Statistical Analysis Plan

Study ID: 213357

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

Approval Date of Document: 04-MAY-2022

STATISTICAL ANALYSIS PLAN

Phase 2 Multicohort Study to Evaluate the Safety and Efficacy of Novel Treatment Combinations in Patients with Recurrent Ovarian Cancer

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

Protocol Number:	3000-02-005
Protocol Version and Date:	v2.0 (Master), October 15, 2021
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Study Drug Name:	TSR-042, Niraparib and Bevacizumab
Phase:	Phase II
Sponsor:	GlaxoSmithKline plc
Analysis Plan Date:	May 04, 2022
Analysis Plan Version:	Version 2.0

SPONSOR SIGNATURE PAGE

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By signing this document, I acknowledge that I have read the document and approve of the planned statistical analyses described herein. I agree that the planned statistical analyses are appropriate for this study, are in accordance with the study objectives, and are consistent with the statistical methodology described in the protocol and all applicable regulatory guidance and guidelines.

Approver:

Ping Wang, PhD Signature:

Biostatistician Date: 04 May 2022

GlaxoSmithKline plc

Vivek Samnotra, MD Signature:

Senior Medical Director Date: 04 May 2022

GlaxoSmithKline plc

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ABBREVIATIONS

Abbreviation	Explanation
ADP	Adenosine Diphosphate
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALP	Alkaline Phosphatase
ALT	Alanine Transaminase
AST	Aspartate Transaminase
ATC	Anatomical Therapeutic Chemical
BIL	Bilirubin
BMI	Body Mass Index
BOR	Best Overall Response
BRCA	Breast Cancer Gene
C2D1	Cycle 2 Day 1
C3D1	Cycle 3 Day 2
CA-125	Cancer Antigen 125
CBC	Complete Blood Count
CI	Confidence Interval
CPS	Combined Positive Score
CR	Complete Response
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease Control Rate
DOR	Duration of Response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronical Case Report Form
EOT	End of Treatment
FT3	Free Triiodothyronine
FT4	Free Thyroxine
gBRCA	Germline Breast Cancer Susceptibility Gene
GSK	GlaxoSmithKline
H_0	Null Hypothesis

Abbreviation	Explanation
Ha	Alternative Hypothesis
HRD	Homologous Recombination Deficiency
HRR	Homologous Recombination Repair
ID	Identification
KM	Kaplan-Meier
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
ORR	Objective Response Rate
OS	Overall Survival
PARP	Polymerase
PD	Progressive Disease
PD-L1	Programmed Death-Ligand 1
PDV	Protocol Deviation
PFS	Progression-Free Survival
PR	Partial Response
PT	Preferred Term
Q3W	Every 3 Weeks
Q6W	Every 6 Weeks
RECIST v1.1	Response Evaluation Criteria in Solid Tumors Version 1.1
Rel	Relative Study
SAE	Serious Adverse Event
SD	Stable Disease
SOC	System Organ Class
STD	Standard Deviation
T3	Triiodothyronine
TEAE	Treatment-Emergent Adverse Event
TSH	Thyroid-Stimulating Hormone
ULN	Upper Limit of Normal

1 INTRODUCTION

This statistical analysis plan is designed to outline the statistical methods in evaluating the efficacy and clinical benefits of dostarlimab (TSR-042), bevacizumab, and niraparib in patients with advanced relapsed, high-grade ovarian, fallopian tube, or primary peritoneal cancer in Cohort A for GlaxoSmithKline (GSK) study protocol 3000-02-005.

This document has been prepared based on Master Protocol, Protocol Supplement A dated 20 March 2018. Details will be described in this analysis plan to ensure that the data listings, summary tables and figures which will be produced, and the statistical methodologies that will be used, are complete and appropriate to allow valid conclusions regarding the study objectives.

2 STUDY DESIGN OVERVIEW

2.1 Overall Study Design

This is a multicenter, multicohort, open-label, Phase 2 study to evaluate the efficacy and safety of niraparib novel treatment combinations in patients with advanced, relapsed, high-grade ovarian, fallopian tube, or primary peritoneal cancer.

Patients will be evaluated for eligibility to enter the study based on both the overall eligibility criteria presented in the master protocol and the eligibility criteria in the supplement protocol for cohort A.

Cohort A includes patients with advanced, relapsed, high-grade ovarian, fallopian tube, or primary peritoneal cancer who have received 1 to 2 prior lines of anticancer therapy, are poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitor-naïve, and have platinum-resistant but not refractory disease.

Treatment with hormonal agents alone are not counted in the number of lines of therapy. Treatment with single-agent bevacizumab or poly(ADP-ribose) polymerase (PARP) inhibitors given as maintenance is not counted as a separate line of therapy. If a therapeutic regimen is modified or changed for a reason other than lack of response or PD (such as allergic reaction, toxicity, or drug availability), this is not counted as a separate line of therapy.

In this protocol, platinum-resistant disease is defined as progression within 6 months from completion of a minimum of 4 cycles of platinum-containing therapy. This should be calculated from the date of the last administered dose of platinum therapy to the date of the radiographic imaging showing disease progression. Patients with primary platinum-refractory disease are defined as those who progressed during or within 4 weeks of completion of first platinum-based chemotherapy.

Cohort A will consist of a Screening Period (Day -21 to Day -1), a Treatment Period, an End of Treatment (EOT) Period occurring within 7 days when study treatment is discontinued for any reason, a Safety Follow-up Visit occurring 30 ± 7 days after the last dose of study treatment, and a Survival Assessment occurring every 90 ± 14 days after the last dose of study treatment until death or the end of study.

Patients in Cohort A will receive treatment with TSR-042, bevacizumab, and niraparib beginning on Cycle 1/Day 1. The schedule of events is summarized in Table 1.

