pemetrexed infusion followed by carboplatin infusion)
- **Part F only:** TSR-022 infusion administered at the study site after completion of TSR-042 infusion, followed by carboplatin-pemetrexed infusion (Order of administration: TSR-042 infusion followed by TSR-022 infusion followed by pemetrexed infusion followed by carboplatin infusion)
- **Part G only:** carboplatin–nab-paclitaxel infusion administered at the study site after completion of TSR-042 infusion (Order of administration: TSR-042 infusion followed by nab-paclitaxel infusion followed by carboplatin infusion)
- **Part H only:** TSR-022 infusion administered at the study site after completion of TSR-042 infusion, followed by carboplatin–nab-paclitaxel infusion (Order of administration: TSR-042 infusion followed by TSR-022 infusion followed by nab-paclitaxel infusion followed by carboplatin infusion)
- **Part I only:** TSR-022 infusion administered at the study site after completion of TSR-042 infusion, followed by carboplatin-paclitaxel infusion (Order of administration: TSR-042 infusion followed by TSR-022 infusion followed by paclitaxel infusion followed by carboplatin infusion)

Day 2

- Blood samples for PK and ADA assessment

Day 3

- **Parts B, D, E, F, G, H, and I:** blood samples for PK assessment

Day 4

- **Parts B, D, G, H, and I:** blood samples for PK assessment

Day 5

- Blood samples for PK and ADA assessment

Day 8

Visit to be conducted at the study site to include the following:

- Blood samples for PK and ADA assessment
- CBC
- Vital signs (BP, pulse, and temperature) and weight
- Concomitant medications
- AE monitoring

Day 15

- Blood samples for PK and ADA assessment
- Laboratory assessments:
  - CBC
  - Serum chemistry
  - Coagulation
- Symptom-directed physical examination
- Vital signs (BP, pulse, and temperature) and weight
- Concomitant medications
- AE monitoring
- For Parts E, F, G, H, and I: blood samples to be obtained predose for exploratory biomarkers

11.2.3. Cycles 2 through 6 and Subsequent Cycles

- Beginning at Cycle 2, all patients will undergo Day 1 procedures at every 21-day cycle as outlined below. At specific cycles, patients will undergo additional procedures as described in the subsequent subsections.
- For patients in Parts G and H, nab-paclitaxel infusion will be administered after other visit procedures are completed on Day 1 of every week (Q1W).
- On-treatment and progression biopsies are optional. In the subset of patients who undergo serial biopsies, biomarkers will be evaluated in new tumor samples obtained at approximately 4 to 6 weeks after initiating study treatment and, whenever possible,

at the time of disease progression (EOT visit) (note: while the biopsy is voluntary, it is highly encouraged). A core biopsy is recommended (details are provided in the Study Laboratory Manual).

Day 1

- Tumor assessment (RECIST v1.1)
  - Radiographic evaluations (CT or MRI of the chest, abdomen, and pelvis) and appropriate testing of serum tumor markers, where applicable (to assess the extent of disease), will be conducted at 12 weeks after receiving the first dose of study treatment (i.e., within 1 week prior to Day 1 of Cycle 5) and every 12 weeks (84 ± 10 days) thereafter until progression while on study treatment independent of cycle delays or dose interruptions, or at any time when progression of disease is suspected. CT or MRI of the head will be conducted if clinically indicated; bone scans will be conducted per standard of care. If a patient discontinues treatment for a reason other than progression, death, withdrawal of consent, or loss to follow-up, radiographic scans and serum tumor markers should continue at the specified intervals.
  - Per RECIST v1.1, CR or PR should be confirmed; tumor imaging for confirmation of 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 (i.e., 12 weeks later), whichever is clinically indicated.
- Laboratory assessments (may be done within 24 hours prior to the visit):
  - CBC
  - Serum chemistry
  - Coagulation (Day 1 of Cycles 2 and 3 only)
  - Urine pregnancy test for females of childbearing potential conducted every 3 cycles for duration of study (i.e., Cycle 4, Cycle 7, etc.).
  - Serum tumor markers (if indicated in conjunction with tumor assessment per RECIST v1.1)
  - Urinalysis
  - TSH, T3 or FT3, and FT4 (performed Q6W beginning at Day 1 of Cycle 2) or equivalent tests if TSH, T3 or FT3, or FT4 are not available
- Symptom-directed physical examination
- Vital signs (BP, pulse, and temperature) and weight
- ECOG performance status
- Concomitant medications
- AE monitoring

