Protocol Cover Page

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Title: A Single-Arm Phase-II Study of Niraparib in Locally Advanced or Metastatic Solid Tumor Patients with PALB2 Mutations

Date: 06December2021

TITLE PAGE

Protocol Title:	**A Single-Arm Phase-II Study of Niraparib in Locally Advanced or Metastatic Solid Tumor Patients with PALB2 Mutations**
Protocol Number:	TMPS-101
Compound Name:	Niraparib (GSK3985771)
Brief Title:	Niraparib in the Treatment of Patients with Advanced PALB2 Mutated Tumors
Study Phase:	Phase II
Sponsor Name and Legal Registered Address:	Tempus Labs, Inc. 600 West Chicago Ave., Suite 510, Chicago, Illinois 60654
Regulatory Agency Identification Numbers:	IND Number: 159142
Approval Date:	December 06, 2021
Version:	Amendment 1

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SPONSOR SIGNATORY

Protocol Title:	A Single-Arm Phase-II Study of Niraparib in Locally Advanced or Metastatic Solid Tumor Patients with PALB2 Mutations
Protocol Number:	TMPS-101
Version:	Amendment 1
Compound Name:	Niraparib (GSK3985771)

[redacted] Medical Director, TEMPUS	Signature: Date:

The signed page is a separate document.

Medical Monitor Name and Contact Information:	Can be found in the Study Manual

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Document History

Document History Document	Date
Amendment 01	06 December 2021
Original Protocol	29 October 2021

Overall Rationale for the Amendment

Amendment 01 is a global amendment created to address regulatory feedback and provides important clarity to facilitate study conduct.

A description and brief rationale for each change is provided below.

Summary of Changes for the Amendment

Summary of Changes for Amendment 01 Section(s) Affected	Description of Change	Brief Rationale
Headers, cover page, Protocol Amendment Summary of Changes, Appendix 12. Protocol Amendment History (new), and throughout	Headers and cover page were updated with new document number and amendment information; Protocol Amendment Summary of Changes section was updated to include rationale for this amendment.	Re-versioning of the document to Amendment 1.
Section 1.1. Synopsis (Exploratory Objectives) Section 1.3. Schedule of Activities (Table 4: Schedule of Activities, footnote m) Section 3 Study Objectives and Endpoints (Table 8 Objectives and Endpoints for Study TMPS-101) Section 8.25 Pharmacokinetic Sample Collection 9.4.4 Exploratory Endpoints	Add sparse PK sampling for all study participants. Added new Section 8.25 Pharmacokinetic Sample Collection. Updated 9.4.4 Exploratory Endpoints section to add PK analysis.	In response to FDA feedback, the Sponsor has committed to conduct sparse PK sampling for all study participants.
Section 1.1. Synopsis Section 1.2 Schedule of Activities (SoA) (Table 3: Schedule of Activities – Screening Biomarker PALB2 Testing)	Updated 'Laboratory Manual' to 'NGS Laboratory Manual' Updated List of Abbreviations and Definitions of Terms to add NGS.	Administrative change to provide clarity between different trial laboratory manuals.

Section 8.1.2. Biomarker Testing for PALB2 and Translational Research Appendix 5: List of Abbreviations and Definitions of Terms		
Section 1.1 Synopsis (Criteria for Inclusion & Methodology) Section 2.1 Study Rationale Section 4.1 Study Design Section 5.1 Participant Inclusion Criteria	Updated title for patient population clarification. Updated Methodology for patient population clarification. Replaced Inclusion #6 Renumbered following inclusion criteria appropriately. Updated Study Rationale & Study Design for patient population clarification.	In response to FDA feedback, the Sponsor has added an inclusion criterion to further specify that patients must have progressed on all available therapies known to confer clinical benefit for their tumor type prior to study participation. Protocol updated to clarify the study population.
Section 1.1 Synopsis (Criteria for Inclusion) Section 5.1 Participant Inclusion Criteria	Added clarification around mild and moderate hepatic impairment definition to Inclusion #10.	Administrative change for clarity.
Section 1.1 Synopsis (Criteria for Inclusion & Criteria for Exclusion:) Section 5.2 Participant Exclusion Criteria	Add new Exclusion #27. Edited Exclusion #25 Removed Exclusion #27 Renumbered exclusion criteria appropriately.	In response to FDA feedback, the Sponsor has updated the protocol to include select patients with HIV.
Section 4.3 Dose Justification Section 11. References Section 1.1 Synopsis (Investigational Product, Dosage, and Mode of Administration – Niraparib)	Add new Section 4.3 Dose Justification. Updated references section. Clarification made to dosing regimen in synopsis.	In response to FDA feedback, the Sponsor has updated the protocol to include dose justification. Administrative change for clarity.
Section 6.2.3 Niraparib Administration Section 6.2.5 Study Drug Handling and Disposal	Updated 'Study Manual' to 'niraparib product guidelines document' to clarify niraparib instructions document.	Administrative change for clarity.
Section 8.1.2 Biomarker Testing for PALB2 and Translational Research	Further clarified requirements regarding new biopsy sample collection.	In response to FDA feedback, the Sponsor has updated the protocol to provide clarification regarding new biopsy sample collection.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Name of Sponsor/Company: Tempus Labs	
Name of Investigational Product: Niraparib	
Name of Active Ingredient: Niraparib	
Title of Study: A Single-Arm Phase-II Study of Niraparib in Locally Advanced or Metastatic Solid Tumor Patients with PALB2 Mutations	
Study Center(s): Multicenter	
Planned Duration (Projected): Estimated date first participant enrolled: Q1 2022 Estimated date of first analysis: Q3 2023 Estimated date of final analysis: Q3 2025	**Phase of development:** Phase II

Study Rationale:

The purpose of this study is to further evaluate the efficacy and safety of niraparib in patients with locally advanced or metastatic solid tumors and a pathogenic or likely pathogenic tumor *PALB2* (tPALB2) mutation.