Niraparib will be administrated at two dose levels as following:

- 300 mg in patients with screening actual body weight ≥77 kg and screening platelet count ≥150,000/μL

- 200 mg in patients with screening actual body weight <77 kg or screening platelet count <150,000/μL

Table 1: Schedule of Events

Cycle/Visit[a]	**Screening**	**Cycle 1**			**Cycle 2**	**Cycle 3**	**Cycle 4**	**Cycle 5**	**Cycle 6**	**Subsequent Cycles**	**EOT**	**Safety Follow -up**	**Survival Assessment**
Day **Procedure**	**-21 to -1**	**1**	**8**	**15**	**1**	**1**	**1**	**1**	**1**	**1**	**+7 days post trt**	**30 ±7 days**	**Every 90 ±14 days**
Informed consent	X												
Inclusion/Exclusion criteria	X	X											
Demographics	X												
Medical, surgical, cancer, and medication history	X												
Tumor assessment (RECIST v1.1)	X						X[b]			X[b]	X[b]		X[bc]
Tumor tissue	X[d]				X[d] (C2D1-C3D1)								
Blood sample	X[d]				X[d] (C2D1-C3D1)								
Ascitic fluid (optional)	X[e]												
Laboratory assessments	X												
CBC[f]	X	X[g]	X	X	X	X	X	X	X	X	X	X	
Serum chemistry	X	X[g]	X		X	X	X	X	X	X	X	X	
Coagulation	X	X[g]			X	X	X	X	X	X	X	X	
Pregnancy test[h]	X				X	X	X	X	X	X		X	
Urinalysis	X	X[g]			X	X	X	X	X	X	X	X	
Urine sample for protein[i]	X	X			X	X	X	X	X	X			
TSH, T3 or FT3, and FT4 or equivalent[j]	X					X		X		X[j]	X	X	
Serum CA-125	X	X			X	X	X	X	X	X	X	X	X[c]
ECG	X	As necessary according to standard of care											

Physical examination	X										X		
Symptom-directed physical examination	X	X			X	X	X	X	X	X		X	
Vital signs, height, and weight[k]	X	X	X	X	X	X	X	X	X	X	X		
ECOG performance status	X										X		
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	
AE monitoring[l]	X	X	X	X	X	X	X	X	X	X	X	X	X
TSR-042 study treatment administered[m]		X			X	X	X	X		X[n]			
Bevacizumab[m]		X			X	X	X	X	X	X[o]			
Niraparib study treatment dispensed/collected		X			X	X	X	X	X	X			
Survival assessment													X

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

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

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

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

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

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

[f] If dose interruption or modification is required at any point on study because of hematologic toxicity, weekly blood draws for CBC will be monitored until

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

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

[h] For women of childbearing potential only.

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

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

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

[l] AEs are required to be captured through 30 days after cessation of study treatment, SAEs are required to be captured through 90 days after cessation of study treatment (or to a minimum of 30 days post-treatment if the patient starts alternate anticancer therapy), and any pregnancies that occur within 180 days post treatment are to be captured. In conjunction with the survival assessment, AESIs (regardless of causality) and study-drug related SAEs will be collected every 90 ± 14 days after the last dose of study treatment, or as otherwise indicated in Protocol Section 12 and the master protocol.

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

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

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

2.2 Sample Size

Under hypothesis

H_0: ORR $\leq$ 25% vs. H_a: ORR $\geqslant$ 45%

Approximately 40 patients are planned for enrollment to provide assessment of clinical activity of the treatment based on ORR. If there are 15 or more responses observed among 40 treated patients, it will be concluded that the lower bound of 80% confidence interval excludes the null hypothesis H_0 and H_0 will be rejected. With 40 patients treated, the cohort has 87% power to rule out a $\leq$ 25% ORR (null hypothesis) when the true ORR is 45% at the 10% type I error rate (1-sided).

Enrollment of patients with carcinosarcoma will be limited to comprise approximately 10% of the cohort (i.e., approximately 4 patients).

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

2.3 Randomization and Blinding

This is an open-label Phase 2 study.

3 STUDY OBJECTIVES

3.1 Primary Objectives

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

3.2 Secondary Objectives

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

3.3 Exploratory Objectives

- To identify potential biomarkers including breast cancer susceptibility gene (BRCA) status, homologous recombination repair (HRR) gene status, homologous recombination deficiency (HRD) score, programmed death-ligand 1 (PD-L1) expression, and other disease-related or treatment-related biomarkers that would associate with tumor responses to the combination of niraparib, TSR-042, and bevacizumab based on the molecular profile of tumor tissue, blood, and optional ascitic fluid samples.
- To evaluate the evolution of the molecular profile of the tumor and tumor microenvironment in response to treatment.

4 STUDY ENDPOINTS AND EVALUATIONS

4.1 Efficacy Endpoints and Evaluations

- Confirmed objective response rate (confirmed ORR)
- Duration of response (DOR)
- Disease control rate (DCR)
- Progression-free survival (PFS)
- Overall survival (OS)

4.2 Safety Endpoints and Evaluations

The safety evaluations include:

- Treatment emergent adverse events (TEAEs)
- Clinical laboratory assessments
  - Hematology (CBC)
  - Serum chemistry
  - Coagulation factors
  - Pregnancy test
  - Urinalysis
  - Thyroid function
  - Serum CA-125
- Physical examination findings
- Vital signs (including weight and baseline height)
- ECOG performance status
- ECG

4.3 Biomarker Endpoints and Evaluations

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

4.4 Other Evaluations

Other evaluations include:

- Demographics and baseline characteristics
- Medical history

  - General medical history
  - Primary and other cancer history
  - Prior blood disorders
- Ovarian cancer pathology
- Prior anticancer treatment
  - Primary anticancer treatment for primary cancer
  - Prior radiotherapy
  - Prior surgery for primary cancer treatment
- Prior and concomitant medications and procedures
  - Prior non-anticancer medications
  - Concomitant medications
  - Prior and concomitant transfusions and growth factors
- Subsequent anticancer treatment
  - Subsequent anticancer therapy
  - Subsequent radiotherapy
  - Subsequent surgery for cancer

5 DEFINITIONS AND CONVENTIONS FOR DATA HANDLING

5.1 Definition of Baseline

For all evaluations unless otherwise noted, baseline is defined as the most recent non-missing measurement prior to or on the first administration of study drug. Baseline can be the same date as first dose, given the measurement is expected prior to first dose when only date information is available.