- **Parts A, B, C, and D only:** TSR-042 study treatment administered at the study site after other visit procedures are completed on Day 1 of every 21-day cycle (Q3W) for the first 4 cycles and on Day 1 of every other cycle (Q6W) thereafter
- **Parts E, F, G, H, and I only:** TSR-042 study treatment administered at the study site after other visit procedures are completed on Day 1 of every 21-day cycle (Q3W)
- **Parts A and C only:** niraparib first dose administered at the study site after completion of all infusions
- **Parts B and D only:** carboplatin-paclitaxel infusion administered at the study site after completion of TSR-042 infusion (Order of administration: TSR-042 infusion followed by paclitaxel infusion followed by carboplatin infusion)
- **Parts C and D only:** bevacizumab infusion administered at the study site following carboplatin infusion
- **Part E only:** carboplatin-pemetrexed infusion administered at the study site after completion of TSR-042 infusion (Order of administration: TSR-042 infusion followed by pemetrexed infusion followed by carboplatin infusion)
- **Part F only:** TSR-022 infusion administered at the study site after completion of TSR-042 infusion, followed by carboplatin-pemetrexed infusion (Order of administration: TSR-042 infusion followed by TSR-022 infusion followed by pemetrexed infusion followed by carboplatin infusion)
- **Part G only:** carboplatin–nab-paclitaxel infusion administered at the study site after completion of TSR-042 infusion (Order of administration: TSR-042 infusion followed by nab-paclitaxel infusion followed by carboplatin infusion)
- **Part H only:** TSR-022 infusion administered at the study site after completion of TSR-042 infusion, followed by carboplatin–nab-paclitaxel infusion (Order of administration: TSR-042 infusion followed by TSR-022 infusion followed by nab-paclitaxel infusion followed by carboplatin infusion)
- **Part I only:** TSR-022 infusion administered at the study site after completion of TSR-042 infusion, followed by carboplatin-paclitaxel infusion (Order of administration: TSR-042 infusion followed by TSR-022 infusion followed by paclitaxel infusion followed by carboplatin infusion)

11.2.3.1. Cycle 2

On-treatment biopsies are optional. In the subset of patients who undergo serial biopsies, biomarkers will be evaluated in new tumor samples obtained 4 to 6 weeks following Dose 1 (will fall within Cycle 2 and Cycle 3).

Day 1

- All Day 1 procedures as outlined in Section 11.2.3
- Blood sample to be obtained predose for exploratory biomarkers

- Blood samples for PK and ADA assessment
- **ECG – Parts A and C only**: ECG monitoring 30 minutes prior to and 2 hours after the niraparib dose

Day 2

- Parts A and C only: blood samples for PK assessment

11.2.3.2. Cycle 4

Day 1

- All Day 1 procedures as outlined in Section 11.2.3
- For Parts A, B, C, and D: blood samples for PK and TSR-042 ADA assessment
- For Parts E, F, G, H, and I: predose blood samples for exploratory biomarkers

Day 2

- For Parts A, B, C, and D: blood samples for PK and TSR-042 ADA assessment

Day 5

- For Parts A, B, C, and D: blood samples for PK and TSR-042 ADA assessment

Day 8

- For Parts A, B, C, and D: blood samples for PK and TSR-042 ADA assessment

Day 15

- For Parts A, B, C, and D: blood samples for PK and TSR-042 ADA assessment

11.2.3.3. Cycle 5

Day 1

- All Day 1 procedures as outlined in Section 11.2.3
- Blood samples for PK and TSR-042 and TSR-022 (as applicable) ADA assessment
- ECG – **Parts A and C only**: ECG monitoring 30 minutes prior to the niraparib dose

Day 2

- Blood samples for PK and TSR-042 and TSR-022 (as applicable) ADA assessment

Day 3

- For Parts E, F, G, H, and I: blood samples for PK and TSR-042 and TSR-022 (as applicable) ADA assessment

