3000-02-005/213357

A PHASE 1B/2 MULTICOHORT UMBRELLA STUDY TO EVALUATE THE SAFETY AND EFFICACY OF NOVEL TREATMENTS AND/OR COMBINATIONS OF TREATMENTS IN PARTICIPANTS WITH OVARIAN CANCER (OPAL)

Sponsor:	TESARO, Inc., a GlaxoSmithKline Company 1000 Winter Street, Suite 3300 Waltham, MA 02451 +1 339 970 0900	TESARO Bio Netherlands B.V, a GlaxoSmithKline Company Joop Geesinkweg 901 1114AB Amsterdam-Duivendrecht The Netherlands +45 31664608
Medical Monitor:	Medical monitor name and contact can be found in each cohort-specific Study Reference Manual	
Clinical Research Organization:	Not applicable	
IND No.:	100,996	
EudraCT No.:	Provided in each cohort-specific supplement	
EU CT Number	Provided in each cohort-specific supplement	
NCT No.	NCT03574779	
Development Phase:	1B and 2	
Date of Original Protocol (Version 1.0):	20 March 2018	
Date of Amendment 1 (Version 2.0)	15 October 2021	
Date of Amendment 2 (Version 3.0)	26 Oct 2023	

©2023 GSK group of companies or its licensor.

SPONSOR SIGNATURE PAGE

Declaration of Sponsor or Responsible Medical Officer

Title (Study Number): A PHASE 1B/2 MULTICOHORT UMBRELLA STUDY TO EVALUATE THE SAFETY AND EFFICACY OF NOVEL TREATMENTS AND/OR COMBINATIONS OF TREATMENTS IN PARTICIPANTS WITH OVARIAN CANCER (OPAL) (PR-3000-02-005/213357)

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

Jimmy Belotte, MD, PhD Medical Director, GSK	Date

INVESTIGATOR'S AGREEMENT

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

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Table 1: Document History

Document	Date of Issue
Amendment 2 (Version 3.0)	26 Oct 2023
Amendment 1 (Version 2.0)	15 October 2021
Original protocol (Version 1.0)	20 March 2018

Amendment 2 (26 Oct 2023)

Overall Rationale for the Amendment

Amendment 2 is a global amendment created to include changes necessary to align with the European Union (EU) Clinical Trials Regulations (CTR) transition, clarifications in study conduct, and editorial and administrative changes. Substantiality is outlined in the cohort-specific amendment.

A general description and brief rationale for the changes are provided in Table 2. The synopsis was updated to be aligned with the changes in the protocol body.

Table 2: Summary of Changes for Amendment 2

Section(s) Affected	Description of Change	Brief Rationale
Headers, title page, Protocol Amendment Summary of Changes (new), List of Abbreviations, Protocol Amendment History (new Appendix), References, and throughout	Headers and title page were updated with new document number and amendment information; Protocol Amendment Summary of Changes section was updated to include rationale for this amendment; editorial revisions for consistency with sponsor's ways of working, minor corrections, formatting updates, and to add clarification and/or remove discrepancies.	Editorial changes to align with the sponsor's standard protocol template/process and ways of working; and for accuracy, clarity, conformity, flow, and typographical error correction.
Sponsor Signature Page	Sponsor Signatory updated	Administrative change
Title Page Section 11.3.6 Submissions and Distribution of Serious Adverse Event Reports Section 15.1 Ethics Review Section 15.2 Ethical Conduct Section 15.3 Written Informed Consent Section 15.4 Recruitment Strategy Section 16.3 Data Protection	EU CT number added and text and/or sections added to comply with EU CTR requirements	To align with GSK protocol template and components aligned with EU CTR.

Section(s) Affected	Description of Change	Brief Rationale
Section 16.4 Dissemination of Clinical Study Data Section 16.5 Study and Site Start and Closure		
Section 4.1.3	Updated text surrounding ZEJULA approvals	Editorial changes to align with updated information/Global Data Sheet.
Section 6.1.1 End of Study Definition	Details added defining the end of study will be defined in the supplements for each cohort.	Clarification and for compliance with EU CTR and alignment with protocol template
Section 7.3.3 Lost to Follow-up	Text included to clarify recording of survival status information	Clarification for study conduct
Section 11.3.1.5 Special Situations: Abuse, Misuse, Medication Errors, Overdose, and Accidental or Occupational Exposure Section 11.3.9 Special Situations	Removed legacy Special Situations Report Form, which is not used in this study.	Clarification in study conduct
Section 11.3.3 Collection and Recording of Adverse Even Section 11.3.9 Special Situations	Added text defining collection from time of signing Informed Consent Forms as defined in each specific cohort	Clarification
Section 12.5 Safety Analyses	Clarification added regarding cohort-specific analyses included in the cohort-specific supplements and/or Statistical Analysis Plans	Clarification

PROCEDURES IN CASE OF EMERGENCY

Medical Monitor Name and Contact Information: Can be found in the Study Reference Manual for each cohort-specific supplement.

1. SYNOPSIS

Name of Sponsor/Company: TESARO, Inc., a GlaxoSmithKline company	
Name of Investigational Product: Various; as determined by each cohort-specific supplement	
Name of Active Ingredient: Various; as determined by each cohort-specific supplement	
Title of Study: A PHASE 1B/2 MULTICOHORT UMBRELLA STUDY TO EVALUATE THE SAFETY AND EFFICACY OF NOVEL TREATMENTS AND/OR COMBINATIONS OF TREATMENTS IN PARTICIPANTS WITH OVARIAN CANCER (OPAL)	
Study center(s): Multicenter global	
Principal Investigator: N/A **Investigators:** Multicenter	
Studied period (years): Date first participant enrolled: 15 November 2018 Estimated date last participant completed: To be determined by each cohort-specific supplement	**Phase of development:** 1B/2

Individual cohorts within this umbrella study may or may not contain a Phase 1B component. The Phase 1B component will be open to patients with any gynecologic malignancy (see below).

Objectives:

The overall objectives for this study are as follows. Cohort-specific objectives will be presented in each cohort-specific supplement, as applicable.

Primary objective:

Phase 1B (Note: Not all cohorts will have a Phase 1B component):

- To determine the recommended Phase 2 dose (RP2D) of the study drug combination as defined in each cohort-specific supplement in patients with advanced, high-grade ovarian, fallopian tube, or primary peritoneal cancer or other advanced gynecologic malignancies

Phase 2:

- To evaluate the efficacy of the study drug or study drug combination as determined in each cohort-specific supplement

Secondary objectives:

Phase 1B (Note: Not all cohorts will have a Phase 1B component):

- To evaluate the safety and tolerability of the study drug combination as defined in each cohort-specific supplement in patients with advanced, high-grade ovarian, fallopian tube, or primary peritoneal cancer or other advanced gynecologic malignancies

Phase 2:

- To evaluate additional measures of clinical benefit of the study drug or study drug combination as determined in each cohort-specific supplement
- To evaluate the safety and tolerability of the study drug or study drug combination as defined in each cohort-specific supplement

Note: Additional secondary objectives may be added as relevant and will be described in each cohort-specific supplement.

Exploratory objectives:

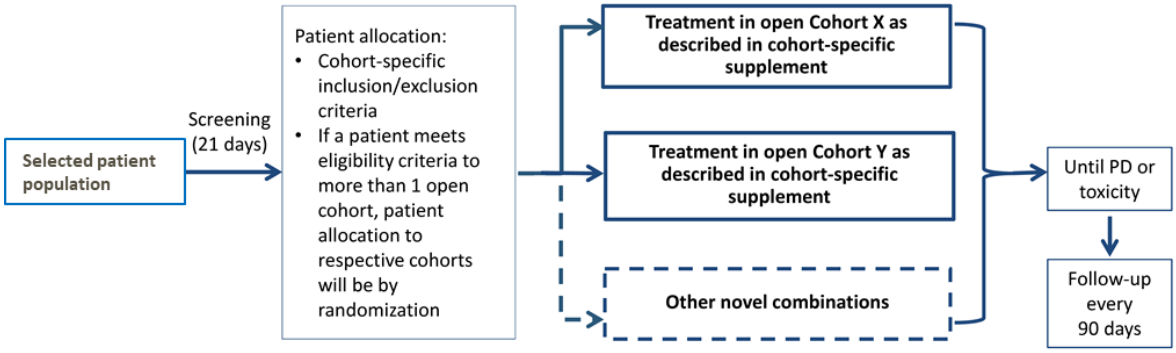
As specified in each cohort-specific supplement.

Methodology:

This is a multicenter, multicohort, open-label, Phase 1B/2 umbrella study. It will consist of several independent Phase 2 studies (called cohorts) to evaluate the safety and efficacy of novel study drugs and/or novel study-drug combinations in patients with ovarian cancer. The study design for each cohort will be described in detail in a cohort-specific supplement.

The intent of this study is to rapidly identify more effective therapies for ovarian cancer. In some cohorts, a Phase 1B lead-in may be required to determine the RP2D of a new drug combination. To expedite completion of this portion for certain cohorts, this study will allow enrollment of patients with other gynecologic malignancies into the Phase 1B (dose escalation) component of specific cohorts (sub-studies). These cancers start in a woman's reproductive organs and are typically divided into ovarian/fallopian tube, uterine, cervical, vaginal, and vulvar cancers.

Overall umbrella study design:



Abbreviation: PD = progressive disease.
Phase 1B (not in all cohorts): Cohort-specific Phase 1B study schemas will be provided in the cohort-specific supplement for that cohort.
Phase 2 (in all cohorts): Cohort-specific Phase 2 study schemas will be provided in the cohort-specific supplement for that cohort.
Note: Study periods may differ between cohorts; if so, it will be clearly stated in the cohort-specific supplement.

Number of participants (planned):

The number of participants planned for each phase and each cohort is provided in each cohort-specific supplement.

Diagnosis and main criteria for inclusion:

The following lists of eligibility criteria are applicable to all patients. Additional cohort-specific criteria are provided in each cohort-specific supplement.

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

1. Participant must be female ≥18 years of age, able to understand the study procedures, and agree to participate in the study by providing written informed consent.
2. Participant must have the following histologic diagnosis unless otherwise specified in a cohort-specific supplement:
    a. Phase 2 cohorts: Participant has histologically diagnosed high-grade epithelial (i.e., serous, endometrioid, mucinous, clear cell) ovarian, fallopian tube, or primary peritoneal cancer or carcinosarcoma of the ovary. Participant with high-grade mixed histology is also eligible.

Note: Cohorts may exclude some ovarian cancer histologies, as specified in the cohort-specific supplement.

b. For the Phase 1B components: Participant has histologically diagnosed gynecologic malignancy (i.e., any cancer that started in a woman's reproductive system). Gynecologic malignancies include cervical cancer; endometrial cancer; vaginal cancer; vulvar cancer; high-grade epithelial (i.e., serous, endometrioid, mucinous, clear cell) ovarian, fallopian tube, or primary peritoneal cancer; or advanced carcinosarcoma of the ovary. Participant with high-grade mixed histology is also eligible.

3. The allowed number of prior lines of anticancer therapy for primary cancer will be specified in each cohort-specific supplement. 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 progressive disease (such as allergic reaction, toxicity, or drug availability), this is not counted as a separate line of therapy.

   Note: Definitions for a prior line of therapy may be modified for certain cohorts. Differences from the definitions presented here will be clearly specified in the cohort-specific eligibility criteria.

4. Phase 2 cohorts: Participant must have measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.

5. Participant has an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2.

   Note: Cohorts may exclude participants with an ECOG performance of 2, as specified in the cohort-specific supplement.

6. Participant has adequate organ function, defined as follows:

   a. Absolute neutrophil count ≥1500/μL, without growth factor support (granulocyte colony-stimulating factor or granulocyte-macrophage colony-stimulating factor administration is not permitted within 2 weeks of Screening)

   b. Platelets ≥100 000/μL without platelet transfusion support within 2 weeks prior to Screening

   c. Hemoglobin ≥9 g/dL without transfusion or growth factor (recombinant erythropoietin) within 2 weeks of Screening

   d. Serum creatinine ≤1.5× upper limit of normal (ULN) or calculated creatinine clearance ≥50 mL/min using Cockcroft-Gault equation

   e. Total bilirubin ≤1.5× ULN, except in participants with Gilbert's syndrome. Participants with Gilbert's syndrome may enroll if direct bilirubin is ≤1.5× ULN.

   f. Aspartate aminotransferase and alanine aminotransferase ≤2.5× ULN, unless liver metastases are present, in which case they must be ≤5× ULN

   g. International normalized ratio or prothrombin time (PT) ≤1.5× ULN unless participant is receiving anticoagulant therapy as long as PT or partial thromboplastin time (PTT) is within therapeutic range of intended use of anticoagulants

   h. Activated PTT ≤1.5× ULN unless participant is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants. Participants with known lupus anticoagulant and elevated PTT may be eligible on a case-by-case basis after discussion with the sponsor's Medical Monitor.