Objectives:

Primary Objective:

- To evaluate overall response rate (ORR) as assessed by Independent Central Review (ICR) using RECIST v1.1

Secondary Objectives:

- To evaluate duration of response (DOR) as assessed by ICR using RECIST v1.1
- To evaluate progression-free survival (PFS) as assessed by ICR using Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1)
- To evaluate ORR as assessed by Investigator using RECIST v1.1
- To evaluate DOR as assessed by Investigator using RECIST v1.1
- To evaluate PFS as assessed by Investigator using RECIST v1.1
- To evaluate Clinical Benefit Rate (CBR) as assessed by ICR and Investigator
- To evaluate intracranial ORR and PFS in participants with untreated measurable CNS lesions as assessed by ICR and Investigator using RECIST v1.1
- To evaluate safety and tolerability per the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 (NCI-CTCAE v5.0)
- To evaluate overall survival (OS)

Exploratory Objectives:

- To evaluate health-related quality of life (HRQoL) and symptoms as assessed by EORTC QLQ-C30 and EuroQol EQ-5D-3L
- To evaluate exploratory biomarkers in tumor and/or blood that may be predictive of response including clinical factors
- To evaluate niraparib concentration or pharmacokinetics (PK)

Methodology:

This is a multicenter study of niraparib in participants with locally advanced or metastatic solid tumors and a confirmed pathogenic or likely pathogenic tPALB2 mutation. Participants must have received all standard therapies appropriate for their tumor type and stage of disease or, in the opinion of the Investigator, the patient would be unlikely to tolerate or derive clinically meaningful benefit from appropriate standard of care therapy, or the participant has no satisfactory alternative treatments.

- Baseline: eligibility scan(s) conducted within 28 (± 7) days prior to enrollment
- Overall progression will be assessed using RECIST v1.1 by ICR and Investigator to measure PFS. ORR will be assessed using RECIST v1.1 by Investigator and ICR.
- Imaging every 8 weeks (56±7 days) from date of enrollment through until radiographic progressive disease (PD) is documented per RECIST v1.1.
- Complete blood count (CBC) will be monitored weekly for the first 4 weeks of the treatment period, and blood pressure (BP) and heart rate will be monitored at least weekly for the first 2 months, then monthly for the first year and periodically thereafter.
- All AEs and serious adverse events (SAEs) will be collected and recorded for each participant from the day of signing the main study informed consent form (ICF) until 30 days after last dose of study treatment. All AEs and SAEs experienced by a participant, irrespective of the suspected causality, will be monitored until the AE or SAE has resolved, until abnormal laboratory values have returned to baseline or normalized, until there is a satisfactory explanation for the changes observed, until the participant is lost to follow-up, or until the participant has died. All SAEs assessed by the Investigator as related to the study treatment and adverse events of special interest (AESIs) will be collected and reported until study closeout. Any pregnancies that occur within 180 days post-treatment will be reported.
- Patient-reported outcomes (PROs) will be collected in a coordinated fashion with imaging while participants remain on study treatment. For participants who discontinue all study treatment, the PROs should be collected at the End-of-Treatment (EOT) Visit.
- Each participant will have an EOT Visit at the time of discontinuation from study treatment, Safety Follow-up Visits at 30 (±7) days, and Survival Follow-up assessments which may be conducted via telephone, email, in person visits to the clinic or back-up contacts every 90 (±14) days for 1 year after last dose and then every 180 (±14) days that will continue until death or the end of study data collection. If available, participants continuing niraparib treatment at the time of final analysis may be offered the option to continue to receive access to treatment.
- Data Review:
    - Investigators will assess efficacy for their enrolled participants. An aggregated data set will be established based on the assessments of each investigator.
    - An ICR will be performed as an independent review and assessment of the efficacy data. An interim and final efficacy analysis will be performed (see Statistical Methods).

Number of Participants (Planned): Approximately 110 participants enrolled based on approximately 140 participants screened.

Diagnosis and Main Criteria for Inclusion:

Criteria for Inclusion:

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

1. Participants must be ≥18 years of age.
2. Participants must have a histologically or cytologically confirmed diagnosis of locally advanced or metastatic solid tumor(s). This study will enrich for lung, breast, and colon cancers; targeting approximately 10 participants for each of these cancer types.
3. Participants must have tested positive for a pathogenic or likely pathogenic tPALB2 gene mutation using a CLIA-certified laboratory as described in the NGS Laboratory Manual.
4. Participants who have stable and asymptomatic CNS disease must be receiving a stable (for at least 7 days) or decreasing corticosteroid dose at the time of study entry.
5. Participants must submit fresh or archived (collected within 24 months of enrollment) FFPE tumor sample to the central laboratory for post-enrollment confirmation of tPALB2 status.
6. Participants must have received all standard therapies appropriate for their tumor type and stage of disease or, in the opinion of the Investigator, the patient would be unlikely to tolerate or derive clinically meaningful benefit from appropriate standard of care therapy, or the participant has no satisfactory alternative treatments.
7. Participants must have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
8. Participants must have a life expectancy of at least 12 weeks.
9. Participants must have adequate organ and bone marrow function defined below. Treatment may be delayed up to 3 weeks from enrollment to allow for these criteria to be met.

Table 1. Organ/Bone Marrow Function Inclusion Criteria

Absolute neutrophil count:	≥1,500/μL
Platelets:	≥100,000/μL
Hemoglobin:	≥9 g/dL or 5.6 mmol/L
Creatinine clearance (CLCr):	>30 mL/min as estimated by the Cockcroft-Gault equation
Total bilirubin*:	≤1.5×upper limit of normal (ULN) (except in participants with Gilbert's syndrome. Participants with Gilbert's syndrome: total bilirubin >1.5×ULN is acceptable if bilirubin is fractionated and direct bilirubin is <35%).

Aspartate aminotransferase (AST) and alanine aminotransferase (ALT)*:	≤ 2.5×ULN (unless liver metastases are present, in which case they must be ≤5×ULN)

Note: CBC test should be obtained without transfusion or receipt of colony-stimulating factors within 4 weeks prior to obtaining sample.

*Participants with mild to moderate hepatic impairment are allowed on the study.