Day 5

- Blood samples for PK and TSR-042 and TSR-022 (as applicable) ADA assessment

Day 8

- Blood samples for PK and TSR-042 and TSR-022 (as applicable) ADA assessment

Day 15

- Blood samples for PK and TSR-042 and TSR-022 (as applicable) ADA assessment

11.2.3.4. Cycle 6

Day 1

- All Day 1 procedures as outlined in Section 11.2.3
- For Parts A, B, C, and D: blood samples for PK and TSR-042 ADA assessment
- For Parts E, F, G, H, and I: predose blood samples for exploratory biomarkers

11.2.3.5. Cycle 7

Day 1

- All Day 1 procedures as outlined in Section 11.2.3
- For Parts A, B, C, and D: blood samples for PK and TSR-042 ADA assessment

11.2.3.6. Cycle 11

Day 1

- All Day 1 procedures as outlined in Section 11.2.3
- For Parts A, B, C, and D: blood samples for PK and TSR-042 ADA assessment
- ECG – **Parts A and C only:** ECG monitoring 30 minutes prior to the niraparib dose

Day 2

- For Parts A, B, C, and D: blood samples for PK and TSR-042 and ADA assessment

Day 5

- For Parts A, B, C, and D: blood samples for PK and TSR-042 and ADA assessment

Day 8

- For Parts A, B, C, and D: blood samples for PK and TSR-042 ADA assessment

Day 15

- For Parts A, B, C, and D: blood samples for PK and TSR-042 and ADA assessment

11.2.3.7. Cycle 12

Day 1

- All Day 1 procedures as outlined in Section 11.2.3
- For Parts A, B, C, and D: blood samples for PK and TSR-042 and ADA assessment

11.2.3.8. Cycle 13

Day 1

- All Day 1 procedures as outlined in Section 11.2.3
- For Parts A, B, C, and D: blood samples for PK and TSR-042 and ADA assessment

11.2.4. End of Treatment

The following procedures will be performed:

- Blood samples for exploratory biomarkers upon disease progression (EOT visit)
- Blood samples for TSR-042 and TSR-022 (as applicable) ADA assessment
- Tumor assessment (RECIST v1.1)
  - A final set of radiographic images is required at the time of disease progression if not done within the last 4 weeks.
  - If a patient discontinues treatment for a reason other than progression or death, withdrawal of consent, or loss to follow-up, radiographic scans and appropriate testing of serum tumor markers testing should continue at the specified intervals.
- Laboratory assessments:
  - CBC
  - Serum chemistry
  - Serum tumor markers (if indicated in conjunction with tumor assessment per RECIST v1.1)
  - Urinalysis
  - TSH, T3 or FT3, and FT4 or equivalent
- ECG
- Physical examination
- Vital signs (BP, pulse, and temperature) and weight
- ECOG performance status
- Concomitant medications
- AE monitoring

- **Parts A and C only:** niraparib study treatment collected
- Progression biopsies are optional. In the subset of patients who undergo serial biopsies, biomarkers will be evaluated in new tumor samples obtained u disease progression (EOT visit).

11.2.5. Safety Follow-up

Safety follow-up visits are required only for those patients who have not started an alternate anticancer therapy. Subsequent anticancer therapy information is required to be captured through post-treatment if the patient starts alternate anticancer therapy.

11.2.5.1. 30 Days ± 7 Days Post-treatment

The following procedures will be performed:

- Blood sample for TSR-042 and TSR-022 (as applicable) ADA assessment
- Tumor assessment (RECIST v1.1)
  - If a patient discontinued treatment for a reason other than progression or death, withdrawal of consent, or loss to follow-up, radiographic scans and appropriate testing of serum tumor markers testing should continue at the specified intervals.
- Laboratory assessments (may be done at the study center's local laboratory or at a laboratory local to the patient if the laboratory is included on Food and Drug Administration [FDA] Form 1572):
  - Serum chemistry
  - Urine pregnancy
  - Serum tumor markers (if indicated in conjunction with tumor assessment per RECIST v1.1)
  - TSH, T3 or FT3, and FT4 (performed only if clinically indicated) or equivalent tests if TSH, T3 or FT3, or FT4 are not available
  - Urinalysis
- Symptom-directed physical examination
- Vital signs (BP, pulse, and temperature) and weight
- Concomitant medications
- AE monitoring: AEs are required to be captured through 30 days after cessation of study treatment, SAEs (see Section 10.6.5) 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), AESIs are required to be captured as described in Section 10.6.7, and any pregnancies that occur within 180 days post-treatment are to be captured..