5.2 Definition of Treatment Period

Treatment period is defined as the time from the first dose of study treatment through minimum of (last dose of study treatment + 21 days, start date of new anti-cancer therapy – 1 day).

5.3 Definition of Relative Study Days

Unless otherwise noted, relative study days (Rel Days) of an evaluation are defined as number of days relative to the first dose date of study drug which is designated as Day 1, and the preceding day is Day -1, the day before that is Day -2, etc. Relative study days are calculated as an evaluation date minus first dose date of study drug, and plus 1 day if evaluation date is on or after first dose date.

Relative study days take negative values if evaluation date occurs prior to first dose date and take positive values if evaluation date occurs on or after first dose date of study drug.

5.4 First Dose Date of Study Treatment

The date of first dose of study treatment is defined as the earliest dose date of study drugs in the treatment regimen.

5.5 Analysis Visit Window

For safety parameters as described in Section 4.2 excluding clinical laboratory data, measurements collected from unscheduled visits will not be included in the by-visit summary tables but will be included in the listings. Early termination visits for safety measurements will not be mapped to any scheduled post-baseline visit but will be used as the last assessment during treatment period.

5.6 Data Handling

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

5.6.1 Handling of Repeated Clinical Laboratory Tests

For laboratories results at unscheduled visits, it will be treated as repeated laboratory results for the closest previous visit. The worst results (furthest outside of normal range, either high or low) within the visit will be used in the summary tables for that visit.

Lab results beyond the detectable limits will be reported as detectable limits for calculating descriptive statistics.

All the laboratory test results will be included in the data listings as reported.

5.6.2 Handling of Partial Dates for AEs

When determining the treatment emergent AE, partial dates will be handled as follows.

- If the day of the month is missing, the onset day will be set to the first day of the month unless it is the same month and year as first dose date. In this case, the onset date will be assumed to be the first date of treatment.
- If the onset day and month are both missing, the day and month will be assumed to be January 1, unless the event occurred in the same year as the study treatment. In this case, the event onset will be coded to the day of treatment to conservatively report the event as treatment-emergent.
- A missing onset date will be coded as the day of treatment. If the resulting onset date is after a reported date of resolution, the onset date will be set equal to the date of resolution.
- Imputation of partial dates is used only to determine whether an event is treatment-emergent; data listings will present the partial date as recorded in the eCRF.

Note: If the imputed date is greater than study end date or death date, then the earliest of these dates will be used as an end date.

5.6.3 Handling of Partial Dates for Medications

When determining prior or concomitant medications, partial dates will be handled as follows. Imputation of partial dates is used only to determine whether a medication is prior or concomitant; data listings will present the partial date as recorded in the eCRF. In the case of complete missing start date, medication will be assumed to be prior medication.

Start dates:

- If the day of the month is missing, the onset day will be set to the first day of the month unless it is the same month and year as first dose date. In this case, the onset date will be assumed to be the first date of treatment, unless the stop date contains a full date and the stop date is earlier than study treatment start date. In this case, the onset date will be set to the first day of the month.
- If the onset day and month are both missing, the day and month will be assumed to be January 1, unless the event occurred in the same year as the study treatment. In this case, the event onset will be assumed to be the first date of treatment,

unless the stop date contains a full date and the stop date is earlier than study treatment start date. In this case, the onset date will be set to January 1.

End dates:

- If the day of the month is missing, '28/29/30/31' will be used for the day (dependent on the month and year).
- If the end day and month are both missing, the day and the month will be assumed to be December 31.

Note: If the imputed date is greater than study end date or death date, then the earliest of these dates will be used as an end date. If the imputed end date is earlier than the start date, then the start date will be considered as the end date.

5.6.4 Handling of Partial Dates for Prior Anti-cancer Treatment

Partial dates of prior anticancer treatment will be handled as follows.

- If the day of the month is missing, then impute day with first day of the month.
- If the day and month are both missing, then impute as January 1st of that year.
- If the date is completely missing, no imputation will be performed.

Note: If the imputed end date is earlier than the start date, then the start date will be considered as the anti-cancer treatment end date.

5.6.5 Handling of Partial Dates for Follow-up Anti-cancer Treatment

- Partial dates of follow-up anticancer treatment will be handled as follows.
- Completely missing start dates will remain missing, with no imputation applied.
- Partial start dates will be imputed using the following convention:
- If both month and day are missing, no imputation will be applied.
- If only day is missing:

  - If the month of partial date is the same as the month of last dosing date, the minimum of (last dosing date + 1, last day of the month) will be used for the day.

  - If the month of partial date is the same as the month of last disease assessment and the last disease assessment is PD, minimum of (last date of disease assessment + 1, last day of the month) will be used for the day.

  - If both conditions above are met, the later date will be used for the day.

  - Otherwise, a ‘01’ will be used for the day.

- Completely or partially missing end dates will remain missing, with no imputation applied.

Note: If end date is earlier than the imputed start date, then the start date will be considered as the therapy end date.

6 PLANNED ANALYSIS

6.1 Changes from Planned Analyses in the Protocol

Data from a data cutoff date of July 24, 2020, was presented at SGO 2021.

The final analysis will occur after Last Patient Last Visit instead of 1 year after the last patient in the cohort has received their last dose of study treatment.The primary efficacy analysis based on the investigator-assessed confirmed ORR per RECIST v1.1. at 6 months after the last participant in the cohort has started study treatment will be reported.

6.2 Interim Analysis

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

If interim analysis is to be performed, the safety analysis in Section 8.5 will be conducted.

6.3 Final Analyses and Reporting

All final planned analyses per protocol and this analysis plan will be performed after database lock.

7 ANALYSIS POPULATIONS AND APPLICATIONS

7.1 All Patients Population

All Patients Population includes all patients who sign an informed consent form.

7.2 Safety Population

Safety Population includes all patients who receive any amount of study drug.

7.3 Efficacy Population

Efficacy Population includes all safety patients who have measurable disease at baseline.

Measurable disease at baseline is defined by the existence of at least one target lesion at baseline tumor assessment.

7.4 Response Evaluable Population

Response Evaluable Population includes all efficacy patients with at least one evaluable post-baseline tumor assessment.