Mild hepatic impairment is defined as total bilirubin ≤1.5×upper limit of normal (ULN), any aspartate aminotransferase (AST); and an alanine aminotransferase (ALT) ≤2.5×ULN.

Moderate impaired hepatic function is defined as total bilirubin >1.5× and ≤3×ULN, any level of AST; and an ALT ≤2.5×ULN.

10. Participants must be able to swallow and retain orally administered study treatment.
11. A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:
    - Is not a woman of childbearing potential (WOCBP).

      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, during the intervention 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 (either a highly sensitive urine or a serum pregnancy test as required by local regulations) within 72 hours before the first dose of study treatment.
    - If a highly sensitive urine test cannot be confirmed as negative (eg, 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.
    - 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.
12. Male participants are eligible to participate if they agree to the following during the intervention period and for at least 90 days after the last dose of study treatment:
    - Refrain from donating sperm

      plus, either:
    - Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent

      or
    - Must agree to use contraception/barrier as detailed below:

- Agree to use a male condom (and should also be advised of the benefit for a female partner to use a highly effective method of contraception as a condom may break or leak) when having sexual intercourse.
- Participants must be able to understand the study procedures and agree to participate in the study by providing written informed consent. Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent to participate in the study.

Criteria for Exclusion:

Participants will be excluded from study entry if any of the following criteria are met:

1. Participants have other active concomitant malignancy that warrants systemic, biologic, or hormonal therapy.
2. Participants who have ovarian or prostate cancer.
3. Participants who have variants of undetermined significance (VUS), but not pathogenic variants of PALB2, at the time of screening.
4. Participants who relapsed while receiving platinum based therapy in the adjuvant/curative setting.
5. Participants progressing within 14-18 weeks while receiving platinum based therapy in the metastatic setting.
6. Participants who have received PARP inhibitor(s) in prior lines of treatment.
7. Participants with leptomeningeal disease, carcinomatous meningitis, symptomatic brain metastases, or radiologic signs of CNS hemorrhage.
8. Participants with germline or somatic BRCA1 or BRCA2 mutations.
9. Participant has systolic BP >140 mmHg or diastolic BP >90 mmHg, despite optimal medical therapy.
10. Participants who have any clinically significant gastrointestinal abnormalities that may alter absorption such as malabsorption syndrome or major resection of the stomach and/or bowels.
11. Participants with current active liver or biliary disease are excluded (with the exception of Gilbert's syndrome or asymptomatic gallstones, liver cancer/metastases, or otherwise stable chronic liver disease per Investigator assessment).
12. Participants who are receiving chronic systemic steroids (prednisone >20 mg per day). Participants with asthma who require intermittent use of bronchodilators or inhaled steroids; or with medical conditions who require topical, local steroid application or injections, would not be excluded from the study.
13. Participants have previously or are currently participating in a treatment study of an investigational agent within 3 weeks of the first dose of therapy preceding the study.
14. Participants have received prior systemic cytotoxic chemotherapy, biological therapy, or hormonal therapy for cancer, or received radiation therapy within 3 weeks of the first dose therapy preceding the study.

15. Participants with toxicity from prior cancer therapy must have recovered to Grade 1. (A participant with Grade 2 neuropathy or Grade 2 alopecia is an exception to this criterion and qualify for this study.)
16. Participants have known hypersensitivity to the components of niraparib or their formulation excipients.
17. Participants have undergone major surgery within 4 weeks of starting the first dose of study treatment or have not recovered from any effects of any major surgery.
18. Participants have other active concomitant malignancy that warrants systemic, biologic, or hormonal therapy.
19. Participants have received a live vaccine within 30 days of study enrollment.
20. Participants have current active pneumonitis or any history of pneumonitis requiring steroids (any dose) or immunomodulatory treatment within 90 days of planned start of the study.
21. Participants who have any clinically significant concomitant disease or condition (such as transfusion-dependent anemia or thrombocytopenia) that could interfere with, or for which the treatment might interfere with, the conduct of the study or that would, in the opinion of the Investigator, pose an unacceptable risk to the participants in this study.
22. Participants who have any psychological, familial, sociological, or geographical condition potentially hampering compliance with the study requirements and/or follow up procedures. Those conditions should be discussed with the participants before study entry.
23. Participants have high medical risk due to a serious, uncontrolled medical disorder; nonmalignant systemic disease; or active, uncontrolled infection (including COVID-19). Examples include, but are not limited to, uncontrolled ventricular arrhythmia, recent (within 90 days) myocardial infarction, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, active uncontrolled coagulopathy, bleeding disorder, or any psychiatric disorder that prohibits obtaining informed consent.
24. Participants who are pregnant, breastfeeding, or expecting to conceive children while receiving study treatment and/or for up to 180 days after the last dose of study treatment.
25. Participants have presence of hepatitis B surface antigen or a positive hepatitis C antibody test result at screening or within 3 months prior to first dose of study treatment. Participants with presence of hepatitis B core antibody should also be excluded.
26. Participants have a known history or current diagnosis of myelodysplastic syndrome (MDS), acute myeloid leukemia (AML) or posterior reversible encephalopathy syndrome (PRES).
27. Participant is immunocompromised. Participants with splenectomy are allowed. Participants with known human immunodeficiency virus (HIV) are allowed if they meet the following criteria:
    - Cluster of differentiation 4 ≥350/μL and viral load <400 copies/mL.
    - No history of acquired immunodeficiency syndrome-defining opportunistic infections within 12 months prior to enrollment.
    - No history of HIV-associated malignancy for the past 5 years.

- Concurrent antiretroviral therapy as per the most current National Institutes of Health (NIH) Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV [NIH, 2021] started <4 weeks prior to study enrollment.

Investigational Product, Dosage, and Mode of Administration - Niraparib:

The dosing regimen for niraparib will be the approved individualized starting dose regimen, which is 300 mg in participants with a baseline body weight ≥77 kg AND baseline platelet count ≥150,000/μL or 200 mg in participants with a baseline body weight <77 kg or baseline platelet count <150,000/μL and for participants with moderate hepatic impairment at baseline. Niraparib will be taken orally once daily throughout each 28-day cycle.