11.2.5.2. 90 Days ± 7 Days Post-treatment

The following procedures will be performed:

- Blood sample for TSR-042 and TSR-022 (as applicable) ADA assessment
- Tumor assessment (RECIST v1.1)
  - If a patient discontinued treatment for a reason other than progression or death, withdrawal of consent, or loss to follow-up, radiographic scans and appropriate testing of serum tumor markers testing should continue at the specified intervals.
- Laboratory assessments (may be done at the study center's local laboratory or at a laboratory local to the patient if the laboratory is included on FDA Form 1572):
  - Serum chemistry to be conducted on Day 90 post-treatment (or to a minimum of 30 days post-treatment if the patient starts alternate anticancer therapy) to assess for possible AESIs (see Section 10.6.7). Serum chemistry measurements may be done at the study center's laboratory or at a laboratory local to the patient, if approved by the Investigator as an adequate laboratory.
  - Serum tumor markers (if indicated in conjunction with tumor assessment per RECIST v1.1)
- AE monitoring: SAEs (see Section 10.6.5) 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), AESIs are required to be captured as described in Section 10.6.7, and any pregnancies that occur within 180 days post-treatment are to be captured.

11.2.6. Survival Assessment

The following procedures will be performed:

- Tumor assessment (RECIST v1.1)
  - Patients who discontinue treatment for reasons other than disease progression, death, withdrawal of consent, or loss to follow-up will be followed for disease assessments, including radiographic scans and appropriate testing of serum tumor markers testing, per the specified schedule.
- Laboratory assessments
  - Serum tumor markers (if indicated in conjunction with tumor assessment per RECIST v1.1)
- AE monitoring
  - Any pregnancies that occur within 180 days post-treatment are to be captured.
  - In conjunction with survival assessment, AESI (regardless of causality) and study-drug related SAEs will be collected via telephone every 90 ± 14 days after the last dose of study treatment.

- Survival assessment
  - Patients will be followed up every 90 ± 14 days for survival status.

11.2.7. Unscheduled Visits

If dose interruption or modification of niraparib is required at any point on study because of hematologic toxicity, CBCs will be performed as described in Section 6.4.1.1.

12. STATISTICAL METHODS

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

All analyses will include summary statistics, including the number and percentage for categorical variables and the number of patients, mean, standard deviation, median, minimum, and maximum for continuous variables. Time-to-event analyses will be performed using Kaplan-Meier methods. Further details will be provided in the study SAP.

12.1. Study Population

Three analysis populations will be defined as follows:

- Safety population: All patients who receive any amount of study treatment. All safety endpoints will be assessed in the safety population, with the exception of DLT assessment, which will include only those patients completing the first cycle of therapy, unless the patient discontinued study treatment due to a DLT. Analyses of baseline characteristics and the primary analysis of efficacy endpoints will be performed on the safety population.
- PK population: All patients who receive at least 1 dose of study treatment and have at least 1 PK sample.
- ADA population: All patients who receive at least 1 dose of study treatment and have provided a predose blood sample and at least 1 postdose blood sample at or after 96 hours.

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

Demographics, baseline characteristics, and medical history information will be summarized by dose level for the Safety population using descriptive statistics. No formal statistical comparisons will be performed. Demographic, baseline characteristics, and medical history data for each patient will be provided in data listings.

12.3. Efficacy Analyses

12.3.1. General Methods

All analyses will include summary statistics, including number and percentage for categorical variables and number of patients, mean, standard deviation, median, minimum, and maximum for continuous variables. Two-sided exact 90% confidence intervals (CIs) based on the Clopper-Pearson[124] will be provided where appropriate. Time-to-event analyses will be performed using Kaplan-Meier methods. Comparisons will be made using descriptive statistics.

12.3.2. Secondary Efficacy Parameter(s)

ORR and DCR will be summarized using descriptive statistics including the number, percentage, and 2-sided 90% CIs.