7.5 Biomarker Population

Biomarker Population includes all patients who have at least 1 follow-up tumor assessment and provide a tumor, blood, or optional ascitic fluid sample. . Here follow-up tumor assessment refers to post-baseline tumor assessment.

7.6 Application of Analysis Populations

Unless otherwise noted, the analysis populations that will be used for creating the summary table(s) of each type is provided in Table 2.

Table 2: Application of Populations on Tables and Figures

Type	All	Safety	Efficacy	Response Evaluable	
Enrollment	X				
Disposition		X			
Demographics and baseline characteristics		X			
Protocol deviations		X			
Medical and disease history		X			
Prior therapies/surgeries		X			

Type	**All**	**Safety**	**Efficacy**	**Response Evaluable**	
Prior and concomitant medications or procedures		X			
Safety evaluations		X			
Treatment exposure		X			
Biomarker Analysis		X		X	
Efficacy evaluations					
ORR, DOR and DCR			X	X[a]	
PFS and OS			X		

X[a]: The supportive analyses of ORR and DCR when applicable.

8 STATISTICAL CONSIDERATIONS

All analyses described in this plan are considered a priori analyses in that they have been defined prior to locking the database. All other analyses, if any, designed subsequently to locking the database, will be considered post hoc analyses and will be described as exploratory analyses in the Clinical Study Report.

All summaries and statistical analysis will be performed by SAS v9.3 or later.

8.1 General Statistical Procedures

Frequency distributions for categorical variables will be provided as number of patients with a response in the category and the percentages out of the total number of patients in that column unless otherwise stated. Percentages will be based on number of patients in the given population as noted. Percentages will be reported to one decimal place.

A 2-sided 80% exact binomial (Clopper-Pearson) confidence interval (CI) for categorical variables without multiplicity adjustment will be provided where appropriate for efficacy analysis.

The descriptive statistics for continuous variables will be number of patients, mean, standard deviation (STD), median, quartiles (Q1, Q3), minimum and maximum. Mean, median, Q1, and Q3 will be reported to 1 more decimal place than the raw data, while the STD will be reported to 2 more decimal places than the raw data. Minimum and maximum will be reported the same as the original data.

Time-to-event analyses will be performed using Kaplan-Meier methods and summarized by 25^{th}, 50^{th}, and 75^{th} percentiles with associated 2-sided 95% confidence intervals (CIs), as well as the number and percent of censored observations.

Otherwise stated, all data listings that contain an evaluation date will also contain relative study day (Rel days) which is defined as number of days relative to the first dose date of study drug (see Section 5.3 for details).

In general, all listings will be ordered by patient ID and visit for available data unless otherwise specified in the text.

Analysis visit windows and safety data handling (repeated laboratory tests, partial dates of AEs and medications) are described in Section 5.5 and Section 5.6.

8.2 Enrollment and Disposition

8.2.1 Patients Enrollment

Number and percentage of patients will be provided for each analysis population. The denominators for percentages are the number of screened patients (who have signed informed consent).

Enrollment information will be provided in a data listing for All Patients Population.

8.2.2 Patients Disposition

The treatment regimen is combination of study drug TSR-042, bevacizumab and niraparib. The treatment regimen is considered discontinued if patients discontinued all drugs in the regimen.

Number and percentage of patients will be tabulated using Safety Population for:

- Patients' discontinuation from treatment and primary reasons
- Patients' discontinuation from study and primary reasons

Discontinued patients from treatment and from study will be provided in a data listing for Safety Population.

8.2.3 Protocol Deviations

Important or significant protocol deviations (PDVs) will be assessed by sponsor personnel following GSK template 2010-00010-CLN "Protocol Deviations Standard Categories and Descriptions".

- A PDV is classified as important if there is the potential to impact the completeness, accuracy, and/or reliability of the study data, or affect a patient's rights, safety, or well-being. The following are PDVs that will be considered important:
    - Failure to obtain informed consent for participation in the clinical trial
    - Enrollment of ineligible patient
    - Patient developed withdrawal criteria during the study but was not withdrawn
    - Patient received incorrect treatment (patient received non-study drug to treat ovarian cancer)
    - Incorrect or non-compliant dosing of a patient, i.e. dosing that is inconsistent with the protocol
    - Administration of an excluded concomitant treatment to a patient

- An important PDV is classified as significant if it is confirmed to adversely impact the completeness, accuracy, and/or reliability of the study data, or affect a patient's rights, safety, or well-being.

If a reported PDV does not meet classification criteria for importance or significance, the PDV will be reported as a protocol deviation without a classification.

All PDVs will be identified and finalized prior to database lock and documented in a separate Medical Data Review Plan.

Number and percentage of patients with a significant or important PDV will be summarized, then tabulated by type of deviation for Safety Population.

All protocol deviations will be listed for All Patients Population.

8.3 Demographics and Baseline Characteristics

8.3.1 Demographics Characteristics

Demographic characteristics will be tabulated using descriptive statistics for Safety Population. The following variables will be included in the tables:

- Age (years) at screening
- Age category (18 to < 65, 65 to < 75; and ≥ 65, ≥ 75)
- Childbearing status
- Race
- Ethnicity

8.3.2 Baseline Characteristics

Baseline (see Section 5.1 for baseline definition) characteristics will be tabulated using descriptive statistics for Safety Population, including:

- Height (cm)
- Weight (kg)
- BMI (body mass index, kg/m^2, calculated as Weight (kg) / Height $(m)^2$)
- ECOG performance status

Conversions for height and weight are as follows:

Height (cm) = Height (inches) x 2.54
Weight (kg) = Weight (lb) x 0.4536

Demographics and baseline characteristics will be listed for Safety Population.

8.3.3 Medical History

The medical history including general medical history will be coded using v24.1 or later of Medical Dictionary for Regulatory Activities (MedDRA) dictionary.

The frequency count and percentage of patients experiencing any medical conditions will be tabulated by system organ classifications (SOC) and preferred term (PT) of MedDRA

for Safety Population. If a preferred term or system organ class was reported more than once for a patient, the patient would only be counted once in the incidence for that preferred term or system organ class.