All supplies indicated above will be provided centrally by the Sponsor or locally by the study site, subsidiary, or designee, depending on local country operational or regulatory requirements. For any commercially available product that is provided by the study site, subsidiary, or designee, every attempt will be made to source these supplies from a single lot/batch number. The study site will be responsible for recording the lot number, manufacturer, and expiry date of any locally purchased product. The Investigator will take responsibility for maintaining the investigational product and will take all steps necessary to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of study treatments in accordance with the protocol and any applicable laws and regulations.

Duration of Treatment:

Participants will continue to receive treatment until radiographic PD is documented per RECIST v1.1 unacceptable toxicity, death, withdrawal of consent, or becoming lost to follow-up, whichever comes first.

Treatment with niraparib will continue until radiographic PD is documented per RECIST v1.1 or another treatment discontinuation criterion is met. If available, participants continuing niraparib treatment at the time of final analysis may be offered the option to continue to receive access to treatment.

Criteria for Evaluation:

Efficacy Analysis

Primary Efficacy Endpoint

This study has the primary efficacy endpoint of ORR. ORR is defined as the proportion of participants who have a partial or complete response to therapy and will be assessed by ICR.

Secondary Efficacy Endpoints

The following secondary efficacy endpoints will be evaluated:

- DOR, defined as the time between initial response to therapy and subsequent disease progression or relapse by ICR using the RECIST v.1.1 criteria.
- PFS, defined as the time from the date of enrollment to the date of first radiographic progression or death from any cause in the absence of progression, whichever occurs first. Progression will be assessed by ICR using the RECIST v.1.1 criteria.
- ORR will be assessed by Investigator.
- DOR will be assessed by Investigator.

- PFS will be assessed by Investigator.
- CBR as assessed by ICR and Investigator. CBR is defined as the percentage of participants who have achieved complete response, partial response and stable disease.
- Intracranial ORR and PFS in participants with untreated measurable CNS lesions as assessed by ICR and Investigator using RECIST v1.1
- OS, defined as the time from enrollment to the date of death by any cause. Participants who are alive will be censored at the date of last contact. OS includes the following: death attributable to any cause, including primary cancer, secondary cancer, or unknown cause.

Safety Analysis

Safety will be evaluated based on the incidence of AEs, SAEs, and AESIs, the incidence of treatment discontinuations, dose interruptions, and dose reductions due to AEs, SAEs, or AESIs, changes in ECOG performance status, changes in clinical laboratory results (hematology, chemistry, thyroid function, and urinalysis), vital sign measurements, observations during physical examination, and use of concomitant medications. All AEs will be coded using the current version of the Medical Dictionary for Regulatory Activities coding system. The severity of AEs will be graded utilizing the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 (NCI-CTCAE v5.0).

Statistical Methods:

Statistical Hypotheses

The primary efficacy endpoint ORR will be assessed using the Bayesian Optimal Phase 2 (BOP2) design (Zhou, Lee and Yuan, 2017). Based on available data the expected ORR in this population is assumed to be at best 15% under standard of care (SOC). Niraparib would be considered promising in this population if an ORR=30% would be achieved. Therefore, if p_{eff} denotes the ORR, the null hypothesis is $H_0: p_{eff} \leq 0.15$,, under which the treatment is deemed as not promising and unacceptable and the alternative hypothesis $H_1: p_{eff} \geq 0.3$, where the treatment is considered promising. These hypotheses will be tested at a one-sided α=0.025 with about 90% power.

Sample Size Determination

For the sample size determination, the BOP2 design will be used with one interim analysis. The following stopping boundaries will be applied (see Table 2) which achieve a statistical power of 0.932 if 90 participants are evaluable for ORR under H_1 and a type I error of one-sided α=0.025. For the primary analysis these stopping criteria (non-binding) will be applied to the overall population, combining all tumor types as it is assumed that this population represents a homogeneous population and results are expected to be similar across the different tumor types.

Table 2. Optimized stopping boundaries based on BOP2 design

Analysis	Sample size	Stop if # responses ≤
Interim	40	5
Final	90	20

In order to achieve 90 evaluable participants a total of approximately 110 participants will be treated.

Analysis Populations

- The All Screened Population will consist of all participants who signed the main study ICF to participate in the clinical study. Participants in this population will be used for screen failure summary.
- The Intent-to-Treat (ITT) Population: all participants who were enrolled in the study and who received at least one dose of study treatment. This population will be the secondary population for the analysis of efficacy data. Any participant who receives a treatment number will be considered to have been enrolled.
- The Response Evaluable Population: all participants who received at least one dose of study treatment, who have an adequate baseline tumor assessment and at least one follow-up tumor assessment will be considered evaluable for anti-tumor efficacy using RECIST version 1.1 criteria. Participants who are treated and removed from study prior to on-study tumor assessment because of disease progression will be considered evaluable for efficacy and counted as failures. This population will be considered the primary population for the analysis of efficacy data.
- The Safety Population will consist of all participants who took at least 1 dose of study treatment.

Statistical Analyses - Efficacy

A BOP2 design will be applied to assess the primary endpoint ORR based in the IRC assessment. An interim analysis at 40 participants will be performed to assess the stopping criteria presented in Table 2. If six or more participants in the Response Evaluable Population demonstrate tumor response the study could continue to enroll a total of 90 participants. If at the interim analysis five or less responders are observed the study could be stopped for futility. At the final analysis for ORR, it can be concluded that niraparib is promising if at least 21/90 responders are observed. In addition to the estimated response rate at each analysis, 95% confidence intervals (CI) will be calculated

ORR is defined as the proportion of participants with a confirmed CR or confirmed PR according to RECIST 1.1 definitions, relative to the response evaluable population as well as the safety population. Confirmed responses are those that persist on repeat tumor assessments for at least 4 weeks after initial documentation or response. Otherwise, the participant will be counted as a non-responder in the assessment of ORR. Assessment of ORR will be based on the ICR assessment. The response evaluable analysis set will be the primary analysis set for ORR. The CBR as assessed by ICR and Investigator will be evaluated as well including the 95% CI.