Note: Definitions for adequate organ function may be modified for certain cohorts. Differences from the definitions presented here will be clearly specified in the cohort-specific eligibility criteria.

7. Participant is not pregnant or breastfeeding, and at least 1 of the following conditions apply:
   - Is not a woman of childbearing potential (WOCBP), as defined in Appendix 1.

     OR
   - Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), with low user dependency, as described in Appendix 1, during the Treatment Period and for at least 180 days after the last dose of study treatment and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction during this period. The investigator should evaluate the effectiveness of the contraceptive method in relation to the first dose of study treatment.
     - A WOCBP must have a negative pregnancy test (highly sensitive urine test or serum test as required by local regulations) within 72 hours before the first dose of study treatment.
       If a urine test cannot be confirmed as negative (e.g., an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.
     - Additional requirements for pregnancy testing during and after study treatment are described in Section 11.3.8.

   The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.
8. Participant must provide sufficient tumor tissue samples based on requirements defined in each cohort-specific supplement.

Main criteria for exclusion:

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

1. Participant has not recovered (i.e., to Grade ≤1 or to baseline) from prior chemotherapy-induced adverse events (AEs). Note: Participant with Grade ≤2 neuropathy or alopecia is an exception to this criterion and may qualify for the study.
2. Participant has a known diagnosis of immunodeficiency or is receiving systemic steroid therapy exceeding an equivalent of prednisone 10 mg daily or any other form of immunosuppressive therapy within 7 days prior to the first dose of study treatment
3. Participant is currently participating in a treatment study or has participated in a study of an investigational agent within 4 weeks of the first dose of treatment
4. Participant has received prior systemic anticancer therapy including cytotoxic chemotherapy, PARP inhibitor, immune checkpoint inhibitors, hormonal therapy given with the intention to treat the primary cancer, or biological therapy within 3 weeks of the first dose of study treatment. This washout period is required to ensure prior therapy is not confounding the toxicity profile of the investigational study drug or study drug combinations in cohorts.
5. Participant has received live vaccine within 14 days of planned start of study therapy
6. Participant has symptomatic uncontrolled brain or leptomeningeal metastases. (To be considered “controlled,” central nervous system [CNS] disease must have undergone treatment [e.g., radiation or chemotherapy] at least 1 month prior to study entry. The

participant must not have any new or progressive signs or symptoms related to the CNS disease and must be taking ≤10 mg of prednisone or equivalent per day or no steroids.) Participant who has untreated brain metastases and who is not symptomatic may enroll if the investigator feels that treatment of these metastases is not indicated. A scan to confirm the absence of brain metastases is not required. Participant with spinal cord compression may be considered if she has received definitive treatment for this and evidence of clinically stable disease for 28 days prior to the first dose of study treatment.

7. Participant had major surgery within 4 weeks of starting the study or participant has not recovered from any effects of any major surgery.
8. Participant has a known additional malignancy that progressed or required active treatment within the last 2 years because reoccurrence of another malignancy would confound interpretation of objective response rate (ORR) by RECIST v1.1 criteria. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin that has undergone potentially curative therapy, or in situ cancer that is considered to be low risk for progression by the investigator.
9. Participant is considered a poor medical risk due to a serious, uncontrolled medical disorder, nonmalignant systemic disease, or active, uncontrolled infection. These include, but are not limited to, coronavirus disease-2019, significant cardiovascular disease (e.g., significant cardiac conduction abnormalities, myocardial infarction, cardiac arrhythmia or unstable angina within 6 months prior to enrollment, New York Heart Association Grade ≥2 congestive heart failure, uncontrolled hypertension, serious cardiac arrhythmia requiring medication, Grade ≥2 peripheral vascular disease, and history of cerebrovascular accident within 6 months prior to enrollment), uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, and any psychiatric disorder that prohibits obtaining informed consent.
10. Participant has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, might interfere with the participant's participation for the full duration of the study treatment, or is not in the best interest of the participant to participate.
11. Participant 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).

Investigational product, dosage, and mode of administration:

Investigational products are described in each cohort-specific supplement.

Duration of treatment:

Overall, treatment in this study will continue until disease progression or toxicity. Treatment-specific treatment limitations are provided in each cohort-specific supplement.

Reference therapy, dosage, and mode of administration:

Not applicable.

Criteria for evaluation:

Additional endpoints may be added as relevant and will be described in each cohort-specific supplement.

Efficacy:

Primary Efficacy Endpoint - Phase 2:

The primary efficacy endpoint is confirmed ORR, which is defined as the proportion of participants who have achieved confirmed complete response (CR) or partial response (PR), evaluated using

RECIST v1.1 based on investigator's assessment. For select cohorts, a primary efficacy endpoint other than confirmed ORR by RECIST v1.1 based on investigator's assessment may be used to evaluate the primary objective of efficacy of the study drug or study drug combination, in which case it will be clearly stated in the cohort-specific supplement.

Secondary Efficacy Endpoints - Phase 2:

Secondary efficacy endpoints include the following:

- Progression-free survival (PFS), defined as the time from the date of the first dose of study treatment to the earliest date of assessment of progression or death by any cause in the absence of progression by RECIST v1.1
- Overall survival (OS), defined as the time from the date of the first dose of study treatment to the date of death by any cause
- Duration of response (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's assessment or death by any cause
- Disease control rate (DCR), defined as the percentage of participants who have achieved best overall response of CR, PR, or stable disease (SD) per RECIST v1.1 based on investigator's assessment

For select cohorts, secondary efficacy endpoints other than PFS, OS, DOR, and DCR may be used to evaluate clinical benefit of the study drug or study drug combination, in which case it will be clearly stated in the cohort-specific supplement.

Safety:

Primary Endpoints - Phase°1B:

The primary endpoints for each Phase 1B component include the following:

- Percentage (number) of participants with dose-limiting toxicities (DLTs)
- Percent of participants with AEs, changes in clinical signs and laboratory parameters

To be considered a DLT, the AE must be considered related to study treatment. DLTs can be hematologic or nonhematologic and are described in each cohort-specific supplement as relevant.

To inform the RP2D, the maximum tolerated dose (MTD), along with pharmacokinetic (PK)/pharmacodynamic data, and acute and chronic toxicity data, will be determined. The MTD is the dose at which the DLT rate is closest to the target toxicity rate of 30%, unless otherwise specified in the cohort-specific supplement.

Safety Parameters – All Phases

Safety parameters evaluated during this study will include AEs, vital signs, symptom-directed physical examination findings, clinical laboratory values (including hematology and serum chemistry, coagulation, thyroid function, and urinalysis), and ECOG performance status, unless otherwise specified in a cohort-specific supplement.

Biomarkers:

Tumor and/or blood samples may be assessed to identify potential disease-related or treatment-related biomarkers that may associate with tumor responses to the study drug or study drug combinations defined in each cohort-specific supplement.

Pharmacokinetics:

Blood samples to assess pharmacokinetics may be collected as defined in each cohort-specific supplement.

Statistical methods:

Sample size determination for each cohort is described in each cohort-specific supplement.

Analysis populations:

Six analysis populations will be defined as follows:

- Intent-to-Treat (ITT) Population: All participants randomized unless otherwise specified in a cohort-specific supplement.
- Safety Population: All participants in each cohort who receive at least 1 dose of study treatment. For RP2D purpose, the population included in the assessment of DLTs will be specified in each cohort-specific supplement.
- Efficacy Population: All safety participants with measurable disease at baseline. Measurable disease at baseline is defined by the existence of at least 1 target lesion at baseline tumor assessment.
- Response-Evaluable Population: All efficacy participants with at least 1 evaluable postbaseline tumor assessment.
- Biomarker Population: All participants who have at least 1 follow-up tumor assessment and provide a tumor or blood sample.
- PK Population (for cohorts that have a PK component): All participants who have at least 1 measurable study drug concentration (above the limit of quantitation) unless otherwise specified in the cohort supplement.

The analysis populations listed here may be reduced or re-defined in the cohort-specific supplement as relevant.

Efficacy analyses:

All analyses will include summary statistics, including number and percentage for categorical variables and number of participants, mean, standard deviation, median, minimum, and maximum for continuous variables. Time-to-event analyses will be performed using Kaplan-Meier methods; results will be summarized, including number and percentage of events, number and percentage of censored participants, and 25th, 50th (median), and 75th percentiles of times to event.

Preliminary clinical activity will be assessed based on investigator's assessment. ORR and DCR will be listed and summarized. Actual values and changes from baseline in tumor burden will be summarized by time-point.

Additional efficacy analysis may be defined in each cohort-specific supplement.

Safety analyses:

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

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

Biomarker analysis:

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

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

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

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

Abbreviation or Specialist Term	Explanation
ADP	adenosine diphosphate
ADR	Adverse drug reaction; An adverse event where a causal relationship between a medicinal product and the adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out. a. In the context of a clinical trial, an ADR can be serious or non-serious. Serious ADRs may be subject to expedited reporting if they are considered unexpected (see SUSAR definition). b. For marketed products, ADRs are subject to expedited reporting within the country where they are authorized
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AML	acute myeloid leukemia
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
BRCA	breast cancer susceptibility gene
BRCA1	breast cancer susceptibility gene 1
BRCA2	breast cancer susceptibility gene 2
BRCAm	breast cancer susceptibility gene mutated
CA-125	cancer antigen 125
CNS	central nervous system
Co-administered (concomitant) products	A product given to clinical trial participants as required in the protocol as part of their standard care for a condition which is not the indication for which the IMP is being tested and is therefore not part of the objective of the study.
Comparator	Any product used as a reference (including placebo, marketed product, GSK or non-GSK) for an investigational product being tested in a clinical trial. This is any product that is being used to assess the safety, efficacy, or other measurable value against the test product (IMP).
COVID-19	coronavirus disease-2019
CR	complete response
CRO	contract research organization
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCR	disease control rate
DLT	dose-limiting toxicity
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EOT	End of Treatment
EU	European Union
EU CTR	European Union Clinical Trial Regulation
GCP	Good Clinical Practice
GSK	GlaxoSmithKline
HPV	human papilloma virus
HR	hazard ratio
IB	Investigator's Brochure
ICF	informed consent form

Abbreviation or Specialist Term	Explanation
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational medicinal product (investigational product); A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorization but used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form.
IRB	Institutional Review Board
ITT	Intent-to-Treat
IV	intravenous
LAR(s)	legally authorized representative(s)
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI	National Cancer Institute
NIH	National Institutes of Health
ORR	objective response rate
OS	overall survival
PARP	poly(ADP-ribose) polymerase
PARP1	poly(ADP-ribose) polymerase 1
PARP2	poly(ADP-ribose) polymerase 2
PD	progressive disease
PK	pharmacokinetic
PFS	progression-free survival
PFTC	primary fallopian tube carcinoma
Placebo	An inactive substance or treatment that looks the same as, and is given in the same way as, an active drug or intervention/treatment being studied.
PR	partial response
PRO(s)	patient-reported outcome(s)
PT	prothrombin time
PTT	partial thromboplastin time
RECIST	Response Evaluation Criteria in Solid Tumors
Rescue medication	Medicines identified in the protocol as those that may be administered to the participants when the efficacy of the IMP is not satisfactory, or the effect of the IMP is too great and is likely to cause a hazard to the patient, or to manage an emergency situation
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SD	stable disease
SDR	Source Document Review
SDV	Source Data Verification
Standard of Care	Medicine(s) for a specific indication, or a component of the standard care for a particular medical indication, based on national and/or international consensus; there is no regulatory significance to this term. • Products/regimens considered standard of care may differ country to country, depending on consensus in individual countries
SOP	standard operating procedure

Abbreviation or Specialist Term	Explanation
SUSAR	suspected unexpected serious adverse reaction; Suspected Unexpected Serious Adverse Reaction; in a clinical trial, a serious adverse reaction that is considered unexpected, i.e., the nature or severity of which is not consistent with the reference safety information (e.g., Investigator's Brochure (IB) for an unapproved investigational medicinal product). All adverse drug reactions (ADRs) that are both serious and unexpected are subject to expedited reporting
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
US	United States
WHO	World Health Organization
WMA	World Medical Association
WOCBP	woman of childbearing potential
WONCBP	women of non childbearing potential

TRADEMARK INFORMATION

Trademarks of the GSK group of companies
ZEJULA

Trademarks not owned by the GSK group of companies
FluMist

4. INTRODUCTION

This umbrella study will evaluate investigational drugs, including niraparib and novel combinations of niraparib and other investigational agents, as described within each cohort-specific supplement. The agents tested will have a scientific rationale for activity in women with ovarian cancer. The investigational drugs and novel combinations will be specified in detail in cohort-specific supplements to this master protocol. The rationale for investigating each therapeutic combination in a particular patient population (such as platinum-sensitive vs platinum-resistant ovarian cancer) will be outlined in each cohort-specific supplement. It should be noted that in some cohorts the safety and efficacy of niraparib monotherapy may be tested in a novel setting (e.g., in the neoadjuvant setting).