Patients' primary cancer history will be summarized including:

- Primary tumor site at initial diagnosis
- Cancer stage at initial diagnosis
- Time from first diagnosis to first dose of study treatment (months), defined as (first dose date of study drug – first diagnosis date + 1)/30.4375
- Metastatic disease sites

Patients' history of blood disorder will be tabulated for Safety Population including

- History of blood disorder
- History of thrombocytopenia, leukopenia, anemia and neutropenia

A data listing of medical history including general medical history, primary and other cancer history, and prior blood disorders history will be provided for Safety Population.

8.3.4 Ovarian Cancer Pathology

Patients' ovarian cancer pathology will be summarized for Safety Population including:

- gBRCA Status
- Histology at initial and most recent diagnosis
- Tumor grade at initial and most recent diagnosis

Listing will be provided for Safety Population.

8.3.5 Prior Anticancer Treatment

Prior anticancer treatment will be tabulated for Safety Population. The following variables will be included in the tables:

- Number of prior regimens
- Number of lines of prior platinum-based therapy. Platinum-based therapy is defined as any drug where the question 'Is this platinum based therapy?' on the eCRF is answered 'Yes'.
- Duration of last platinum-based therapy (months), defined as (end date of last platinum-based therapy – start date of last platinum-based therapy + 1)/30.4375. The last platinum-based therapy is defined as the therapy with the latest end date.
- Reason for discontinuation of last platinum-based therapy
- Platinum-free interval: Time from end of last dose of prior platinum-based therapy to the date of progressive disease (months), defined as (date of

progressive disease after last prior platinum-based therapy – stop date of last prior platinum-based therapy)/30.4375

- Best response during last platinum-based therapy
- Reason for administration of last therapy
- Any surgeries related to primary cancer
- Any radiotherapy prior to informed consent

Handling of partial missing date in determination of duration of last platinum-based therapy and platinum-free interval is described in Section 5.6.4.

A data listing of prior anticancer treatment including surgical/procedures, previous and concomitant radiotherapy will be provided for Safety Population.

8.3.6 Prior and Concomitant Medication and Procedures

All medications as documented by the investigator will be coded using Anatomical Therapeutic Chemical (ATC) classification based on the GSKDrug Dictionary (v4.0).

Prior non-anticancer medications are defined as any medications, other than study treatment, prior medications for non-anticancer treatment and pre-medications for study treatment, which ended prior to the first dose date of study treatment.

Concomitant medications are medications other than study treatments, being taken on or after the initial study treatment dosing date through 30 days after the last dose or until the start of subsequent antitumor therapy.

The count and percentage of patients who took prior and concomitant medications will be provided by GSK Medication Class (ATC level 4 if non-missing, otherwise, ATC level 3) and preferred term (PT) for Safety Population. For the summary tables, if a patient has taken a prior or concomitant medication more than once, the patient will be counted only once for the medication.

Patients' prior and concomitant transfusions and growth factors will be summarized by count and percentage for the Safety Population.

By-patient data listings will be provided for use of prior and concomitant medications, concomitant procedures, prior and concomitant transfusions and growth factors for Safety Population.

8.4 Efficacy Analysis

8.4.1 Objective Response Rate

The primary efficacy analysis will be based on the investigator-assessed confirmed ORR per RECIST v1.1. At each evaluation, the criteria in Table 3 were used to define each patient's overall response at that evaluation.

Table 3: Overall Response for Patients with Measurable Disease at Study Entry

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-CR/Non-PD/Not evaluated	No	PR
SD	Non-CR/Non-PD/Not evaluated	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Abbreviations: CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease.

Radiographic evaluations to assess extent of disease will be conducted every 9 weeks (63 ± 7 days) while on study treatment independent of cycle delays or dose interruptions, or at any time when progression of disease is suspected. After 1 year of radiographic assessments, patients will have imaging performed every 12 weeks (84 ± 14 days). The minimum criteria for SD duration are at least 9 weeks minus 7 days (9 x 7 – 7 =56 days) from the date of first dose of study treatment.

As confirmed CR/PR is required, the best overall response (BOR) will be determined as shown in Table 4. To confirm CR or PR response, tumor imaging may be performed at the earliest 4 weeks after the first indication of response or at the next scheduled scan (i.e., 9 or 12 weeks later), whichever is clinically indicated. Tumor imaging for confirmation of response occurred less than 4 weeks after the first indication of response of CR or PR may be used for clinical decision, but it will NOT be used for determination of BOR.

Table 4: Best Overall Response when Confirmation of CR and PR Required

Overall Response First Time Point	Overall Response Subsequent Time Point	Best Overall Response
CR	CR	CR
CR	PR	SD provided minimum criteria for SD duration met, otherwise, PD
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD provided minimum criteria for SD duration met, otherwise, NE
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
SD	SD	SD provided minimum criteria for SD duration met, otherwise, NE
SD	PD	SD provided minimum criteria for SD duration met, otherwise, PD
SD	NE	SD provided minimum criteria for SD duration met, otherwise, NE
NE	NE	NE

Abbreviations: CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

For each patient, BOR will be determined based on the overall responses at all time points between the date of first dose and the date of first documented radiological disease progression, or the date of subsequent anti-cancer therapy, or the date of study discontinuation, whichever occurs first. Specifically:

- Day 1 can be determined from the "dose administration date" field on the "niraparib first dose" form.
- The date of radiological disease progression can be determined by selecting the earliest date from the "date of the radiological scan or assessment on which the response evaluation was based" field on the "evaluation of response (RECIST)" form where "overall response" = PD.
- Subsequent anti-cancer therapy can be determined by checking for any entries made on the "follow up anti-cancer therapy" form.

- The date of premature study discontinuation can be determined by using the "date of study discontinuation" field on the "discontinuation of study" form. This date should be compared to the date on the "discontinuation of treatment" forms where the primary reason for discontinuation is listed as "sponsor decision to terminate study". If these dates differ, select the earlier date.
- For each patient, select all "evaluation of response (RECIST)" forms meeting the following criteria:
    - The "date of the radiological scan or assessment on which the response evaluation was based" is after Day 1.
    - The "date of the radiological scan or assessment on which the response evaluation was based" is on or before the date of radiological disease progression, date that anti-cancer therapy first began, and the date of study discontinuation. If the patient did not experience radiological disease progression, begin anti-cancer therapy, or discontinue the study prematurely, select all forms after Day 1.