DOR, PFS, and OS will be analyzed by the Kaplan-Meier method and survival estimates such as median survival and landmark rates at 6, 12, 18 and 24 months reported along with respective 95% CIs.

The primary analysis will be applied to the overall population (response evaluable population), combining all tumor types as it is assumed that this population represents a homogeneous population and results are expected to be similar across the different tumor types. In addition, ORR will be evaluated for each tumor type.

The study will be monitored on an ongoing basis to permit the early decision to proceed to the end of the study. The formal futility decision will be made at the pre-specified interim analysis with less than 6 responders out of 40 patients.

Statistical Analyses - Safety

Adverse events will be graded by the Investigator according to the NCI CTCAE most current version and coded using the Medical Dictionary for Regulatory Activities (MedDRA) most current version. The focus of AE summaries will be on treatment-emergent AEs, those with initial onset or increasing in severity after the first dose of study medication. The number and percentage of participants who experienced any AE, treatment-emergent AEs, SAE, treatment-related AE, and treatment-related SAE, AEs leading to treatment discontinuation, adverse events of special interest, will be summarized according to worst toxicity grades. The summaries will present AEs both on the entire study period and by cycle (Cycle 1 and cycles beyond 1). Serious AEs will be listed separately. This analysis will be performed for all participants pooled regardless of tumor type.

A more detailed description of the analyses of safety including other endpoints like laboratory data, vital signs, ECG will be described in a separate SAP.

Interim analysis

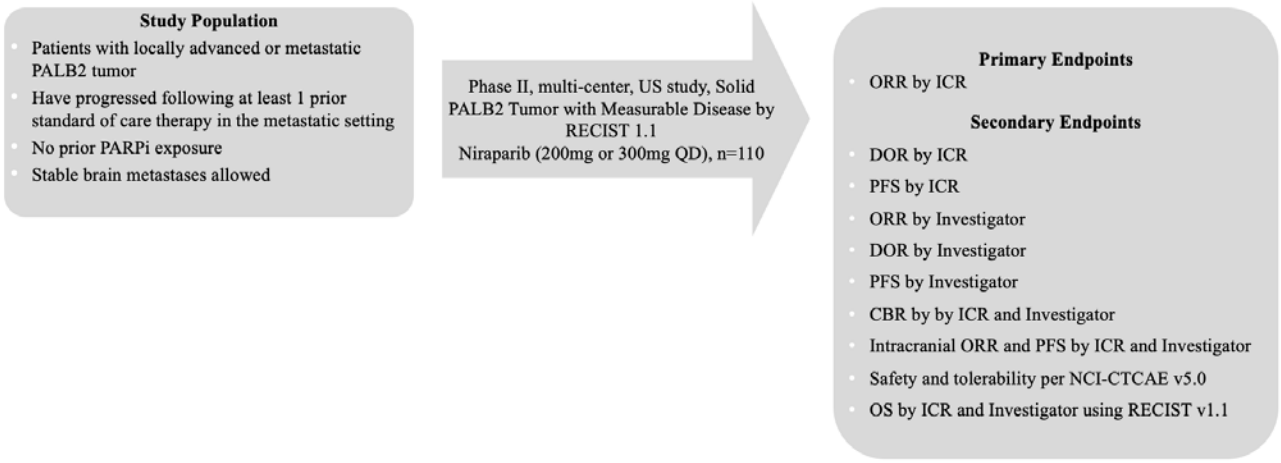
One interim analysis is planned when 40 participants have completed their assessment of efficacy (ORR assessed by IRC). According to the BOP2 design the stopping criteria at time of the interim analysis will be if ≤5 responders are observed, the study could be stopped for futility.

Handling of missing data

As a general rule, missing data will not be imputed in the study. Conventions on how to manage missing data in the analysis will be detailed in the SAP.

1.2. Schema

Figure 1: Overall Study Schema



1.3. Schedule of Activities (SoA)

The schedule of activities (SoA) for this study are presented in Table 3 and Table 4.

The study will be conducted in conformance with the protocol, Good Clinical Practice (GCP), and applicable regulatory requirements. Regulatory, ethical, and study oversight considerations are provided in the protocol.

Table 3. Schedule of Activities – Screening Biomarker PALB2 Testing

Visit: **Information or Procedure:**	**Screening**	**Notes**
Clinical report from a validated genetic test	X	Results from local next generation sequencing (NGS) testing from tissue and/or blood performed by a CLIA-certified laboratory as described in the NGS Laboratory Manual may be used to meet molecular eligibility. Test report must state that the participant has a PALB2 mutation classified as pathogenic or likely pathogenic.
Tumor tissue*	X	30 FFPE slides or 1 block equivalent of tumor tissue collected from the most recent biopsy (sample collected within the past 24 months of enrollment) must be provided. For participants with only germline PALB2 mutations, archival tissue from a primary or metastatic tumor may be provided. For participants with somatic PALB2 mutations, a metastatic tissue sample is requested; if not available, a primary tumor sample may be provided and a new biopsy will be requested, though optional, so that a metastatic disease sample may be submitted for testing.
Pathology report submitted	X	Pathology reports will be submitted with tumor tissue.
Blood sample for assessing PALB2 and biomarkers associated with PALB2*	X	3 tubes with stabilization solution (e.g. Streck cfDNA tubes); ~ 30 mLs of peripheral blood

Abbreviation: FFPE=formalin-fixed paraffin-embedded

*All samples will be collected and managed centrally, when possible, and distributed either directly or subsequently to designated translational research laboratories for biomarker testing as needed. Details on tissue and blood sample description, collection, processing, storage, shipping, and

handling instructions can be found in the NGS Laboratory Manual. For participants with an available archival sample, the existing sample may be used for tissue requirement.