The intent of this study is to rapidly identify more effective therapies for ovarian cancer. In some cohorts, a Phase 1B lead-in may be required to determine the recommended Phase 2 dose (RP2D) of a new drug combination. To expedite completion of this portion for certain cohorts, this study will allow enrollment of patients with other gynecologic malignancies into the Phase 1B (dose escalation) component of specific cohorts (sub-studies). Gynecologic malignancies are cancers that start in a woman's reproductive organs and are typically divided into ovarian/fallopian tube, uterine, cervical, vaginal, and vulvar cancers. To date, there is no cure for any of these conditions once they have metastasized, therefore for patients with these conditions, who have disease progression after standard of care therapy, a Phase 1B study can often be a reasonable option. The majority of sites that open this study will have access to patients in gynecologic oncology clinics, thus this should not create significant difficulties but rather an opportunity for faster enrollment.

4.1. Background

4.1.1. Disease Background

Gynecologic malignancies are cancers that arise from female reproductive organs and are typically managed by a gynecologic oncologist or a medical oncologist specializing in gynecologic malignancies. It is estimated that in 2021 in the US over 113 520 will be diagnosed with a gynecologic malignancy and over 33 620 women will die from a gynecologic malignancy [American Cancer Society, 2021]. The incidence rate of gynecologic cancers among women varies by cancer type. The most common gynecologic cancer is uterine cancer (26.82 cases per 100 000) and the least common is vaginal cancer (0.66 per 100 000). The incidence also varies by ethnicity. For example, the incidence rate of cervical cancer among Hispanic women is 9.60 per 100 000 while for white women it is 7.10 per 100 000. White women have the highest incidence rate of uterine (27.16 per 100 000), ovarian (11.50 per 100 000), and vulvar (2.80 per 100 000) cancer. The highest incidence rate of vaginal cancer is among black women (0.90 per 100 000).

Ovarian cancer, although not the most common gynecologic cancer, is the most common cause of gynecologic cancer death in the US, with 21 410 new cases of ovarian cancer estimated to be diagnosed in 2021 and 13 770 women expected to die from this disease [American Cancer Society, 2021]. Most patients with ovarian cancer present with advanced disease at diagnosis, and the majority of these patients will relapse after initial treatment. Recurrence within 6 months of platinum-based chemotherapy is defined as platinum-resistant disease, which confers a

significantly worse prognosis, with median overall survival (OS) reported in clinical studies ranging from less than a year to 19 months [ten Bokkel Huinink, 1997; Gordon, 2001; Pujade-Lauraine, 2014; Pignata, 2015]. Genetic mutation of breast cancer susceptibility gene 1 (*BRCA1*) or *BRCA2* are identified risk factors for ovarian cancer. As mentioned above, the intent of this study is to rapidly identify more effective therapies for ovarian cancer; therefore, it is anticipated that every cohort will enroll women with ovarian cancer.

Primary fallopian tube carcinoma (PFTC) is very rare and accounts for 0.3% to 1.6% of all gynecologic cancers, with about 300 to 400 new cases annually in the US. The metastatic spread pattern is similar to ovarian cancer. Another similarity to ovarian cancer is that the number of patients diagnosed at early stages is very small. Generally, the diagnosis is made during surgery performed for other reasons. It is most commonly spread by intraperitoneal and lymphoid routes. However, unlike ovarian cancer, PFTC has higher rates of retroperitoneal and distant metastases [Akkaya, 2018]. It has no obvious symptoms and 20% of patients are asymptomatic. The most common symptom is vaginal bleeding, observed in 50% of patients. Discharge or bleeding is accompanied by pain in 26% to 50% of patients and a palpable mass may be present in the pelvic area. International Federation of Gynecology and Obstetrics adapted the staging of ovarian cancer to PFTC and suggested that it is surgically staged like ovarian cancer. PFTCs are rare, so there are insufficient data on treatment approaches in the literature. Total abdominal hysterectomy with bilateral salpingo-oophorectomy and infracolic omentectomy, appendectomy, peritoneal washing, and peritoneal biopsy constitute the primary treatment of choice for PFTC; inclusion of pelvic and para-aortic lymphadenectomy has been controversial [Akkaya, 2018]. The overall 5-year survival for patients with PFTC is 22% to 57%. The approaches to treatment are generally determined in accordance with the data obtained from ovarian cancer and it is typical to include these patients in ovarian cancer studies. Therefore, unless otherwise specified, patients with PFTC will be enrolled into every cohort alongside with patients with ovarian cancer.

In the US, cancer of the endometrium (the lining of the uterus) is the most common cancer of the female reproductive organs. The American Cancer Society estimates for cancer of the uterus body or corpus in the US for 2020 were about 65 620 newly diagnosed cases and about 12 590 deaths. Unlike ovarian cancer, most cases of endometrium cancer are detected early (about 70%) and the 5-year relative survival rate is about 80% (all stages combined). Approximately 13% of all endometrial cancers recur. The prognosis for recurrent disease is poor; the median survival hardly exceeds 12 months. Histologically and genetically, cancer of the endometrium is distinct from ovarian cancer and thus, women with this condition will only be enrolled into the Phase 1B portions of various cohorts.

Cervical cancer ranks third in cancer incidence worldwide and is the most frequent gynecological cancer in developing countries. The frequency of cervical cancer after treatment for dysplasia is lower than 1% and mortality is less than 0.5%, with a 5-year survival rate over 90%. Based on the implementation of cervical screening programs with the referred adoption of improved screening methods in cervical cytology with the knowledge of the important role of the human papilloma virus (HPV), its incidence is decreased in the developed world. Cervical cancer is usually diagnosed at a younger age (median age 50 years) than other gynecologic cancers, while vaginal and vulvar cancers are typically diagnosed at an older age (median age 67 years). Among women aged <50 years, cervical cancer is the most common

gynecologic cancer; among women 50 years or older, uterine cancer is the most common. Cervical cancer and about 40% to 70% of vaginal and vulvar cancer are linked to HPV. Cervical cancer is histologically and genetically distinct from ovarian cancer and is managed quite differently from ovarian cancer; therefore, women with this condition will only be enrolled into the Phase 1B portions of various cohorts.

Over 6000 women in the US are diagnosed yearly with vulvar cancer. Vulvar cancer makes up about 6% of gynecological and less than 1% of all cancers in women. Recent research has shown that about 69% of vulvar cancers diagnosed from 2008 through 2012 were due to HPV. The 5-year survival rate for local vulvar cancer is 86%. Around 59% of vulvar cancer is diagnosed at this local stage. For cancer that has spread to surrounding tissues or organs and/or the regional lymph nodes, the 5-year survival rate is 53%. The survival rate is almost 23% if the cancer has spread to a distant part of the body. Women with this cancer will only be enrolled into the Phase 1B portions of various cohorts.

4.1.2. Study Drug Mechanism of Action: PARP Inhibition

Poly(adenosine diphosphate [ADP] ribose) polymerase (PARP)1 and PARP2 are key enzymes for repairing single-strand DNA breaks. When PARP1 and PARP2 are inhibited, single-strand DNA breaks become double-strand DNA breaks after DNA replication, forcing cancer cells to rely on double-strand break repair mechanisms, in particular homologous recombination, for survival and proliferation.

PARP inhibitors selectively kill a subset of cancer cells with deficiencies in the homologous recombination repair pathway. For example, a tumor arising in a patient with a germline breast cancer susceptibility gene mutated (*BRCA*m) has a defective homologous recombination DNA repair pathway and would be increasingly dependent on base excision repair, a pathway blocked by PARP inhibitors, for maintenance of genomic integrity. In addition to *BRCA* mutations, homologous recombination defects can be caused by germline or somatic alterations to dozens of genes in the homologous recombination DNA repair pathway. In an analysis of ~500 high-grade serous ovarian cancer tumors, approximately 50% contained homologous recombination defects, which could sensitize tumors to PARP inhibitors [TCGA, 2011]. This concept of inducing tumor cell death in tumors with inherent defects in DNA repair using PARP inhibitors is called synthetic lethality [Kaelin, 2005].

4.1.3. Clinical Experience

Niraparib (GSK3985771, formerly MK-4827) is an orally available, potent, highly selective PARP1 and PARP2 inhibitor. The crystalline tosylate monohydrate salt of niraparib is being developed as a monotherapy agent or in combination with cytotoxic/radiotherapy/biologic agents to treat solid tumors.

ZEJULA (niraparib) is approved for the maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response (PR) to first-line platinum-based chemotherapy. ZEJULA is also approved for the maintenance treatment of adult patients with deleterious or suspected deleterious germline *BRCA*-mutated recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy.

Niraparib has been or is currently under evaluation in Phase 1 through Phase 3 clinical sponsor-initiated studies [Niraparib IB]. The highest dose studied is 400 mg once daily, and the dose-limiting toxicity (DLT) at this dose was thrombocytopenia. The recommended dose of niraparib monotherapy is 300 mg once daily for patients with a body weight of ≥77 kg (≥170 lbs) AND a platelet count of ≥150 000/μL, otherwise the recommended dose is 200 mg. The niraparib drug product is formulated as CCI [redacted] for oral administration.

Additional clinical experience with niraparib monotherapy or combination therapy, as relevant, is presented in each cohort-specific supplement.

4.2. Rationale for Current Trial

Given the unmet medical need of patients with ovarian cancer, this umbrella study is designed to rapidly identify more effective therapies for ovarian cancer. Ovarian cancer, when discovered in advanced stages (Stage III or IV), is typically incurable. In some cohorts, niraparib monotherapy will be examined in novel treatment settings (e.g., in the neoadjuvant setting). In other cohorts, new study drug combinations that may require a dose escalation phase to determine a RP2D will be examined. To ensure rapid accrual to a Phase 1B dose escalation cohort, the inclusion criteria for the Phase 1B component of the cohort may be broader than for the corresponding Phase 2 cohort and may allow enrollment of patients with other gynecologic malignancies or lacking the biomarker required for the Phase 2 cohort. Each cohort-specific supplement will clearly state whether there is a Phase 1B component. In addition, each cohort-specific supplement will clearly identify the unique population of patients with ovarian cancer who are eligible to enroll and possibly benefit from the specific combination to be tested in the Phase 2 cohort. These unique ovarian cancer populations may be defined by prior lines of anticancer therapy, sensitivity to platinum, particular biomarkers (e.g., patients with *BRCA*m tumors), or a combination thereof.

5. TRIAL OBJECTIVES AND PURPOSE

The overall objectives for this study are as follows. Cohort-specific objectives will be presented in each cohort-specific supplement, as applicable.

5.1. Primary Objective

Phase 1B (Note: Not all cohorts will have a Phase 1B component):

- To determine the RP2D of the study drug combination as defined in each cohort-specific supplement in patients with advanced, high-grade ovarian, fallopian tube, or primary peritoneal cancer or other advanced gynecologic malignancies

Phase 2:

- To evaluate the efficacy of the study drug or study drug combination as determined in each cohort-specific supplement

5.2. Secondary Objectives

Phase 1B (Note: Not all cohorts will have a Phase 1B component):

- To evaluate the safety and tolerability of the study drug combination as defined in each cohort-specific supplement in patients with advanced, high-grade ovarian, fallopian tube, or primary peritoneal cancer or other advanced gynecologic malignancies

Phase 2:

- To evaluate additional measures of clinical benefit of the study drug or study drug combination as determined in each cohort-specific supplement
- To evaluate the safety and tolerability of the study drug or study drug combination as defined in each cohort-specific supplement

Note: Additional secondary objectives may be added as relevant and will be described in each cohort-specific supplement.

5.3. Exploratory Objectives

As specified in each cohort-specific supplement.

6. INVESTIGATIONAL PLAN

6.1. Overall Study Design

This is a multicenter, multicohort, open-label, Phase 1B/2 umbrella study. It will consist of several independent Phase 2 studies (called cohorts) to evaluate the safety and monotherapy efficacy of novel study drugs and/or novel study-drug combinations in patients with ovarian cancer (Figure 1). The study design for each cohort will be described in detail in a cohort-specific supplement.