ORR is defined as the proportion of patients who have achieved confirmed BOR of CR or PR.

Number of responders, ORR, and its 2-sided 80% confidence interval along with a 1-sided p-value for testing the null hypothesis based on the binomial distribution will be provided for Efficacy Population and Response Evaluable Population. The exact (Clopper-Pearson) method will be used to calculate 2-sided 80% CI. This can be programmed in SAS by appending the "/BINOMIAL(EXACT)" option to the end of the appropriate "TABLE" statement.

The following plots will be provided using Response Evaluable Population:

- Spider plots, which display the percent change from baseline in the sum of the diameter of all target lesions for each patient over the period of patient evaluation.
- Waterfall plots, which display the best percentage change from baseline in the sum of the diameter of all target lesions.
- Swim lane plots of time on study treatment with symbols indicating response start, progression, and withdrawal from study, where applicable.

Unless otherwise stated, detailed tumor time-point response will be listed for Efficacy Population.

8.4.2 Duration of Response

DOR is defined as the time from the first documentation of response (CR or PR) until the time of the first documentation of disease progression by RECIST v1.1 based on investigator's assessment or death by any cause, calculated as:

(Date of Event or Censoring – Date of first confirmed CR or PR + 1)/30.4375

DOR will be calculated only for patients who responded to the study treatment using the censoring rules specified in Table 5.

Due to small number of response events, DOR will be listed only for Efficacy Population and Response Evaluable Population and summarized descriptively for the Response Evaluable Population.

Table 5: Censoring Rules Used for DOR Analysis

Situation	Date of Event or Censoring	Outcome
Start of subsequent anti-cancer therapy without a prior documented progression or death	Date of last evaluable radiologic tumor assessment prior to or on the date of initiation of the subsequent anti-cancer therapy	Censored
No documented radiologic progression and no subsequent anti-cancer therapy started	Date of last evaluable radiologic tumor assessment	Censored
Documented radiologic progression or death after two or more consecutive missing radiologic assessments	Date of last evaluable radiologic tumor assessment before the missed tumor assessments	Censored
Documented radiologic progression or death	Earliest date of documented radiologic progression or death	Event

8.4.3 Disease Control Rate

DCR is defined as the proportion of patients who have achieved confirmed BOR of CR, PR, or stable disease (SD) per RECIST v1.1.

DCR will be summarized using the same methods for ORR for Efficacy Population and Response Evaluable Population.

8.4.4 Progression Free Survival

PFS 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.

PFS in months will be calculated as following using the censoring rules specified in Table 6:

- (Earlier Date of Event or Censoring – First dose date of study treatment + 1)/30.4375

The Kaplan-Meier (KM) method will be used to estimate the distribution of PFS for Efficacy Population SAS PROC LIFETEST with method = PL option (Kaplan-Meier estimates, also known as the product-limit estimates) will be used. The 25th, 50th, and 75th percentiles of times-to-event with 95% CIs will be estimated using the Brookmeyer-Crowley method (Brookmeyer & Crowley, Biometrics, Vol. 38, No. 1, Mar., 1982, pp. 29-41). Summaries of the number and percentage of events and censored patients will also be provided. Survival risks at 6 and 12 months will be provided if applicable.

A KM plot will be provided to graphically present the PFS.

Table 6: Censoring Rules Used for PFS Analysis

Situation	Date of Event or Censoring	Outcome
No baseline tumor assessments	First dose date	Censored
No post-baseline tumor assessments and no death	First dose date	Censored
Start of subsequent anti-cancer therapy prior to a documented radiologic progression or death	Date of last evaluable radiologic tumor assessment prior to or on the date of initiation of the subsequent anti-cancer therapy	Censored
No documented radiologic progression, no subsequent anti-cancer therapy started, and no death	Date of last evaluable radiologic tumor assessment	Censored
Documented radiologic progression or death after two or more consecutive missing radiologic assessments	Date of last evaluable radiologic tumor assessment before the missed tumor assessments	Censored
Documented radiologic progression or death	Earliest date of documented radiologic progression or death	Event

8.4.5 Overall Survival

Overall survival (OS) is defined as the time from first dose of treatment to the date of death of any causes. If the patient did not experience an event, he/she will be censored at the last follow-up date.

The KM method will be used to estimate the distribution of OS for Efficacy Population. SAS PROC LIFETEST with method = PL option (Kaplan-Meier estimates, also known as the product-limit estimates) will be used. The 25th, 50th, and 75th percentiles of times-to-event with 95% CIs will be estimated using the Brookmeyer-Crowley method (Brookmeyer & Crowley, 1982). Summaries of the number and percentage of events and

censored patients will also be provided. Survival risks at 6 and 12 months will be provided if applicable.

A KM plot will be provided to graphically present the OS.

8.5 Biomarker Analysis

All biomarkers will be listed for Safety Population. Analysis for interested biomarkers is described as follows.

8.5.1 Analysis of BRCA, HRD, HRR, and PD-L1

BRCA, HRD status and HRR gene status are determined by tumor samples at screening via the Myriad myChoice Plus test. The PD-L1 expression is determined by tumor sample at screening via the PD-L1 IHC DAKO 22C3 test.

HRR gene status may be explored if applicable.