Table 4. Schedule of Activities – Screening Period Through End of Study for All Cohorts

Visit: / Cycle:	Screening	Niraparib Treatment Period (28-day cycles)						EOT (or ED)	Safety FUP	Survival FUP	Notes
		C1				C2	C(n)				
Day: Procedure:	Up to 28 days before D1	1	8	15	22	1	1	Within 7 days of last dose (or decision to discontinue)	30 (±7) days after last dose	Every 90 (±14) days for 1 year after last dose and then every 180 (±14) days	C1D8, C1D15 and C1D22 visits can be done ±1 day. C(n)D1 can be done ±3 days from previous visit.
Informed consent	X										
Eligibility	X										
Demography	X										
Disease characteristics	X										Current significant medical conditions should also be collected.
Tumor characteristics	X										Tumor characteristics to be collected include, but are not limited to, histologic tumor type, tumor grade, tumor stage (both clinical and pathologic staging as per AJCC 8th edition), and response to chemotherapy and/or other therapies (as applicable). Primary pathology reports will be collected from biopsy for PALB2 testing.
Anticancer and radiation therapy prior to Screening	X										
Medical history	X										Includes medical, surgical, cancer (including genotyping), and medication history

Visit:	**Screening**	**Niraparib Treatment Period (28-day cycles)**						**EOT (or ED)**	**Safety FUP**	**Survival FUP**	**Notes**
Cycle:		**C1**				**C2**	**C(n)**				
Day: Procedure:	Up to 28 days before D1	1	8	15	22	1	1	Within 7 days of last dose (or decision to discontinue)	30 (±7) days after last dose	Every 90 (±14) days for 1 year after last dose and then every 180 (±14) days	C1D8, C1D15 and C1D22 visits can be done ±1 day. C(n)D1 can be done ±3 days from previous visit.
Substance use history	X										
12-lead ECG	X										Additional ECGs will be performed only if clinically necessary
ECOG performance status	X	X				X	X	X			
Physical examination	X	X				X	X	X	X		Full physical examination should be performed at the time of Screening. Symptom-directed physical examinations may be performed thereafter.
Height	X										
Vital signs and weight	X	X				X	X	X	X		

Visit:	**Screening**	**Niraparib Treatment Period (28-day cycles)**						**EOT (or ED)**	**Safety FUP**	**Survival FUP**	**Notes**
Cycle:		**C1**				**C2**	**C(n)**				
Day: Procedure:	Up to 28 days before D1	1	8	15	22	1	1	Within 7 days of last dose (or decision to discontinue)	30 (±7) days after last dose	Every 90 (±14) days for 1 year after last dose and then every 180 (±14) days	C1D8, C1D15 and C1D22 visits can be done ±1 day. C(n)D1 can be done ±3 days from previous visit.
Blood pressure and heart rate monitoring	X	X	X	X	X	X D1, D8, D15 D22	X	X	X		Must be monitored weekly for the first 2 months, then on Day 1 of each subsequent cycle. Blood pressure and heart rate assessments can occur during on-site scheduled clinic visits, at a local laboratory/clinic, or may also be reported to the site by a home nurse, or by another method deemed by the investigator and sponsor to be reliable. Three readings of BP and heart rate should be performed at a clinic visit. The first reading should be rejected and the second and third averaged to give the measurement to be recorded in the CRF.

Visit: / Cycle:	Screening	Niraparib Treatment Period (28-day cycles)						EOT (or ED)	Safety FUP	Survival FUP	Notes
		C1				C2	C(n)				
Day: Procedure:	Up to 28 days before D1	1	8	15	22	1	1	Within 7 days of last dose (or decision to discontinue)	30 (±7) days after last dose	Every 90 (±14) days for 1 year after last dose and then every 180 (±14) days	C1D8, C1D15 and C1D22 visits can be done ±1 day. C(n)D1 can be done ±3 days from previous visit.
Serum or highly sensitive urine pregnancy test (WOCBP only)[a]	X	X				X	X	X			A serum or highly sensitive urine pregnancy test will be performed for WOCBP at Screening (within 72 hours prior to the first dose of study treatment) and on Day 1 of every cycle for the duration of the Treatment Period. The test result must be available and negative before the first dose of study treatment. If Screening serum pregnancy test results are not available before dosing, a highly sensitive urine pregnancy test may be performed.
HIV, hepatitis B, and hepatitis C screening[b]	X										If participant was tested within 3 months prior to first dose of study treatment, testing at Screening is not required.
Hematology	X	X	X	X	X	X	X	X	X		If dose interruption or modification is required at any point on study because of hematologic toxicity, weekly blood draws for CBC will be monitored until the AE resolves, and for 4 weeks after AE resolution, after which monitoring every 4 weeks may resume. See Table 14 for specific parameters to be measured.

Visit: / **Cycle:**	**Screening**	**Niraparib Treatment Period (28-day cycles)**						**EOT (or ED)**	**Safety FUP**	**Survival FUP**	**Notes**
		C1				**C2**	**C(n)**				
Day: Procedure:	Up to 28 days before D1	1	8	15	22	1	1	Within 7 days of last dose (or decision to discontinue)	30 (±7) days after last dose	Every 90 (±14) days for 1 year after last dose and then every 180 (±14) days	C1D8, C1D15 and C1D22 visits can be done ±1 day. C(n)D1 can be done ±3 days from previous visit.
Clinical chemistry	X	X				X	X	X	X		Serum/plasma chemistry parameters that will be measured are listed in Table 14.
Urinalysis	X										
Coagulation	X										Specific coagulation factors will be evaluated as presented in Table 14.
PRO collection: EORTC QLQ-C30 and EQ-5D-3L		X				X	X	X			Complete PROs prior to any clinical procedures.
AE monitoring and review	Reporting of safety events is to begin at the time of PALB2 mutation confirmation. All AEs and SAEs are required to be captured from the signing of the main study ICF through 30 days after the last dose of study treatment or start of new anticancer therapy. SAEs assessed by the Investigator as related to study treatment and all AESIs, regardless of causality, are to be collected until study closeout. Any pregnancies that occur within 180 days post-treatment discontinuation are to be captured.										
Concomitant medication review	X	X	X	X	X	X	X	X	X		
Niraparib dispensed/ collected		X				X	X				
Follow-up status (survival assessment)										X	May be conducted via telephone, email, in person visits to the clinic or back-up contacts to confirm OS.
Blood sample for niraparib PK[c]		X				X	X C4 C7	X			