In some cases, when the proposed combination requires additional dose confirmation, a Phase 2 cohort evaluating a novel study drug combination will require a Phase 1B lead-in to determine the RP2D of the combination. The Phase 1B (dose escalation) component will be open to patients with any advanced gynecologic cancer. The Phase 2 cohorts in this umbrella study will be restricted to patients with ovarian cancer, primary peritoneal cancer, or fallopian tube cancer who meet the eligibility criteria for that specific cohort.

All cohorts within this umbrella study will have a Screening Period (Day -21 to Day -1), a Treatment Period, an End of Treatment (EOT) Period when study treatment is discontinued for any reason, a Safety Follow-up Visit occurring 30±7 days after the last dose of study treatment, and a Survival Assessment occurring every 90±14 days after the last dose of study treatment, unless otherwise stated in the cohort-specific supplement.

Participants will be evaluated for eligibility to enter the study based on both the overall eligibility criteria presented in this master protocol (see Section 7.1 and Section 7.2) and the eligibility criteria for each specific cohort that is currently enrolling patients (cohort-specific eligibility criteria are provided in each cohort-specific supplement). In order to minimize allocation bias, the sponsor will use randomized allocation for those patients meeting the eligibility criteria of more than 1 contemporarily enrolling treatment cohort.

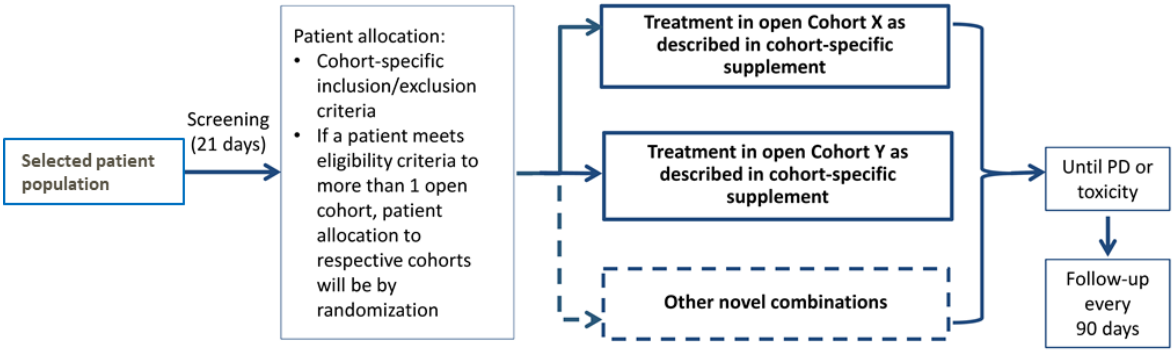
All participants will begin treatment on Cycle 1 Day 1; specific treatment details are provided in each cohort-specific supplement. For cohorts that include a Phase 1B component, details on the data requirements and dose escalation decision process will be provided in the dose escalation plan.

Safety assessments performed will include collection of AEs, vital signs measurements, symptom-directed physical examinations, electrocardiograms (ECGs), clinical laboratory assessments, and Eastern Cooperative Oncology Group (ECOG) performance status. Radiographic evaluations (computed tomography [CT]/magnetic resonance imaging [MRI] of chest, abdomen, and pelvis) to assess the 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, participants will have imaging performed every 12 weeks (84±14 days). Radiographic evaluations will continue until progressive disease (PD), start of alternate anticancer therapy, participant discontinuation of the study, withdrawal of consent to study procedures, becoming lost to follow-up, death, or end of the study. If a participant discontinues treatment for a reason other than PD or death, scans and cancer antigen 125 (CA-125) testing should continue at the specified intervals (i.e., every 9 weeks for the first year of study treatment and every 12 weeks thereafter until PD) unless the participant withdraws consent to these procedures. Tumor and

blood sampling for biomarker evaluations will be conducted. Additional details and specific timing for each of these assessments are provided in each cohort-specific supplement. A cohort may deviate from this generalized schedule, and if so, it will be clearly specified in the cohort-specific supplement.

In cohorts with an accompanying Phase 1B component, different dose combinations may be tested in order to determine the RP2D. The RP2D will be determined after review of all available data for that cohort and will be the dose judged by the sponsor to likely have the greatest efficacy with an acceptable toxicity profile.

Figure 1: Overall Umbrella Study Design



Phase 1B (not in all cohorts): Cohort-specific Phase 1B study schemas will be provided in the cohort-specific supplement for that cohort.
Phase 2 (in all cohorts): Cohort-specific Phase 2 study schemas will be provided in the cohort-specific supplement for that cohort.
Note: Study periods may differ between cohorts; if so, it will be clearly stated in the cohort-specific supplement.

6.1.1. End of Study Definition

The end of study definitions for the cohorts are detailed in each cohort-specific supplement.

6.2. Number of Participants

The number of participants planned for each cohort is provided in each cohort-specific supplement.

6.3. Treatment Assignment

In order to minimize allocation bias, the sponsor will use randomized allocation for those patients meeting the eligibility criteria of more than 1 contemporarily enrolling treatment cohort.

Treatment assignment is described in each cohort-specific supplement.

6.4. Dose Adjustment Criteria

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

Safety criteria for adjustment or stopping doses are described in each cohort-specific supplement.

6.4.2. Pharmacokinetic Criteria for Adjustment or Stopping Doses

Pharmacokinetic (PK) criteria for adjustment or stopping doses are described in each cohort-specific supplement, as applicable.

6.4.3. Guidelines for Events of Special Interest

Guidelines for study treatment dose adjustment for events of special interest are described in each cohort-specific supplement.

6.5. Criteria for Study Termination

The sponsor may terminate this study or a particular cohort at any time. The sponsor will notify the investigators when the study or a cohort is to be placed on hold, completed, or terminated.

6.6. Study Conduct

6.6.1. Schedule of Events

Schedule of event tables for each cohort are presented in each cohort-specific supplement.

6.6.2. Procedures by Visit

Procedures by visit are detailed in each cohort-specific supplement.

6.6.3. General Guidance for Treatment Continuity When Participants are Unable to Come Into the Clinic

Owing to the significant challenges that face the health care system and participants due to coronavirus disease-2019 (COVID-19) as well as the potential for enduring or additional quarantine measures, the following guidance is being provided in this protocol. In the spirit of global diversity in the COVID-19 pandemic and its impact on health care in each individual country as well as the recently issued guidance by several regulatory authorities, the autonomy of each investigative site to assess the benefit/risk for their participants participating in the niraparib clinical studies should be maintained.

Prior to utilization of any of the measures outlined in this section, discussion and approval must be obtained from the sponsor/contract research organization (CRO).

It is expected that sites participating in clinical studies will make every effort to ensure proper monitoring and well-being of enrolled participants by adhering to safety monitoring as outlined in the protocol schedule of events. The use of local laboratories and local radiology centers to reduce the need for the participant to come into the hospital are supported, if deemed necessary for the well-being of the participant, and permitted by applicable local regulations. These local facilities should be added to regulatory documents, as required.

A global telemedicine platform that allows for continued monitoring of AEs, concomitant medications, protocol deviations, etc., may be engaged. Discussions around utilization of this

technology should be held on a per-site basis, and appropriate documentation of utilization should be captured.

Where applicable country and local regulations and infrastructure for home healthcare allow, home healthcare may take place at a location other than the clinical trial site to perform study assessments, which may include collection of blood samples and measurement of vital signs and weight. It is the responsibility of the investigator to inform GSK when this occurs.

If allowed by country regulation/ethics, then study intervention can be shipped direct-to-patient from the investigational site to the participant's home address. The process for this shipment must be agreed with GSK who will provide the relevant documentation and links to courier sites required to ensure shipments are adequately temperature controlled (if required) throughout transportation.

The following are general rules for participants with limited possibility to travel (see Table 3):

- If possible, replace in-person visits with phone contact or alternative location for assessment, such as local laboratories and imaging centers.
- In instances where it is desired to reduce participant exposure in clinic, in-person visits every other cycle are acceptable if there are no ongoing AEs or new AEs; however, every effort must be made to maintain the prespecified schedule of imaging assessments to determine response. At this time, these missed visits will be considered protocol deviations.
- Delay in niraparib treatment for up to 28 days will not result in study discontinuation if the participants do not have access to local laboratories and the site's pharmacy will not dispense the study treatment unless participant is cleared with laboratory tests by the Principal Investigator per the institution's standard operating procedure (SOP).
  - If an interruption longer than 28 days is required, contact the sponsor's Medical Monitor around Day 28 of interruption. This will be reviewed, and recommendations will be made on a case-by-case basis.
- Drug dispensation for niraparib is possible for multiple cycles, with a maximum of 3 months' supply dispensed at once to participants who have not experienced a serious adverse event (SAE) related to the study treatment within the last 3 months (i.e., no ongoing "related" SAE).

If on-site monitoring is no longer permitted, GSK will consider remote Source Data Verification/Source Document Review (SDV/SDR) where permitted by the clinical site/institution. Remote SDV/SDR will be proposed to study sites to meet a participant and/or critical quality need, such as to assess participant safety or to ensure data integrity. In case of remote SDV/SDR, GSK will work with the site to ensure participant privacy.

Table 3: Critical Data Collection and Safety Precautions

Assessment	Recommendation
Follow-up assessment	Contact participant by phone. This discussion should include assessment of new therapies and OS.
PROs on study treatment and follow-up	For cohorts where PROs are collected, individual patient-based devices are provided allowing PROs completion by the participant at home.
Blood sample for biomarker testing	Local laboratory, if possible. Arrangements for the use of a local laboratory should be made by the site.
Hematology	Assessments may be performed through at-home nursing or at local laboratory. Arrangements for at-home nursing or the use of a local laboratory should be made by the site including the reporting of results to the PI for review.
Clinical chemistry	Assessments may be performed through at-home nursing or at local laboratory. Arrangements for at-home nursing or the use of a local laboratory should be made by the site, including the reporting of results to the PI for review.
Vital signs	Assessments may be performed through at-home nursing or at local laboratory. Arrangements for at-home nursing or the use of a local laboratory should be made by the site including the reporting of results to the PI for review.
Adverse events	• Ongoing AEs and SAEs - reviewed by phone. • If hematologic AE are ongoing, a local CBC is desirable. • New AEs/SAEs - may be assessed by phone (please remember to submit SAE documentation within 24 hours of learning of the event).
Concomitant medications	Reviewed by phone and via medical record review.
Niraparib study medication/dose modifications	• Confirm the current dose the participant is on to ensure adequate drug supply coverage. • Shipments sent directly to participants of niraparib/placebo are possible **but must be prospectively discussed and approved by sponsor**. All required country-level, IEC/IRB, and/or institutional approvals must be in place, prior to any shipment. Shipments made by sites to the participant must comply with protocol requirements. The participant must also have given consent for direct shipment; this consent must be documented in the participant's source notes. • If there have been dose modifications due to AE(s) within the last cycle and require monitoring - recommended a weekly CBC, done locally; nonhematologic AEs may be monitored by phone. • Participant missed doses - assess by phone.
Disease recurrence (RECIST v1.1)	CT/MRI if possible.
Pregnancy test	Local laboratory, if available. Arrangements for the use of a local laboratory should be made by the site including the reporting of results to the PI for review.

Abbreviations: CBC = complete blood count; IEC = Independent Ethics Committee; IRB = Institutional Review Board; PI = Principal Investigator; PRO = patient-reported outcome; RECIST = Response Evaluation Criteria in Solid Tumors.

7. SELECTION AND WITHDRAWAL OF PARTICIPANTS

The following lists of eligibility criteria are applicable to all participants. Additional cohort-specific criteria are provided in each cohort-specific supplement.

7.1. Inclusion Criteria

1. Participant must be female ≥18 years of age, able to understand the study procedures, and agree to participate in the study by providing written informed consent.
2. Participant must have the following histologic diagnosis unless otherwise specified in a cohort-specific supplement:
   a. Phase 2 cohorts: Participant has histologically diagnosed high-grade epithelial (i.e., serous, endometrioid, mucinous, clear cell) ovarian, fallopian tube, or primary peritoneal cancer or carcinosarcoma of the ovary. Participant with high-grade mixed histology is also eligible.
      Note: Cohorts may exclude some ovarian cancer histologies, as specified in the cohort-specific supplement.
   b. For the Phase 1B components: Participant has histologically diagnosed gynecologic malignancy (i.e., any cancer that started in a woman's reproductive system). Gynecologic malignancies include cervical cancer; endometrial cancer; vaginal cancer; vulvar cancer; high-grade recurrent epithelial (i.e., serous, endometrioid, mucinous, clear cell) ovarian, fallopian tube, or primary peritoneal cancer; or advanced carcinosarcoma of the ovary. Participant with high-grade mixed histology is also eligible.
3. The allowed number of prior lines of anticancer therapy for primary cancer will be specified in each cohort-specific supplement. Treatment with hormonal agents alone are not counted in the number of lines of therapy. Treatment with single-agent bevacizumab or 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.