The ORR, DCR, and DOR will be summarized for following each type of biomarkers defined as following:

- BRCA mutation status
  - BRCAmut: patients with BRCA deleterious or suspected deleterious mutation
  - BRCAwt: patients without BRCA deleterious or suspected deleterious mutation
  - BRCAunk: BRCA test result not available (e.g. test canceled, incomplete or inconclusive, or data missing for a patient, etc.)
- HRD status
  - HRDpos: BRCAmut or HRD score ≥ 42
  - HRDneg: BRCAwt/unknown and HRD score < 42
  - HRDunk: HRD unknown (e.g. test canceled, incomplete or inconclusive, or data missing for a patient, etc.)
- HRR status
  - HRR positive: patients with deleterious or suspected deleterious mutation in at least one of the Myriad IDE validated HRR gene panel (ATM, BARD1, BRCA1, BRCA2, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D, RAD54L)
  - HRR negative: patients without deleterious or suspected deleterious mutation in any of the Myriad IDE validated HRR gene panel (ATM, BARD1, BRCA1, BRCA2, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D, RAD54L)
  - HRR unknown: HRR gene mutation result not available (e.g. test canceled, incomplete or inconclusive, or data missing for a patient, etc.)
- PD-L1 expression

- PDL1-positive: PD-L1 CPS ≥ 1 (tumor that scores ≥ 1)
- PDL1-negative: PD-L1 CPS < 1 (tumor that scores < 1)
- PDL1-unk: PD-L1 CPS unknown. PD-L1 test result not available (e.g. test canceled, incomplete or inconclusive, or data missing for a patient. etc)

8.5.2 Analysis of CD8+ TIL

The CD8+ TIL density is determined by tumor samples at screening and on-treatment. Descriptive summary tables will be provided including:

- Baseline CD8+ TIL: density of CD8+ TIL (count/mm^2)in tumor sample collected at screening.
- On-treatment CD8+ TIL: density of CD8+ TIL (count/mm^2)in tumor samples collected on treatment between C2D1 to C3D1.

8.6 Safety Analysis

8.6.1 Adverse Events

AEs will be coded using MedDRA v24.1 or later and will be classified by SOC and PT of MedDRA. Severity of AEs will be assessed by investigators according to CTCAE (v4.03).

A treatment-emergent AE (TEAE) will be defined as any new AE that begins, or any preexisting condition that worsens in severity from first dose date until 30 days after the last dose of study treatment (or until the start of new anticancer therapy, whichever occurred first).

TEAEs are classified as Related or Unrelated to each study drug niraparib, TSR-042, and bevacizumab by the Investigator. Any TEAEs for which the relationship to study drug is missing will be considered as related to study drug.

The number and percentage of patients who experienced an AE will be summarized.

The following types of summaries will be provided:

- Overview of TEAEs
- TEAEs by SOC and PT
- TEAEs by PT in decreasing frequency
- Immune-related TEAEs by PT in decreasing frequency
- Drug-related TEAEs by PT in descending frequency
  - Niraparib-related TEAEs by PT in descending frequency
  - TSR-042-related TEAEs by PT in descending frequency
  - Bevacizumab-related TEAEs by PT in descending frequency
- Drug-related AEs by PT in descending frequency

  - Niraparib-related AEs by PT in descending frequency
  - TSR-042-related AEs by PT in descending frequency
  - Bevacizumab-related AEs by PT in descending frequency
- Drug-related TEAEs by SOC and PT
  - Niraparib-related TEAEs by SOC and PT
  - TSR-042-related TEAEs by SOC and PT
  - Bevacizumab-related TEAEs by SOC and PT
- TEAEs by SOC, PT, and Maximum CTCAE toxicity grade
- Drug-related TEAEs by SOC, PT, and Maximum CTCAE toxicity grade
  - Niraparib-related TEAEs by SOC, PT, and Maximum CTCAE toxicity grade
  - TSR-042-related TEAEs by SOC, PT, and Maximum CTCAE toxicity grade
  - Bevacizumab-related TEAEs by SOC, PT, and Maximum CTCAE toxicity grade
- Serious AEs by SOC and PT
- Non-serious AEs by SOC and PT
- Drug-related serious AEs by SOC and PT
  - Niraparib-related Serious AEs by SOC and PT
  - TSR-042-related Serious AEs by SOC and PT
  - Bevacizumab-related Serious AEs by SOC and PT
- TEAEs leading to study drug discontinuation by SOC and PT
  - TEAEs leading to Niraparib discontinuation by SOC and PT
  - TEAEs leading to TSR-042 discontinuation by SOC and PT
  - TEAEs leading to Bevacizumab discontinuation by SOC and PT
- Drug-related TEAEs leading to study drug discontinuation by SOC and PT
  - Drug-related TEAEs leading to Niraparib discontinuation by SOC and PT
  - Drug-related TEAEs leading to TSR-042 discontinuation by SOC and PT
  - Drug-related TEAEs leading to Bevacizumab discontinuation by SOC and PT
- TEAEs leading to Niraparib reduction or delay by SOC and PT
- TEAEs leading to study drug interruption or delay by SOC and PT
  - TEAEs leading to TSR-042 infusion interruption or delay by SOC and PT
  - TEAEs leading to Bevacizumab infusion interruption or delay by SOC and PT
- Death and primary reasons causing death
- TEAEs of special interest by SOC and PT

The AESIs for this study are myelodysplastic syndrome (MDS), acute myeloid leukemia (AML) and secondary cancers (new malignancies other than MDS/AMLTable 5 outlines the AESI with the criteria of mapping MedDRA PTs for each AESI using Standardized MedDRA Queries (SMQs), High Level Terms (HLTs), and/or PTs.

Table 5: Adverse Events of Special Interest Group Term	**MedDRA V18.1 Criteria for Selection of Preferred Terms1**
AESI (MDS/AML events)	MedDRA PTs associated with MDS/AML
AESI (new malignancies other than MDS/AML)	Malignant tumor SMQ (other than MDS/AML)

Abbreviations: AESI = adverse event of special interest; AML = acute myelogenous leukemia; MDS = myelodysplastic syndrome; MedDRA = medical dictionary for regulatory activities; PT = preferred term; SMQ = Standardized MedDRA Query.

If a preferred term or system organ class was reported more than once for a patient, the patient would only be counted once in the incidence for that preferred term or system organ class.

In tabulation by severity (i.e., CTCAE toxicity grade),

- For a given preferred term, only the most severe preferred term for each patient will be included.
- For a given system organ class, only the most severe system organ class for each patient will be included.

The following tables presented as listings will be provided:

- Deaths
- Serious AEs
- TEAEs leading to dose reduction, interruption or delayed.
- TEAEs leading to treatment discontinuation
- Listing of COVID-19 assessment and symptom assessments for COVID-19 positive subjects

AEs will be listed for All Patients Population.