Visit: / Cycle:	Screening	Niraparib Treatment Period (28-day cycles)						EOT (or ED)	Safety FUP	Survival FUP	Notes
		C1				C2	C(n)				
Day: Procedure:	Up to 28 days before D1	1	8	15	22	1	1	Within 7 days of last dose (or decision to discontinue)	30 (±7) days after last dose	Every 90 (±14) days for 1 year after last dose and then every 180 (±14) days	C1D8, C1D15 and C1D22 visits can be done ±1 day. C(n)D1 can be done ±3 days from previous visit.
Blood sample for exploratory biomarker testing	Please see Table 3 for biomarker testing schedule for Screening	X	Every 8 weeks (56±7 days) from randomization until disease recurrence.					X			Sample (2 tubes with stabilization solution of peripheral blood, ~ 20 mL) will be collected prior to niraparib administration on Cycle 1/Day 1. During the remainder of the Treatment Period, samples (2 x ~10CC tubes with stabilization solution of peripheral blood, ~ 20 mL) will be collected every 8 weeks from randomization until disease recurrence. If a participant discontinues study treatment for any reason other than disease recurrence per RECIST v1.1, death, withdrawal of consent, or loss to follow-up, then sample collection should continue at the specified intervals until disease recurrence is confirmed per RECIST v1.1.
CT/MRI chest/abdomen/pelvis	X	Every 8 weeks (56±7 days) from date of enrollment until radiographic PD is documented per RECIST v1.1[d]									Participants with either a PR or CR should have an additional set of scans to confirm the response at least 28 (+7) days after scans showing the PR or CR.
MRI of Brain	X	Every 8 weeks (56±7 days) from date of enrollment until radiographic PD is documented per RECIST v1.1[d]									Only for participants with documented CNS disease.

[a] Additional pregnancy testing may be necessary if required by local practices or regulations or if potential pregnancy is suspected.
[b] HBsAg, HBsAb, HBcAb; HIV-1 and HIV-2 antibodies; hepatitis C Ab

[c] Blood samples for PK analysis will be collected on Cycle 1/Day 1, and Cycle 2/Day 1 predose (within 1 hour prior to dosing) and 3 hours postdose (±15 minutes). Additional predose blood samples on Cycle 4/Day 1 and Cycle 7/Day 1 will be collected (within 1 hour before scheduled dose). dose). Blood will be also collected at the EOT visit if the participant discontinued before Cycle 7. If study treatment is held 1 day prior to and on Cycle 2/Day 1, PK sample collection on that day is not required. Participants will be instructed to hold their niraparib dose until the predose PK sample has been taken. See the study-specific laboratory manual for additional details

[d] CT scan of the chest, and IV contrast enhanced CT of the abdomen, and pelvis; IV contrast-enhanced MRI of the abdomen and pelvis plus noncontrast CT of the chest should only be conducted if clinically indicated (eg, if participant is sensitive to IV CT contrast). If MRI is performed at Baseline, it should be preferentially continued throughout the study. The same imaging and anatomical coverage should be used throughout the study. If scans are performed outside of the 8 weeks (± 7 day) window interval and the participant has not progressed, every attempt should be made to perform the subsequent scans at their scheduled time points. If a participant discontinues study treatment for any reason other than death, withdrawal of consent, or loss to follow-up, then scans should continue at the specified intervals until disease progression is confirmed. If an equivocal new lesion is observed on a postbaseline radiological assessment, a follow-up scan should be acquired at least 4 weeks later to reassess. On the follow-up scan, if the equivocal new lesion becomes unequivocal, the date of progression is the date of the scan when the new lesion first appeared (refer to Appendix 3).

All radiological images/scans, scheduled and unscheduled, must be submitted (preferably electronically) to a central imaging vendor for QC, storage, and analysis by ICR (refer to section 8.2.2).

Abbreviations: AE=adverse event; AESI=AE of special interest; AJCC=American Joint Committee on Cancer; ICR= independent central review; BP=blood pressure; C=cycle; CBC=complete blood count; CRF=case report form; CT=computed tomography; D=day; DFS=disease-free survival; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EORTC QLQ-C30=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; EOT=End of Treatment; EQ-5D-3L=European Quality of Life 5-Dimensions 3-Level Scale FUP=Follow-up Period; HIV=human immunodeficiency virus; ICF=informed consent form; MRI=magnetic resonance imaging; n=number of subsequent cycles; PK= pharmacokinetic; PRO=patient-reported outcome; QC=quality control; RECIST=Response Evaluation Criteria in Solid Tumors; SAE=serious adverse event; WOCBP=women of childbearing potential.

2. INTRODUCTION

Advanced solid tumors harboring PALB2 mutations have been associated with a variety of cancer types. Beyond first-line, standard of care, systemic therapies, patients with advanced disease and PALB2 mutations have limited options for effective treatment. Because PALB2 is a potent regulator of the homologous recombination repair (HRR) pathway, one potential avenue to treat this population is with poly (ADP-ribose) polymerase inhibitors (PARPi), which prevent DNA damage repair and promote cancer cell cytotoxicity.

Niraparib is an orally available, potent, highly selective PARP-1 and -2 inhibitor that is dosed once daily. Niraparib is approved in 36 countries worldwide including the US, EU, Switzerland, Australia, Canada, and Saudi Arabia. Niraparib was approved by the Food and Drug Administration (FDA) on 27 March 2017 (NDA 208447) and received European Commission approval on 16 November 2017 as maintenance therapy for women with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in complete response or partial response to platinum-based chemotherapy. Additionally, niraparib was approved by the FDA on 23 October 2019 for patients with advanced ovarian, fallopian tube, or primary peritoneal cancer treated with three or more prior chemotherapy regimens and whose cancer is associated with homologous recombination deficiency (HRD)-positive status. In 2020, the use of niraparib was further expanded as maintenance therapy for patients with advanced ovarian, fallopian and primary peritoneal carcinomas which have shown prior complete/partial response to chemotherapy (Zejula USPI. Zejula (niraparib) US Prescribing Information. 2021).