   Note: Definitions for a prior line of therapy may be modified for certain cohorts. Differences from the definitions presented here will be clearly specified in the cohort-specific eligibility criteria.
4. Phase 2 cohorts: Participant must have measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.
5. Participant has an ECOG performance status of 0 to 2.

   Note: Cohorts may exclude participants with an ECOG performance of 2, as specified in the cohort-specific supplement.
6. Participant has adequate organ function, defined as follows:
   a. Absolute neutrophil count ≥1500/μL, without growth factor support (granulocyte colony-stimulating factor or granulocyte-macrophage colony-stimulating factor administration is not permitted within 2 weeks of Screening)

b. Platelets ≥100 000/µL without platelet transfusion support within 2 weeks prior to Screening
c. Hemoglobin ≥9 g/dL without transfusion or growth factor (recombinant erythropoietin) within 2 weeks of Screening
d. Serum creatinine ≤1.5× upper limit of normal (ULN) or calculated creatinine clearance ≥50 mL/min using Cockcroft-Gault equation
e. Total bilirubin ≤1.5× ULN, except in participants with Gilbert's syndrome. Participants with Gilbert's syndrome may enroll if direct bilirubin is ≤1.5× 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 participant 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 participant is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants. Participant with known lupus anticoagulant and elevated PTT may be eligible on a case-by-case basis after discussion with the sponsor's Medical Monitor.

Note: Definitions for adequate organ function may be modified for certain cohorts. Differences from the definitions presented here will be clearly specified in the cohort-specific eligibility criteria.

7. Participant is not pregnant or breastfeeding, and at least 1 of the following conditions apply:

   – Is not a woman of childbearing potential (WOCBP), as defined in Appendix 1.

     OR

   – Is a WOCBP using a contraceptive method that is highly effective (with a failure rate of <1% per year), with low user dependency, as described in Appendix 1, during the Treatment Period and for at least 180 days after the last dose of study treatment and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction during this period. The investigator should evaluate the effectiveness of the contraceptive method in relation to the first dose of study treatment.

     - A WOCBP must have a negative pregnancy test (highly sensitive urine test or serum test as required by local regulations) within 72 hours before the first dose of study treatment.
       If a urine test cannot be confirmed as negative (e.g., an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.
     - Additional requirements for pregnancy testing during and after study treatment are described in Section 11.3.8.

   The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

8. Participant must provide sufficient tumor tissue samples based on requirements defined in each cohort-specific supplement.

7.2. Exclusion Criteria

1. Participant has not recovered (i.e., to Grade ≤1 or to baseline) from prior chemotherapy-induced AEs. Note: Participant with Grade ≤2 neuropathy or alopecia is an exception to this criterion and may qualify for the study.
2. Participant has a known diagnosis of immunodeficiency or is receiving systemic steroid therapy exceeding an equivalent of prednisone 10 mg daily or any other form of immunosuppressive therapy within 7 days prior to the first dose of study treatment
3. Participant is currently participating in a treatment study or has participated in a study of an investigational agent within 4 weeks of the first dose of treatment
4. Participant has received prior systemic anticancer therapy including cytotoxic chemotherapy, PARP inhibitor, immune checkpoint inhibitors, hormonal therapy given with the intention to treat cancer, or biological therapy within 3 weeks of the first dose of study treatment. This washout period is required to ensure prior therapy is not confounding the toxicity profile of the investigational study drug or study drug combinations in cohorts.
5. Participant has received live vaccine within 14 days of planned start of study therapy
6. Participant has symptomatic uncontrolled brain or leptomeningeal metastases. (To be considered "controlled," central nervous system [CNS] disease must have undergone treatment [e.g., radiation or chemotherapy] at least 1 month prior to study entry. The participant must not have any new or progressive signs or symptoms related to the CNS disease and must be taking ≤10 mg of prednisone or equivalent per day or no steroids.) Participant who has untreated brain metastases and who is not symptomatic may enroll if the investigator feels that treatment of these metastases is not indicated. A scan to confirm the absence of brain metastases is not required. Participant with spinal cord compression may be considered if she has received definitive treatment for this and evidence of clinically stable disease for 28 days prior to the first dose of study treatment
7. Participant had major surgery within 4 weeks of starting the study or participant has not recovered from any effects of any major surgery.
8. Participant has a known additional malignancy that progressed or required active treatment within the last 2 years because reoccurrence of another malignancy would confound interpretation of objective response rate (ORR) by RECIST v1.1 criteria. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin that has undergone potentially curative therapy, or in situ cancer that is considered to be low risk for progression by the investigator.
9. Participant is considered a poor medical risk due to a serious, uncontrolled medical disorder, nonmalignant systemic disease, or active, uncontrolled infection. These include, but are not limited to, COVID-19, significant cardiovascular disease (e.g., significant cardiac conduction abnormalities, myocardial infarction, cardiac arrhythmia or unstable angina within 6 months prior to enrollment, New York Heart Association Grade ≥2

congestive heart failure, uncontrolled hypertension, serious cardiac arrhythmia requiring medication, Grade ≥2 peripheral vascular disease, and history of cerebrovascular accident within 6 months prior to enrollment), uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, and any psychiatric disorder that prohibits obtaining informed consent.

10. Participant has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, might interfere with the participant's participation for the full duration of the study treatment, or is not in the best interest of the participant to participate.
11. Participant 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).

7.3. Withdrawal Criteria

7.3.1. Discontinuation from Treatment

Participants may be discontinued from study treatment in any cohort at any time. Specific examples of reasons for discontinuing all study treatments, regardless of cohort, are given below.

- AE
- PD as outlined in Appendix 2 or based on clinical criteria by investigator
- Risk to participant, as judged by the investigator or sponsor
- Severe noncompliance with the protocol, as judged by the investigator or sponsor
- Participant request
- Participant becomes pregnant
- Sponsor decision to terminate study

Discontinuation of treatment may be considered by the investigator after discussion with the sponsor's Medical Monitor for participants who have attained a confirmed complete response (CR) and have received study treatment for at least 24 months. In this instance, participants may be permitted to resume treatment only after discussion with the sponsor's Medical Monitor.

Additional guidance for discontinuation from cohort-specific treatment is provided in each cohort-specific supplement.

Participants who discontinue from all study treatments will continue to receive follow-up assessments until the end of study unless they are discontinued from the study. Discontinuation of study treatment does not impact a participant's participation in the study. The participant should comply with the protocol schedule of assessments and data collection should continue.

The date and reasons for discontinuation of study treatment should be captured in the eCRF.

7.3.2. Discontinuation from the Study

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

- Withdrawal of consent by the participant, who is at any time free to discontinue their participation in the study, without prejudice to further treatment
- Loss to follow-up
- Incorrectly enrolled/randomized participant (i.e., participant does not meet the eligibility criteria for the cohort), unless the participant benefits from the treatment received in the investigator's opinion
- Death from any cause
- Sponsor's decision to terminate study
- Investigator's decision

A participant who considers withdrawing from the study must be informed by the investigator about modified follow-up options (e.g., telephone call, contact with a relative or treating physician, or providing consent to continued collection of information from medical records for study purposes).

If a participant withdraws consent, she will be specifically asked if she is withdrawing consent to further participation in the study including any further follow-up or if she is willing to continue long-term follow-up through one of the modified follow-up options permitted. If the participant is willing to continue long-term follow-up, she has **not** discontinued the study.

7.3.3. Lost to Follow-up

A participant may be considered potentially lost to follow-up if she fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). At least 3 documented attempts, including 1 by certified mail, should be made to contact the participant before the participant is deemed lost to follow-up. These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, she will be considered to have discontinued from the study.

Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomized, including those who did not receive study intervention. Public sources may be searched for vital status information. If the vital status of the participant is determined as known alive or deceased, this will be documented along with other relevant study information, and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

8. TREATMENT OF PARTICIPANTS

8.1. Description of Study Drug

Descriptions of study treatments are provided in each cohort-specific supplement.

8.2. Concomitant Medications

Any medication the participant takes other than the study treatment, including herbal and other nontraditional remedies, is considered a concomitant medication. All concomitant medications must be recorded in the eCRF.

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

8.2.1. Prohibited Medications

Known prior medications, such as other cancer therapies, that exclude a participant from participating in the study are described in the exclusion criteria (see Section 7.2) and in each cohort-specific supplement.

Participants in all cohorts are prohibited from receiving the following therapies during the screening and treatment phase of this study. Additional cohort-specific prohibited medications are presented in each cohort-specific supplement.

- Systemic anticancer or biological therapy
- Immunotherapy (except study treatment specified in the relevant cohort-specific supplement)
- Chemotherapy (except study treatment specified in the relevant cohort-specific supplement)
- Hormonal therapy given with the intention to treat the primary cancer
- Radiation therapy is prohibited within 3 weeks prior to Day 1 and during study treatment. Note: Palliative radiation therapy to a small field while on study should be discussed with the sponsor's Medical Monitor on a case-by-case basis.
- Any surgery not prespecified in the cohort-specific schedule of events that involves tumor lesions; however, specific situations should be discussed on a case-by-case basis with the sponsor's Medical Monitor. Paracentesis while the participant is on study will be permitted after discussion with the sponsor. Note: Administration of radiation therapy or surgery done that involves tumor lesions will be considered as disease progression at the time the procedure is performed.
- 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, Bacillus Calmette-Guérin, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed.

The use of live COVID-19 adenoviral vaccines within 14 days prior to the first dose of treatment or while participating in the study must be discussed with the sponsor's Medical Monitor. Intranasal influenza vaccines (e.g., FluMist) are live attenuated vaccines and are not allowed.

8.2.2. Contraception

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. Note: A highly sensitive urine pregnancy test may be performed if the serum pregnancy result is not available before dosing. Female participants 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 highly effective contraception (see Appendix 1), or be of non-childbearing potential, as defined in Appendix 1.

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

8.2.3. Rescue Medications and Supportive Care Guidelines

Cohort-specific rescue medications and supportive care guidelines are provided in each cohort-specific supplement.

8.2.4. Other Study Restrictions

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

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

8.3. Treatment Compliance

Compliance with inclusion and exclusion criteria will be assessed as outlined in Section 7.1 and Section 7.2, respectively. Study treatment accountability will be monitored as detailed in Section 9.6. Cohort-specific treatment compliance is described in each cohort-specific supplement.

8.4. Randomization and Blinding

8.4.1. Participant Identification

All patients who enter 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 consented and been screened, and when all eligibility criteria have been confirmed in the eCRF.

Rescreening is permitted both within a given cohort and for a different cohort if applicable. The patient identification number must remain constant throughout the entire study; it must not be changed at the time of enrollment.

8.4.2. Allocation to Treatment Cohorts

In order to minimize allocation bias, the sponsor may use randomized allocation for those patients meeting the eligibility criteria of more than 1 contemporarily enrolling treatment cohort. If applicable, randomized allocation will occur centrally using an interactive voice response system/integrated web response system. Enrollment in each treatment cohort may be stratified based on histology; details are provided in each cohort-specific supplement.

9. STUDY DRUG MATERIALS AND MANAGEMENT

9.1. Study Drug

Descriptions of the study treatments being evaluated in each cohort are provided in each cohort-specific supplement.

9.2. Study Drug Packaging and Labeling

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 nonparticipant specific. Additional details on treatments and dosing are provided in each cohort-specific supplement.

9.3. Study Drug Storage

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

9.4. Study Drug Preparation

Descriptions of the preparation of the study treatments are provided in each cohort-specific supplement.

9.5. Administration

Administration of the study treatments is described in each cohort-specific supplement.

9.6. Study Drug Accountability

The investigator or designee is responsible for maintaining accurate dispensing records of the study treatments throughout the clinical study. Study treatment accountability for niraparib should be maintained by the investigational site based on the amount of niraparib dispensed versus the amount of niraparib returned to the investigational site at each visit and the number of days since the last visit. Accountability for other study medications will be outlined in each cohort-specific supplement.

Details of maintaining study treatment accountability, including information on the accountability log, will be provided in the Study Reference Manual.

All dispensation and accountability records will be available for sponsor review. The pharmacist will dispense study treatment for each participant according to the protocol and Study Reference Manual, if applicable.

9.7. Study Drug Handling and Disposal

At the end of the study, when all participants have stopped protocol treatment, complete drug reconciliation per batch should be available at the investigational 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 participants entered in this study.