DOR and PFS will be summarized using Kaplan-Meier analysis, including the number and percentage of events, number and percentage of censored patients, and the 25th, 50th, and 75th percentiles of times-to-event with 95% CIs.

12.4. Safety Analyses

The primary endpoints in the safety analysis are as follows:

- Determination of the RP2D based on the number of DLTs observed during the first cycle (i.e., during the first 21 days of treatment [Day 1 to Day 21 of Cycle 1]).
- Incidence of TEAEs occurring while patients are on treatment or up to 30 days after the last dose of study treatment
- Incidence of SAEs and AESIs occurring while patients are on study treatment or up to 90 days after the last dose of study treatment
- Changes in clinical laboratory parameters (hematology, serum chemistry, coagulation, thyroid function, and urinalysis), vital signs, ECOG performance status, ECG parameters (including QTc calculated using QTcF), physical examinations, and use of concomitant medications

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding system and displayed in tables and data listings using system organ class and preferred term.

Analyses of AEs will be performed for those events that are considered treatment-emergent, where treatment-emergent is defined per protocol as any AE with onset beginning at the day of first administration of study treatment, throughout the treatment period until 30 days after the last dose of study treatment, any SAE or AESI that occurs through 90 days after cessation of study treatment (or to a minimum of 30 days post-treatment if the patient starts alternate anticancer therapy), or any event that was present at baseline but worsened in intensity or was subsequently considered drug-related by the Investigator through the end of the study. DLTs will be tabulated by dose level.

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

The occurrence of and reasons for any requirement for dose interruption or modification will be tabulated, and distinguished as to presumptive causality from niraparib, TSR-042, TSR-022, carboplatin-paclitaxel, carboplatin-pemetrexed, carboplatin–nab-paclitaxel, or bevacizumab, if known.

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

Additional safety summaries will be provided for clinical laboratory tests, vital signs, ECOG performance status, ECGs, physical examinations, and usage of concomitant medications.

12.5. Pharmacokinetic Analyses

The analysis set for the PK parameters will be the PK population. Non-compartmental methods will be used to evaluate the PK characteristics as appropriate. Parameters of interest are AUC, minimum observed plasma or serum concentration (C_{min}), maximum observed plasma or serum concentration (C_{max}), clearance (after oral administration [CL/F] and after IV administration [CL]), volume of distribution (after oral administration [V_z/F] and after IV administration [V_z]), area under the plasma or serum concentration-time curve at steady state (AUC_{ss}), minimum observed plasma or serum concentration at steady state ($C_{min,ss}$), and maximum observed plasma or serum concentration at steady state ($C_{max,ss}$).

12.6. Immunogenicity Analyses

The analysis set for ADA analyses will be the ADA population. The number and percent of patients who become positive for ADAs and who develop neutralizing antibodies will be summarized by dose and regimen, by visit, and overall.

12.7. Biomarker Analyses

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

12.8. Determination of Sample Size

An initial sample size of approximately 12 to 24 patients is estimated for Part A of the study to provide an initial understanding of the incidence of DLTs and safety profiles of TSR-042 and niraparib combination treatment.

A total of approximately 12 patients will be enrolled in Part B of the study to provide an initial understanding of the safety profiles of TSR-042 and carboplatin-paclitaxel combination treatment.

A sample size of approximately 6 to 24 patients is estimated for Part C of the study to provide an initial understanding of the incidence of DLTs and safety profiles of TSR-042, niraparib and bevacizumab combination treatment.

A total of approximately 6 to 12 patients will be enrolled in Part D of the study to provide an initial understanding of the safety profiles of TSR-042, carboplatin-paclitaxel and bevacizumab combination treatment.

A total of approximately 6 to 12 patients will be enrolled in Part E of the study to provide an initial understanding of the safety profiles of TSR-042 and carboplatin-pemetrexed combination treatment.

A total of approximately 6 to 24 patients will be enrolled in Part F of the study to provide an initial understanding of the safety profiles of TSR-042, TSR-022, and carboplatin-pemetrexed combination treatment.

A total of approximately 6 to 12 patients will be enrolled in Part G of the study to provide an initial understanding of the safety profiles of TSR-042 and carboplatin–nab-paclitaxel combination treatment.