8.6.2 Study Drug Exposure

Study drug will be summarized using descriptive statistics including:

- Duration of drug exposure
- Number of treatment cycles (1 cycle, 2 cycles, etc.)
- Actual dose intensity
- Relative dose intensity

Dose reduction, dose interruption or delay will be summarized by cycle:

- Number of patients with infusion interruption for TSR-042
- Number of patients with infusion delay for TSR-042
- Number of patients with infusion interruption for Bevacizumab
- Number of patients with infusion delay for Bevacizumab
- Number of patients with Niraparib dose reduction

- Number of patients with Niraparib dose delay

Duration of exposure and dose intensity will be calculated as described in Table 7 for each drug.

Swimmer plots displaying the duration of treatment for each patient will be presented by including indicators:

- Treatment status (ongoing or discontinued)
- Response at each tumor assessment

Details of study treatment exposure will be listed for Safety Population.

Table 7: Extent of Study Drug Exposure

Parameter	Niraparib	TSR-042	Bevacizumab
Dosing schedule	Dose level 1: 200mg daily Dose level 2: 300mg daily	500mg Q3W (first 4 cycles), followed by 1,000mg Q6W beginning on Cycle 5 Day 1	15 mg/kg Q3W
Intended dose	(mg/day) Dose level 1: 200/1 Dose level 2: 300/1	(mg/day) First 4 Cycles: 500/21 After Cycle 5: 1000/42	(mg/kg /day) 15/21
Duration of Treatment (unit)	(day) Last dose date - Start dose date +1	(day) First 4 cycles: Last dose date prior to cycle 5 – Start dose date + 21 After cycle 5: Last dose date – First Dose Date at or after Cycle 5 + 42	(day) Last dose date - Start dose date + 21
Actual Cumulative Dose (unit)	(mg) Sum of the doses (mg) consumed by a patient during the treatment period The sum of the doses consumed (mg) is the total number of capsules consumed multiplying by 100. The total number of capsules consumed is the sum of the number of capsules dispensed less the sum of the number of capsules returned by the patient during the study. Unused capsules not returned will be assumed to have been consumed	(mg) Sum of the doses (mg) administered to a patient during the treatment period Calculated separately for the first 4 cycles and cycles after cycle 5	(mg/kg) Sum of the doses (mg/kg) administered to a patient during the treatment period
Actual Dose Intensity (unit)	(mg/day) Actual Cumulative Dose / Duration of treatment	(mg/day) Actual Cumulative Dose /Duration of treatment Calculated separately for the first 4 cycles and cycles at or after cycle 5	(mg/kg/day) Actual Cumulative Dose /Duration of treatment
Relative Dose Intensity (%)	Actual Dose Intensity/Intended Dose Note for TSR-042, it needs to be calculated separately for the first 4 cycles and cycles after cycle 5		

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

8.6.3 Clinical Laboratory Tests

All laboratory parameters collected at each center's local laboratory will be normalized by converting values in original units to values in SI units and classified as normal, low, or high based on normal ranges supplied by the local laboratories and upon employing standardization.

For hematology, coagulation, serum chemistry, thyroid function and serum CA-125 laboratory parameters which are normalized in SI units, descriptive summary tables for observed values and changes from baseline will be provided by visit for Safety Population.

The laboratory test results will be categorized according to NCI CTCAE v4.03 toxicity grades. Shift tables will be provided from baseline toxicity to maximum post-baseline toxicity grade ONLY for each applicable hematology and chemistry laboratory parameter in Safety Population.

Urinalysis laboratory parameters at each visit will be summarized. The categorical urinalysis parameters will be summarized using frequency table.

Liver function tests will be summarized for the following categories. To be counted in the denominator, the patient must have at least one post-baseline lab chemistry measurement for the specified lab tests (e.g. in the 'ALT ≧3xULN and BIL ≧2xULN' category, the denominator should include subjects who had both a post-baseline ALT value AND a post-baseline BIL value that was up to 28 days after ALT).

- ALT ≥ 3×ULN and BIL ≥ 2×ULN
- ALT ≥3xULN and INR >1.5
- ALT ≥ 3×ULN and BIL ≥ 2×ULN and ALP < 2×ULN
- Hepatocellular injury is defined as ((ALT/ALT ULN)/(ALP/ALP ULN)) ≧5 and ALT ≧3xULN. ALT and ALP values must occur on the same day. The denominator should include subjects who had both a post-baseline ALT and ALP on the same day.
- Hepatocellular injury and BIL ≥2xULN. The denominator should include subjects who had both a post-baseline ALT and ALP on the same day as well as BIL on or up to 28 days of that day.
- ALT ≥ 3×ULN, ALT ≥5×ULN, ALT ≥10×ULN, ALT ≥20×ULN

The BIL elevation must occur on or up to 28 days after the ALT elevation. Categories are not mutually exclusive. ULN is the upper limit of normal.

A scatter plot of maximum total bilirubin versus maximum ALT will be generated, as well as a scatter plot of maximum vs baseline for ALT.

Separate listings will be provided for all laboratory tests including pregnancy testing for Safety Population.

8.6.4 Vital Signs

The vital signs parameters will be summarized in a change from baseline descriptive summary table by visit for the Safety Population.

A patient-detailed listing of vital signs including systolic and diastolic blood pressure (mmHg), pulse (bmp), temperature (ºC)) and weight (kg) will be provided for Safety Population.

Conversion of temperature is as following:

Temperature (ºC) = (Temperature (ºF) – 32) x 5/9

8.6.5 Physical Examination Findings

Physical examination will be presented in listing for Safety Population.

8.6.6 ECOG Performance Status

The number and percentage of ECOG performance status by each visit will be summarized. The denominators for calculating the percentages will be based on the number of patients with non-missing values.

The ECOG shift from baseline grade to worst (highest) post-baseline grade during the on-treatment period will be summarized for Safety Population.

Listings will be presented for Safety Population.

8.6.7 Electrocardiogram (ECG)

ECG findings will be listed for Safety Population.