10. ASSESSMENT OF EFFICACY

10.1. Primary Efficacy Endpoint - Phase 2

The primary efficacy endpoint is confirmed ORR, which is defined as the proportion of participants who have achieved confirmed CR or PR, evaluated using RECIST v1.1 (Appendix 2) based on investigator's assessment. Tumor assessments after the initiation of alternate anticancer therapy are excluded for the assessment of best overall response.

For select cohorts, a primary efficacy endpoint other than confirmed ORR by RECIST v1.1 based on investigator's assessment may be used to evaluate the primary objective of efficacy of the study drug or study drug combination, in which case it will be clearly stated in the cohort-specific supplement.

10.1.1. Evaluation of Tumor Response

10.1.1.1. Overview

The efficacy of each study drug or study drug combination will be evaluated by assessment of tumor response to treatment according to RECIST v1.1 per investigator's assessment [Nishino, 2015]. Serum tumor marker data (e.g., CA-125) will not be used to define objective responses or disease progression, unless otherwise specified in a cohort-specific supplement; however, serum tumor marker data can be used for clinical decisions. Response to treatment will be based on investigator's evaluation of radiographic images.

Tumor imaging (chest, abdomen, and pelvis [plus head if clinically indicated]) should be performed by CT with IV contrast (preferred, if no contraindication to IV contrast). MRI should only be used if clinically appropriate, when CT is contraindicated, or for imaging of the head, but the same imaging technique should be used in a participant throughout the study, unless this is not feasible. CT scan is the more commonly used modality and is preferred for the majority of participants. The CT portion of positron emission tomography (PET)/CT may be used according to RECIST v1.1 guideline if the CT scan is of diagnostic quality. If the chest or head CT/MRI is clear at screening, repeat imaging of these areas is not required in the absence of clinical indication requiring follow-up. Bone scans should be conducted per standard of care.

Images will be collected and sent to the central imaging vendor for storage and potential central review unless otherwise specified in a cohort-specific supplement.

10.1.1.2. Timing of Radiographic Evaluations

All participants 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 the date of first dose.

Unless otherwise specified in a cohort-specific supplement, 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, participants will have imaging performed

every 12 weeks (84±14 days). 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. Radiographic evaluations will continue until PD, start of alternate anticancer therapy, participant discontinuation of the study, withdrawal of consent to study procedures, becoming lost to follow-up, death, or end of the study.

Per RECIST v1.1 (see Appendix 2), CR or PR should be confirmed (unless otherwise specified in a cohort-specific supplement); 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., 9 or 12 weeks later), whichever is clinically indicated. Imaging should be continued until whichever of the following occurs:

- PD (except as noted below)
- The start of alternate anticancer therapy
- Participant discontinuation of the study
- Withdrawal of consent to study procedures
- Lost to follow-up
- Death
- End of study

There is accumulating evidence indicating clinical benefit in a subset of participants treated with immunotherapy despite initial evidence of PD [Nishino, 2015]. Participants with PD may continue study treatment at the investigator's discretion only after discussion with the sponsor, until the investigator has determined that the participant is no longer experiencing clinical benefit or until study treatment is no longer tolerated by the participant.

Participants 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 per schedule of events in each cohort-specific supplement.

10.1.1.3. Assessment of Response by RECIST v1.1

RECIST v1.1 per investigator's assessment will be used 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, nontarget, and new lesions and definitions of response, are provided in Appendix 2.

10.2. Secondary Efficacy Endpoints - Phase 2

The secondary efficacy endpoints used to evaluate the secondary objective of clinical benefit are progression-free survival (PFS), OS, duration of response (DOR), and disease control rate (DCR). Definitions for these endpoints are provided in Section 10.2.1, Section 10.2.2, Section 10.2.3, and Section 10.2.4, respectively.

For select cohorts, secondary efficacy endpoints other than PFS, OS, DOR, and DCR may be used to evaluate clinical benefit of the study drug or study drug combination, in which case it will be clearly stated in the cohort-specific supplement.

10.2.1. Progression-free Survival

PFS is defined as the time from the date of the first dose of study treatment to the earliest date of assessment of progression or death by any cause in the absence of progression by RECIST v1.1 (Appendix 2).

An alternative definition of PFS may be provided in cohort-specific supplements.

10.2.2. Overall Survival

OS is defined as the time from the date of the first dose of study treatment to the date of death by any cause. Participants without documented death at the time of the final analysis will be censored at the last date they were known to be alive.

An alternative definition of OS may be provided in cohort-specific supplements.

10.2.3. Duration of Response

DOR is defined as the time from first documentation of response (CR or PR) until the time of first documentation of disease progression by RECIST v1.1 (Appendix 2) based on investigator's assessment or death by any cause.

10.2.4. Disease Control Rate

DCR is defined as the percentage of participants who have achieved best overall response of CR, PR, or stable disease (SD) per RECIST v1.1 based on investigator's assessment (Appendix 2).

10.3. Biomarker Endpoints

Tumor and/or blood samples may be assessed to identify potential disease-related or treatment-related biomarkers that may associate with tumor responses to the study drug or study drug combination defined in each cohort-specific supplement.

Additional details are provided in each cohort-specific supplement.

10.4. PK Endpoints

Blood samples to assess PK may be collected as defined in each cohort-specific supplement.

11. ASSESSMENT OF SAFETY

11.1. Primary Endpoints - Phase 1B

The primary endpoints for each Phase 1B component will include the following:

- Percentage (number) of participants with DLTs
- Percent of participants with AEs, changes in clinical signs and laboratory parameters

To be considered a DLT, the AE must be considered related to study treatment. DLTs can be hematologic or nonhematologic and are described in each cohort-specific supplement as relevant (see Section 11.3.1.6).

To inform the RP2D, the maximum tolerate dose (MTD), along with PK/pharmacodynamic data, and acute and chronic toxicity data, will be determined. The MTD is the dose at which the DLT rate is closest to the target toxicity rate of 30%, unless otherwise specified in the cohort-specific supplement.

11.2. Safety Parameters

Safety parameters evaluated during this study will include AEs, vital signs, symptom-directed physical examination findings, ECGs, clinical laboratory values (including hematology, serum chemistry, coagulation, thyroid function, and urinalysis), and ECOG performance status, unless otherwise specified in a cohort-specific supplement.

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

11.2.1. Demographic/Medical History

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

11.2.1.1. Disease History

For disease history the following will be documented, as relevant:

- Date of first diagnosis
- Tumor type
- Stage at time of initial diagnosis
- Histology and grade of disease at diagnosis and most recent biopsy if additional biopsy performed
- Information on first anticancer therapy:
  - Intent (adjuvant, neoadjuvant, curative, and palliative)
  - Date of start of first treatment
  - Agents used in first treatment

  - Date of last dose of first treatment
- Information on second and subsequent anticancer therapies:
  - Intent (adjuvant, neoadjuvant, curative, and palliative)
  - Dates of start of all subsequent treatments
  - Agents in all subsequent treatments
  - Dates of last dose of all subsequent treatments
- Best response and reason for treatment discontinuation (including PD and toxicities) for each prior anticancer therapy
- Date of PD for each prior anticancer therapy

Other aspects of disease history may be recorded and will be specified in each cohort-specific supplement.

11.2.1.2. Medical and Surgical History

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

11.2.1.3. Previous and Concomitant Medications

Previous and concomitant medications will be documented as described in Section 8.2. Medications will be coded using World Health Organization (WHO) Anatomical Therapeutic Chemical classification.

11.2.2. Vital Signs

Vital signs will be measured in all participants and include blood pressure, pulse rate, and temperature. Any abnormal vital signs assessed as clinically significant should be recorded as an AE or SAE. If SAE criteria are met or the abnormality is an adverse event of special interest (AESI) (see Section 11.3.7), the event should be recorded and reported according to the SAE reporting process (see Section 11.3.5).

11.2.3. Weight and Height

Weight and height will be measured in all participants. Height will be measured at screening only.

11.2.4. Physical Examination

Physical examinations, including height (screening only), weight, and vital signs (blood pressure, pulse rate, and temperature), will be performed in accordance with the schedule of events provided in each cohort-specific supplement.

Any abnormality in 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 11.3.7), the event should be recorded and reported according to the SAE reporting process (see Section 11.3.5).

11.2.5. Electrocardiogram

All participants will undergo ECGs in accordance with the schedule of events in each cohort-specific supplement. If clinic schedule allows, ECGs should be preferably performed prior to any blood draws. Participants will be supine or in a semirecumbent position (about 30 degrees of elevation) and rested for approximately 2 minutes before ECGs are recorded.

If SAE criteria are met or the abnormality is an AESI (see Section 11.3.7), the event should be recorded and reported according to the SAE reporting process (see Section 11.3.5).

11.2.6. Laboratory Assessments

The following laboratory variables will be determined in accordance with the schedule of events presented in each cohort-specific supplement.

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

Any abnormal laboratory value assessed as clinically significant should be recorded as an AE. If SAE criteria are met or the abnormality is an AESI (see Section 11.3.7), the event should be recorded and reported according to the SAE reporting process (see Section 11.3.5).

Laboratory testing may occur more frequently than is specified in the schedule of events, if additional testing is medically indicated per investigator judgment or if the event meets the criteria for study treatment dose adjustment (see Section 6.4 and each cohort-specific supplement). Additional tests may be performed at a laboratory facility other than the investigational site, but the test results must be reported to the investigational site, the investigational site must keep a copy of test results with the participant's study file, and the results must be entered into the eCRF.

Any suspected case of MDS/AML or other leukemia reported while a participant is receiving treatment or followed for post-treatment assessments must be referred for evaluation and a bone marrow aspirate and biopsy to a local hematologist. Testing completed as part of standard of care is sufficient if the methods are acceptable to the sponsor's Medical Monitor. The investigational site must receive a copy of the hematologist's report of aspirate/biopsy findings, which must include a classification according to WHO, and other sample testing reports related to MDS/AML. Reported data will be entered in the appropriate eCRF pages, and the site must keep a copy of all reports with the participant's study file.

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

The following clinical laboratory assessments will be performed, unless otherwise specified in a cohort-specific supplement:

- **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 participants with high-grade thrombocytopenia.)
- **Coagulation factors:**
  - International normalized ratio
  - aPTT
- **Serum chemistry:**
  - Sodium
  - Amylase
  - Potassium
  - Total bilirubin
  - Calcium
  - Alkaline phosphatase
  - Magnesium
  - AST
  - Chloride
  - Glucose (fasting at baseline)
  - 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
- Serum CA-125
- Serum pregnancy testing/urine pregnancy testing

A negative serum or urine pregnancy test is required within 72 hours prior to Cycle 1 Day 1 for females of childbearing potential; a urine pregnancy test may be performed if the serum pregnancy result is not available before dosing. Urine pregnancy testing will be performed in females of childbearing potential on Day 1 of each subsequent cycle and at the Safety Follow-up visit, unless otherwise specified in a cohort-specific supplement. Any pregnancies that occur within 180 days post-treatment are to be reported as described in Section 11.3.8.

11.2.7. ECOG Performance Status

Performance status will be assessed using the ECOG scale (see Appendix 3) in accordance with the schedule of events in each cohort-specific supplement. The same observer should assess performance status each time.

11.3. Adverse Events and Special Situations

11.3.1. Definitions

11.3.1.1. Adverse Event

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

AEs may include the onset of new illness and the exacerbation of pre-existing medical conditions. An AE can include an undesirable medical condition occurring at any time after the time of randomization or treatment assignment, including baseline or washout periods, even if no study treatment has been administered. (See Section 11.3.3 for information about AE collecting and recording.)

11.3.1.2. Serious Adverse Event

Any untoward medical occurrence that, at any dose

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

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

**Medical and scientific judgment should be exercised in determining whether situations or events should be considered SAEs: an important medical event may not be immediately life-threatening or result in death or require hospitalization but may jeopardize the participant or require intervention to prevent one of the above outcomes. Examples of such events are allergic

bronchospasm, blood dyscrasias, or convulsions that may require intensive treatment in an emergency room or at home but do not result in hospitalization; development of drug dependency or drug abuse; and transmission of disease associated with the administration of the study treatment. (See Section 11.3.5 for information about SAE reporting.)

11.3.1.3. Treatment-Emergent Adverse Event

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

11.3.1.4. Adverse Event of Special Interest

Any AE (serious or nonserious) that is of scientific and medical concern specific to the study treatment, for which ongoing monitoring and rapid communication by the investigator to the sponsor is appropriate.

11.3.1.5. 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 participant harm while the study treatment is in the control of the health care professionals or participants. 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 participant at a dose greater than that which was assigned to that participant per the study protocol within the specified administration window and under the direction of the investigator.
  In the event of an overdose, the investigator should:
  - Contact the Medical Monitor immediately.
  - Closely monitor the participant for AE/SAE and laboratory abnormalities until the investigational product can no longer be detected systemically.
  - Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF.

  Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. Associated AEs (signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication) should be treated and monitored by the investigator. The dosage of study treatment administered, any associated AEs, or treatment provided to the participant because of the overdose should be documented on the applicable sections within the eCRF. A serious overdose (including an SAE resulting from the overdose, if any) will be reported as described in Section 11.3.5.

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

Reporting Special Situations: All SAEs associated with occurrences of abuse, misuse, medication error, overdose, and accidental or occupational exposure with any study treatment must be reported on an SAE Report Form to the sponsor within 24 hours of awareness.

11.3.1.6. Dose-Limiting Toxicities

In Phase 1B components of select Phase 2 cohorts, DLTs will be monitored. The definition of a DLT, which may be hematologic or nonhematologic, may vary with the class of agent studied and will be provided in each cohort-specific supplement as relevant.

To be considered a DLT, the AE must be considered related to study treatment. If multiple toxicities occur, the presence of DLT will be graded based on the most severe toxicity observed.

11.3.2. Assessment of Adverse Events

11.3.2.1. Severity Assessment

All AEs will be assessed by the investigator for severity* according to the current version of CTCAE [Common Terminology Criteria for Adverse Events (CTCAE), 2021] that is relevant for that cohort and will be clearly specified in the cohort-specific supplement; National Institutes of Health (NIH), NCI. The CTCAE severity Grades 1 through 5 provide unique clinical descriptions of severity of each AE.

*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 11.3.1.2. 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.

11.3.2.2. Relationship to Study Intervention

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

- Related: A causal relationship between the medicinal product (or study procedures) and AE is a reasonable possibility. For example, the occurrence of the AE cannot be

explained by other causative factors. The AE, however, can be explained by pharmacological effect of the medicinal product such as a similar event having been reported previously, alteration of the dose effect, or the timing or seriousness of the AE, etc. Positive rechallenge/dechallenge is supportive.

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

11.3.2.3. Expectedness

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

11.3.3. Collection and Recording Adverse Events

AEs may be volunteered spontaneously by the participant, 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 treatment as a result of the AE, assessment of the seriousness of the AE, and assessment of the causal relationship of the AE to study treatment or study procedure. All AEs will be collected and recorded for each participant from the day the ICF is signed as outlined in the cohort-specific supplement.

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

All SAEs will be collected from the signing of the ICF for this study through the Safety Follow-up Visit and recorded in the eCRF. SAEs will also be reported on an SAE form as described in Section 11.3.5 of this protocol. SAEs considered by the investigator to be related to study treatment are reported throughout the Survival Assessment Period.

All AEs, regardless of the source of identification (e.g., physical examination, laboratory assessment, ECG, or reported by participant), will be collected and recorded in the eCRF for each participant from the time of randomization or treatment assignment through the Safety Follow-up Visit.

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 participant's disease, these AEs/SAEs must be reported per AE/SAE reporting requirements described in Section 11.3.5.

11.3.4. Follow-Up of Adverse Events

All AEs experienced by a participant, 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 participant is lost to follow-up, or until the participant has died.

If an investigator becomes aware of an SAE after the specified Follow-up Period and considers the SAE related to the study treatment, the investigator should report the SAE to the sponsor according to timelines for reporting SAEs described in Section 11.3.5.

11.3.5. Reporting

The investigator must report all SAEs and all follow-up information to the sponsor on an SAE Report Form (electronic [preferred] or paper) 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), 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.

11.3.6. Submission and Distribution of Serious Adverse Event Reports

Per regulatory requirements, if an event is assessed by the sponsor as a suspected unexpected serious adverse reaction (SUSAR), it is the responsibility of the sponsor to submit the SUSAR to Regulatory Authorities according to applicable regulations. Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

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

11.3.7. Adverse Events of Special Interest

AESI for niraparib are the following:

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

Serious AESIs should be collected and reported as follows:

- MDS and AML along with other secondary cancers should be reported to the sponsor throughout the Survival Assessment Period

Other AESIs for other cohort-specific study treatments are described in each cohort-specific supplement, as relevant.

11.3.8. 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 treatment may have interfered with the effectiveness of a contraceptive medication. The investigator must follow-up all pregnancies, document the course and the outcome, and report this information to the sponsor on a Pregnancy Outcome Report Form within 24 hours of becoming aware—even if the participant 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.

11.3.9. Special Situations

All occurrences of abuse, misuse, medication error, overdose, and accidental or occupational exposure to any study treatment must be reported as outlined in Section 11.3.1.5 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 must be submitted to the sponsor within 24 hours of awareness.

12. STATISTICS

This section provides an overall description of the statistics for this study. Additional details are provided in each cohort-specific supplement and accompanying statistical analysis plan.

12.1. Sample Size Determination

Sample size determination for each cohort is described in each cohort-specific supplement.

12.2. Analysis Population

Six analysis populations will be defined as follows:

- ITT Population: All participants randomized unless otherwise specified in a cohort-specific supplement.
- Safety Population: All participants in each cohort who receive at least 1 dose of study treatment. For RP2D purpose, the population included in the assessment of DLTs will be specified in each cohort-specific supplement.
- Efficacy Population: All safety participants with measurable disease at baseline. Measurable disease at baseline is defined by the existence of at least 1 target lesion at baseline tumor assessment.
- Response-Evaluable Population: All efficacy participants with at least 1 evaluable post-baseline tumor assessment.
- Biomarker Population: All participants who have at least 1 follow-up tumor assessment and provide a tumor or blood sample.
- PK Population (for cohorts that have a PK component): All participants who have at least 1 measurable study drug concentration (above the limit of quantitation) unless otherwise specified in the cohort supplement.

The analysis populations listed here may be reduced or re-defined in the cohort-specific supplement as relevant.

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

Demographics, baseline characteristics, medical history, and concomitant medication information will be summarized for the Safety Population using descriptive statistics. No formal statistical comparisons will be performed. Demographics, baseline characteristics, concomitant medications, and medical history data for each participant will be provided in data listings.

12.4. Efficacy Analyses

All analyses will include summary statistics, including number and percentage for categorical variables; and number of participants, mean, standard deviation, median, minimum, and maximum for continuous variables. Time-to-event analyses will be performed using Kaplan-Meier methods; results will be summarized, including number and percentage of events, number

and percentage of censored participants, and 25th, 50th (median), and 75th percentiles of times to event.

Preliminary clinical activity will be assessed based on investigator's assessment. ORR and DCR will be listed and summarized. Actual values and changes from baseline in tumor burden will be summarized by time-point. Best overall response will be summarized by number and percentage.

Additional efficacy analyses may be defined in each cohort-specific supplement.

12.5. Safety Analyses

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

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

12.6. Biomarker Analysis

Exploratory endpoints of this trial may include identification of potential biomarkers that would associate with tumor responses. The incidence of biomarkers may be summarized using descriptive statistics. Correlation of clinical activity with biomarker subpopulations may be performed. Further details will be provided in the cohort-specific supplement.

13. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

13.1. Study Monitoring

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

- Determine the adequacy of the facilities
- Discuss with the investigator(s) and other personnel their responsibilities with regard to protocol adherence and the responsibilities of the sponsor or its representatives. This will be documented in a Clinical Study Agreement between the sponsor and the investigator

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

- Provide information and support to the investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the eCRFs, and that study treatment accountability checks are being performed
- Perform SDV and SDR. SDV includes a comparison of the data in the eCRFs with the patient's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each patient (e.g., clinic charts). SDR involves a review of source documentation to check the quality of source, review protocol compliance, ensure critical processes and source documentation are adequate.
- Record and report any protocol deviations not previously sent to the sponsor
- Confirm AEs and SAEs have been properly documented on eCRFs and confirm any SAEs have been forwarded to the sponsor and those SAEs that met criteria for reporting have been forwarded to the IRB or IEC

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

13.2. Audits and Inspections

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

13.3. Institutional Review Board/Independent Ethics Committee

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

14. QUALITY CONTROL AND QUALITY ASSURANCE

To ensure compliance with GCPs and all applicable regulatory requirements, the sponsor may conduct a quality assurance audit. Please see Section 13.2 for more details regarding the audit process.

15. ETHICS

15.1. Ethics Review

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

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

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

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

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

15.2. Ethical Conduct of the Study

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

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS international ethical guidelines
- Applicable ICH GCP guidelines
- Applicable laws and regulations

15.3. Written Informed Consent

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

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

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

- If the participant is incapacitated and cannot provide consent, the legally authorized representative (LAR)(s) can provide consent by signing the ICF on their behalf.
- The investigator needs to explain to the LAR(s) of the incapacitated participant of the potential benefits directly linked to the medical condition that the participant suffers and if this benefit outweighs the risk involved with participating in the trial.

15.4. Recruitment Strategy

Participants will be identified for potential recruitment using the clinical database and IEC/IRB-approved newspaper/radio/social media advertisements prior to consenting to take part in this study.

16. DATA HANDLING AND RECORDKEEPING

16.1. Inspection of Records

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

16.2. Retention of Records

Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final Clinical Study Report/equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

16.3. Data Protection

- Participants will be assigned a unique identifier by the investigator. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- GSK will ensure protection of the personal data of the investigator and site staff, which is collected within the framework of and for the purpose of the study.
- The participant/LAR(s) must be informed that their personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant/LAR(s), that their data will be used as described in the informed consent.
- The participant/LAR(s) must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The contract between sponsor and study sites specifies responsibilities of the parties related data protection, including handling of data security breaches and respective communication and cooperation of the parties.
- Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.GSK and/or trusted third parties working on behalf of GSK and/or institutions working with GSK for the purposes of this study are contractually bound to protect participant coded data. GSK will protect participant coded data and will only share it as described in the ICF.

16.4. Dissemination of Clinical Study Data

- The key design elements of this protocol and results summaries will be posted on www.ClinicalTrials.gov and/or GSK Clinical Study Register in compliance with applicable regulations/GSK policy. GSK will aim to register protocols summaries prior to study start and target results summaries submission within 12 months of primary/study completion date. Where external regulations require earlier disclosure, GSK will follow those timelines.
- Where required by regulation, summaries will also be posted on applicable national or regional clinical study registers.
- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the study report, and provided reasonable access to statistical tables, figures, and relevant reports. GSK will also provide the investigator with the full summary of the study results, including a summary of trial results understandable to laypersons. The investigator is encouraged to share the plain language summary with the study participants, as appropriate. The full study report will be made available upon request, after decision on marketing authorization by regulatory authorities.
- GSK will provide the investigator with the randomization codes and participant-level line listings for their site only after completion of the full statistical analysis.
- GSK intends to make anonymized participant-level data from this study available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by study participants are used to maximum effect in the creation of knowledge and understanding.

16.5. Study and Site Start and Closure

Start of study and first act of recruitment

The start of study and the first act of recruitment are defined as First Patient First Visit (FPFV; first ICF signature date) at a country-level.

Study/Site Termination

GSK or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of GSK. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

For study termination:

- Discontinuation of further study intervention development

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator
- Total number of participants included earlier than expected

If the study is prematurely terminated or temporarily suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or temporary suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

17. PUBLICATION POLICY

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

18. LIST OF REFERENCES

Akkaya E, Sanci M, Kulhan NG, Kulhan M, Nayki U, Nayki C, et al. Prognostic factors of primary fallopian tube carcinoma. *Contemp Oncol (Pozn)*. 2018; 22(2): 99-104.

American Cancer Society. https://cancerstatisticscenter.cancer.org, accessed on May 19, 2021.

Burger RA, Brady MF, Bookman MA, Fleming GF, Monk BJ, Huang H, et al. Incorporation of bevacizumab in the primary treatment of ovarian cancer. *N Engl J Med.* 2011;365(26):2473-2483

Centers for Disease Control and Prevention. https://www.cdc.gov/cancer/gynecologic/basic_info/what-is-gynecologic-cancer.htm, access on May 19, 2021.

Common Terminology Criteria for Adverse Events (CTCAE). https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm, access on June 03, 2021

Gordon AN, Fleagle JT, Guthrie D, Parkin DE, Gore ME, Lacave AJ. Recurrent epithelial ovarian carcinoma: a randomized phase III study of pegylated liposomal doxorubicin versus topotecan. *J Clin Oncol*. 2001;19(14):3312-3322

Kaelin WG, Jr. The concept of synthetic lethality in the context of anticancer therapy. *Nat Rev Cancer*. 2005;5(9):689-698

Niraparib Investigator's Brochure. GSK document No. RPS-CLIN-053021 (or most current available version).