A total of approximately 6 to 24 patients will be enrolled in Part H of the study to provide an initial understanding of the safety profiles of TSR-042, TSR-022, and carboplatin–nab-paclitaxel combination treatment.

A total of approximately 6 to 24 patients will be enrolled in Part I of the study to provide an initial understanding of the safety profiles of TSR-042, TSR-022, and carboplatin-paclitaxel combination treatment.

13. ETHICAL, LEGAL, AND ADMINISTRATIVE ASPECTS

13.1. Data Quality Assurance

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

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

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

13.2. Access to Source Data/Documents

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

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

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

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

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

13.3. Archiving Study Documents

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

13.4. Good Clinical Practice

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

13.5. Informed Consent

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

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

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

13.6. Protocol Approval and Amendment

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

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

protocol amendment(s) will be submitted to the Investigational New Drug application under which the study is being conducted.

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

13.7. Patient Confidentiality and Data Protection

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

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

13.8. Study Monitoring

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

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

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

13.9. Audits and Inspections

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

13.10. Ethical Considerations

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki. The IRB/IEC will review all appropriate study documentation in order to safeguard the rights, safety, and well-being of the patients. The study will only be conducted at sites where IRB/IEC approval has been obtained. The protocol, Investigator's Brochure, informed consent,

advertisements (if applicable), written information given to the patients, safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC by the Investigator.

13.11. Publication Policy

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

13.12. Study Committee

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

14. LIST OF REFERENCES

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APPENDIX A. DRUGS KNOWN TO INHIBIT OR INDUCE OR ARE SUBSTRATES OF CYP450 ISOZYMES

Table 57: Drugs Known to Inhibit or Induce or are Substrates of CYP3A4 or CYP2C8

Category	CYP3A4	CYP2C8
Inhibitor	Atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin	Gemfibrozil
Inducer	Rifampin and carbamazepine	Rifampin
Substrate	Midazolam, buspirone, felodipine, lovastatin, eletriptan, sildenafil, simvastatin, and triazolam	Repaglinide and rosiglitazone

Source: [125]
Abbreviations: CYP = cytochrome P450.

APPENDIX B. RESPONSE EVALUATION CRITERIA IN SOLID TUMORS VERSION 1.1

Evaluation of Target Lesions

Evaluation of target lesions will be performed as detailed in Table 58 and below:

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

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

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of ≥1 new lesion is also considered progressions).

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

Evaluation of Non-Target Lesions

Evaluation of target lesions will be performed as detailed in Table 59 and below:

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

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

Non-CR/Non-PD: Persistence of ≥1 nontarget lesion and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of ≥1 new lesion and/or unequivocal progression of existing nontarget lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

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

Evaluation of Best Overall Response

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

Table 58: RECIST v1.1 Response for Patients with Measurable Disease (i.e., Target Disease)

Target Lesions	Nontarget Lesions	New Lesions	Overall Response	Best Overall Response When Confirmation is Required[a]
CR	CR	No	CR	>4 weeks confirmation[b]
CR	Non-CR/non-PD	No	PR	>4 weeks confirmation[b]
CR	Not evaluated	No	PR	
PR	Non-CR/non-PD/not evaluated	No	PR	
SD	Non-CR/non-PD/not evaluated	No	SD	Documented at least once >4 weeks from baseline[b]
PD	Any	Yes or no	PD	No prior SD, PR, or CR
Any	PD[c]	Yes or no	PD	
Any	Any	Yes	PD	

Source: [120]
Abbreviations: CR = complete response; PD = progressive disease; PR = partial response; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1; SD = stable disease.
Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment.
[a] See RECIST v1.1 publication[120] for further details on what is evidence of a new lesion.
[b] Only for nonrandomized trials with response as primary endpoint.
[c] In exceptional circumstances, unequivocal progression in nontarget lesions may be accepted as disease progression.

Table 59: RECIST v1.1 Response for Patients With Nonmeasurable Disease (i.e., Nontarget Disease)

Non-target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	Not evaluated
Unequivocal PD	Yes or no	PD
Any	Yes	PD

Source: [120]
Abbreviations: CR = complete response; PD = progressive disease; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1; SD = stable disease.
[a] 'Non-CR/non-PD' is preferred over 'stable disease' for nontarget disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

APPENDIX C. EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS

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

Source: [126]