Nishino M, Tirumani SH, Ramaiya NH, Hodi FS. Cancer immunotherapy and immune-related response assessment: The role of radiologists in the new arena of cancer treatment. *Eur J Radiol.* 2015;84(7):1259-1268

Pignata S, Lorusso D, Scambia G, Sambataro D, Tamberi S, Cinieri S, et al. Pazopanib plus weekly paclitaxel versus weekly paclitaxel alone for platinum-resistant or platinum-refractory advanced ovarian cancer (MITO 11): a randomised, open-label, phase 2 trial. *Lancet Oncol*. 2015;16(5):561-568

Pujade-Lauraine E, Hilpert F, Weber B, Reus A, Poveda A, Kristensen G, et al. Bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian cancer: The AURELIA open-label randomized phase III trial. *J Clin Oncol*. 2014;32(13):1302-1308

TCGA. Integrated genomic analyses of ovarian carcinoma. *Nature*. 2011;474(7353):609-615

ten Bokkel Huinink W, Gore M, Carmichael J, Malfetano J, Hudson I, Broom C, et al. Topotecan versus paclitaxel for the treatment of recurrent epithelial ovarian cancer. *J Clin Oncol*. 1997;15(6):2183-2193

19. APPENDICES

APPENDIX 1. CONTRACEPTION GUIDELINES

Niraparib is known to have properties that require participants to use contraception. For details on niraparib, refer to the niraparib Investigator's Brochure (IB). Based on its mechanism of action, niraparib may cause teratogenicity and/or embryo-fetal death when administered to a pregnant woman.

Participants who are women of childbearing potential (WOCBP) (see WOCBP definition) may only be enrolled if they have a negative serum pregnancy test within 72 hours prior to taking study treatment. Note: A highly sensitive urine pregnancy test may be performed if the serum pregnancy result is not available before dosing. Participants must agree to abstain from activities that could result in pregnancy from Screening through 180 days after the last dose of study treatment, be willing to use a highly effective contraception (see Table 4), or be considered women of non-childbearing potential (WONCBP) (see WONCBP definition).

Participants should be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study. To participate in the study, they must adhere to the contraception requirements described below. If there is any question that a participant will not reliably comply with the requirements for contraception, that participant should not be enrolled in the study.

Table 4: Contraceptives Allowed During the Study

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE THE FOLLOWING:
Highly Effective[b] Methods that Have Low User Dependency (*Failure rate of <1% per year when used consistently and correctly)*
• IUD
• IUS
• Bilateral tubal occlusion
• Azoospermic partner (vasectomized or due to a medical cause) – Azoospermia is a highly effective contraceptive method, provided that the partner is the sole sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, then an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days. **Note:** Documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE THE FOLLOWING:
Highly Effective[b] Methods that Are User Dependent (*Failure rate of <1% per year when used consistently and correctly)*
• Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[c]: – Oral route – Intravaginal route – Transdermal route
• Progestogen-only hormonal contraception associated with inhibition of ovulation[c]: – Oral – Injectable
• Sexual abstinence – Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant. Periodic abstinence (calendar, symptom-thermal, and postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method are **not acceptable** methods of contraception.

Abbreviations: IUD = intrauterine device; IUS = intrauterine hormone-releasing system.
[a] Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.
[b] Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.
[c] If locally required, in accordance with Clinical Trial Facilitation Group guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.

Definition of WOCBP

Women in the following categories are considered **WOCBP** (fertile):

- Following menarche
- From the time of menarche until becoming postmenopausal unless permanently sterile (see Notes below)

Definition of WONCPB

Women in the following categories are considered **WONCBP** (not fertile):

- Premenopausal female with permanent infertility due to 1 of the following (for the purpose of this study):
  a. Documented hysterectomy

b. Documented bilateral salpingectomy
c. Documented bilateral oophorectomy

- Postmenopausal female

Notes:

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
  - A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than 1 FSH measurement is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use 1 of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.
- For individuals with permanent infertility due to an alternate medical cause other than those previously listed, (e.g., Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied when determining study entry.
- If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study treatment, additional evaluation should be considered.
- Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

APPENDIX 2. RESPONSE EVALUATION CRITERIA IN SOLID TUMORS V1.1

Please note the following:

- The same diagnostic method, including use of contrast when applicable, must be used throughout the study to evaluate a lesion. Contrast agents must be used in accordance with the Image Acquisition Guidelines.
- All measurements should be taken and recorded in mm, using a ruler or calipers.
- Ultrasound is not a suitable modality of disease assessment. If new lesions are identified by ultrasound, confirmation by computed tomography (CT) or magnetic resonance imaging (MRI) is required.
- Fluorodeoxyglucose (FDG)-positron emission tomography (PET) is generally not suitable for ongoing assessments of disease. However, FDG-PET can be useful in confirming new sites of disease where a positive FDG-PET scans correlates with the new site of disease present on CT/MRI or when a baseline FDG-PET was previously negative for the site of the new lesion. FDG-PET may also be used in lieu of a standard bone scan providing coverage allows interrogation of all likely sites of bone disease and FDG-PET is performed at all assessments.
- If PET/CT is performed, then the CT component can only be used for standard response assessments if performed to diagnostic quality, which includes the required anatomical coverage and prescribed use of contrast. The method of assessment should be noted as CT on the case report form.

CT and MRI: **Contrast-enhanced CT with 5 mm contiguous slices is recommended**. Minimum size of a measurable baseline lesion should be twice the slice thickness, with a minimum lesion size of 10 mm when the slice thickness is 5 mm. MRI is acceptable, but when used, the technical specification of the scanning sequences should be optimized for the evaluation of the type and site of disease and lesions must be measured in the same anatomic plane by use of the same imaging examinations. Whenever possible, the same scanner should be used.

X-ray: In general, X-ray should not be used for target lesion measurements owing to poor lesion definition. Lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung; however, chest CT is preferred over chest X-ray.

Brain Scan: If brain scans are required, then contrast-enhanced MRI is preferable to contrast-enhanced CT.

Evaluation of Target Lesions

Evaluation of target lesions will be performed as detailed in Table 5 and below:

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

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

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

Evaluation of target lesions will be performed as detailed in Table 6 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 or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of ≥1 new lesion 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).

New Lesions

New malignancies denoting disease progression must be unequivocal. Lesions identified in follow-up in an anatomical location not scanned at baseline are considered new lesions.

Any equivocal new lesions should continue to be followed. Treatment can continue at the discretion of the investigator until the next scheduled assessment. If at the next assessment the new lesion is considered to be unequivocal, progression should be documented.

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 5: RECIST v1.1 Response for Participants 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: Eisenhauer, 2009.
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: Participants 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 for further details on what is evidence of a new lesion.13
[b] Only for nonrandomized studies with response as primary endpoint.
[c] In exceptional circumstances, unequivocal progression in nontarget lesions may be accepted as disease progression.

Table 6: RECIST v1.1 Response for Participants with Nonmeasurable Disease (i.e., Nontarget Disease)

Nontarget 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: Eisenhauer, 2009
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 studies so to assign this category when no lesions can be measured is not advised.

References

Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45(2):228-247

APPENDIX 3. EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS

Description	Grade
Fully active, able to carry on all pre-disease performance without restriction.	0
Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature, i.e., light house work, office work.	1
Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.	2
Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	3
Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	4

Source: Oken, 1982

References

Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol*. 1982;5(6):649-655

APPENDIX 4. WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Adopted by the 18th World Medical Association (WMA) General Assembly, Helsinki, Finland, June 1964 and amended by the:

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

Preamble

1. The WMA has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

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

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

General Principles

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

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

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

Risks, Burdens, and Benefits

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

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

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in

comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

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

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

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

Vulnerable Groups and Individuals

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

All vulnerable groups and individuals should receive specifically considered protection.

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

Scientific Requirements and Research Protocols

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

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

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

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

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance, and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor, and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is

to be performed, as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

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

Privacy and Confidentiality

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

Informed Consent

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

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

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

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.
28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the LAR. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research

cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

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

Use of Placebo

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

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

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

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

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

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers, and host country governments should make provisions for post-trial access for all participants who still need an intervention

identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

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

Unproven Interventions in Clinical Practice

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

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

Appendix 5: Protocol Amendment History

Amendment 1 (15 October 2021)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment

Amendment 1 is a global amendment created to increase the flexibility to evaluate new study drugs and study drug combinations in new cohorts in a wider ovarian cancer population as part of this study.

A general description and brief rationale for the changes are provided in Table 2. The synopsis was updated to be aligned with the changes in the protocol body.

Table 2: Summary of Changes for Amendment 1

Section(s) Affected	Description of Change	Brief Rationale
Headers, title page, Protocol Amendment Summary of Changes (new), and throughout	Headers and title page were updated with new document number and amendment information; Protocol Amendment Summary of Changes section was updated to include rationale for this amendment; editorial revisions for consistency with sponsor's ways of working and to add clarification and/or remove discrepancies.	Editorial changes to align with the sponsor's standard protocol template and ways of working and for accuracy, clarity, conformity, flow, and typographical error correction.
Study title Section 5. Introduction Section 6.1. Primary Objective Section 6.2. Secondary Objectives Section 7.1. Overall Study Design Section 8.1. Inclusion Criteria Section 8.2. Exclusion Criteria Section 12.1. Primary Endpoints – Phase 1B	Sections were updated to include Phase 1B study components, including objectives, endpoints, inclusion and exclusion criteria, and information on dose-limiting toxicities and gynecological cancer as a whole.	Study design was adjusted to include Phase 1B study components to increase the flexibility to test new study drugs and study drug combinations in a wider ovarian cancer population as part of this study.

Section(s) Affected	Description of Change	Brief Rationale
Section 6.1. Primary Objective Section 6.2. Secondary Objectives Section 11.1. Primary Efficacy Endpoint – Phase 2 Section 11.2. Secondary Efficacy Endpoints – Phase 2	Objectives and endpoints were reworded using more general terminology. Inclusion and exclusion criteria were updated to allow enrollment of patients with primary ovarian cancer.	All sections were updated to increase the flexibility to test new study drugs and study drug combinations in a wider ovarian cancer population as part of this study. Of note: Although the wording of objectives and endpoints were changed, the actual objectives and endpoints for ongoing cohorts of the study were not changed.
Section 7.1. Overall Study Design Appendix 2. Response Evaluation Criteria in Solid Tumors V1.1	Clarification was added around the timing and conduct of radiographic evaluations.	Previously omitted, added for completeness.
Section 7.6.3. General Guidance for Treatment Continuity When Participants are Unable to Come Into the Clinic	Language was added to describe options for participants to reduce the number of clinic visits in extreme situations.	Added to include flexibility to allow the study/study procedures to continue for as long as possible without disturbances due to significant challenges to the health care system by, for instance, COVID-19.
Section 8.1. Inclusion Criteria Appendix 1. Contraception Guidelines	Contraception rules were changed to align with sponsor's standard template.	Due to a sponsor change, the contraception guidelines were changed to align with the sponsor's standard template.
Section 8.2. Exclusion Criteria Section 9.2.1. Prohibited Medications	Administration of COVID-19 vaccines within 14 days prior to the first dose was added to the list of prohibited medications/ exclusion criteria.	COVID-19 vaccines are included in the list of prohibited medications because the effect of these vaccines on outcomes measured in the study, particularly in the context of immunotherapy or immune-based oncology treatment, is unknown.
Section 8.3.2. Discontinuation From the Study Section 8.3.3. Lost to Follow-up	Text was added to clarify how potential loss of data may be prevented. Text was added to clarify the definition of lost to follow-up.	Text was aligned with sponsor-approved standard practice and template to provide more flexibility for the participant to participate in the study to reduce potential loss of data.

Section(s) Affected	Description of Change	Brief Rationale
Section 12.3.1.5. Special Situations: Abuse, Misuse, Medication Errors, Overdose, and Accidental or Occupational Exposure	Text was added to clarify the rules around reporting of events of overdose.	Text was aligned with the sponsor's standard template.
Section 12.3.7. Adverse Events of Special Interest	Pneumonitis and embryo-fetal toxicity were removed as AESIs.	Pneumonitis and embryo-fetal toxicity were removed as AESIs for niraparib because they are no longer considered AESIs per niraparib IB.
Section 14.1. Study Monitoring	SDR was added.	Text was aligned with the sponsor's standard template and standard practice.
Section 17.2. Retention of Records	The retention of records was updated.	Text was aligned with the sponsor's standard template and standard practice.

Abbreviations: AESI = adverse event of special interest; COVID-19 = coronavirus disease 2019; IB = Investigator's Brochure; SDR = Source Document Review.

Signature Page for 213357 TMF-16435547 v1.0

Reason for signing: Approved	Name: PPD Role: Approver Date of signature: 26-Oct-2023 13:16:29 GMT+0000

Signature Page for TMF-16435547 v1.0