2.1. Study Rationale

Efficacious treatment options for patients with advanced, PALB2-mutated solid tumors remains a high unmet need. Therapy is needed with an acceptable safety profile that delivers clinically meaningful improvement in ORR, DoR, and PFS.

This study will evaluate the efficacy of niraparib monotherapy in participants with advanced or metastatic solid tumors harboring a confirmed pathogenic or likely pathogenic tumor PALB2 mutation (tPALB2). Tumors in patients with PALB2 pathogenic mutations have deficiencies in Homologous Recombination, and therefore are sensitive to growth inhibition by knocking out the PARP pathway. Participants must have received all standard therapies appropriate for their tumor type and stage of disease or, in the opinion of the Investigator, the patient would be unlikely to tolerate or derive clinically meaningful benefit from appropriate standard of care therapy, or the participant has no satisfactory alternative treatments. By limiting eligible participants to those with a pathogenic or likely pathogenic tPALB2 alteration in a tumor-agnostic setting, a genetically homogenous patient group with limited standard therapy options will be enrolled.

Niraparib has shown an acceptable clinical and nonclinical safety profile. The proposed evaluation of niraparib at the approved dose in advanced solid tumors harboring PALB2 mutations is based on clinical data demonstrating a favorable benefit-risk ratio of niraparib in patients with tumors having mutations in a similar Homologous Recombination gene, BRCA 1/2.Furthermore, the study builds on preclinical and clinical data describing PALB2 mutations leading to HRD-positive tumors, which should bestow similar sensitivity to niraparib in PALB2 mutated tumors as what has been demonstrated in BRCA 1/2 mutated cancers.

2.1.1. PALB2 in the HRR pathway

While BRCA mutations are the most well-characterized, several other genes are involved in the HRR pathway. Following data of improved survival in HRD-positive tumors with and without gBRCA mutations, there has been a new effort to identify HRR-related biomarkers beyond gBRCA1/2 that may indicate sensitivity to PARPi. PALB2 has recently been studied given its role as the localizer of BRCA2. Acting as a signal mediator between BRCA1 and the BRCA2/RAD51 complex, PALB2 facilitates HRR by recruiting BRCA2 and RAD51 to the sites of DNA double-strand breaks (Xia et al., 2006).

2.1.2. Hereditary/Germline PALB2 Mutations (gPALB2)

PALB2 plays a critical role in DNA repair as a partner and nuclear localizer of BRCA2. Because of its biologic function, mutations in PALB2 have been described as susceptibility gene mutations for hereditary breast, ovarian, and pancreatic cancer (Rahman et al., 2007 & Yang et al., 2020). Although gPALB2 mutations are present at a much lower frequency than other HRR-related genes, the alteration is still associated with an increased risk of cancer development. About 35% of females carrying gPALB2 mutations may develop breast cancer before turning 70 years old, and the risk increases to 58% in carriers with a history of breast cancer (Antoniou et al., 2014). When compared to non-PALB2 mutation carriers, data support that patients with gPALB2 mutations have a shorter 10-year survival (Cybulski, et al., 2015). Given this increased risk associated with gPALB2 and the increased sensitivity of PALB2-deficient cells to platinum-based chemotherapy and PARPi, HRD-targeting treatments such as niraparib can potentially provide clinical benefit to breast cancer patients with gPALB2 mutations (Nikkila, et al., 2013; Foo et al., 2017; Isaac et al., 2018).

Besides breast cancer, gPALB2 mutations can increase risk for the development of other cancer types such as ovarian and pancreatic cancers (Yang, 2020). In ovarian cancer, gPALB2 carriers had a risk rising from <1% at age 50 to 5% in age 80, 5x higher than that of the general population. In addition, the risk of developing ovarian cancer by age 80 in gPALB2 carriers was 5% for women without a family history of ovarian cancer but increased to 16% for women with a family history of ovarian cancer. Regarding pancreatic cancer, the risk of disease development

in gPALB2 carriers at age 80 was 2.2% for women and 2.8% for men. In both cases, this was >2x the risk than observed in the general population.

Based on the known increased risk of developing cancers for individuals with gPALB2 mutations, the American College of Medical Genetics and Genomics (ACMG) developed guidelines for surveillance and treatment (Tischkowitz et. al. 2021). Recommendations include (1) Enhanced breast surveillance as offered for patients with BRCA1/2 mutations and consideration for risk-reducing interventions on an individualized risk basis, (2) surveillance for ovarian cancer is not recommended (insufficient evidence of testing sensitivity) but consideration of risk-reducing interventions for those <50 years old, and (3) surveillance for pancreatic cancer in the clinical trial setting. In addition, PALB2 heterozygotes should be evaluated for treatment or clinical trials similar to those with BRCA1/2, in particular PARPi therapy.

2.1.3. Somatic PALB2 Mutations (sPALB2)

Like many hereditary predisposition mutations, PALB2 mutations are typically germline but somatic mutations can exist. Data is limited and the incidence of sPALB2 mutations is unclear; however, in a recent publication regarding breast cancer tumors, the frequency of germline mutations was noted as much higher than somatic mutations (Hu et al., 2020). To further understand the incidence of somatic mutations, large-scale, unbiased genomic sequencing data needs to be compiled. For example, a study from Memorial Sloan Kettering Cancer Center used MSK-IMPACT whole-exome sequencing (WES) with matched normal DNA, allowing for the detection of somatic alterations that would have otherwise been missed (Zehir et al., 2017).

2.1.4. Comprehensive Genomic Testing

Testing for PALB2 increased with its inclusion on multigene cancer panels starting around 2012–2013 (Tischkowitz, 2021). In line with the findings from MSK-IMPACT, PALB2 mutations can be differentially detected from germline or somatic sources with a combined test using a tumor and normal samples (Zehir et al., 2017). Germline PALB2 mutations are stable over time, therefore the use of archival tissue in this study is appropriate. For patients assumed to have a gPALB2 mutation, a fresh blood draw taken at any time can be used to confirm (Ong, 2019). Regarding somatic mutations, on the other hand, FFPE tissue is typically utilized for archival samples (Wang et al., 2015).

2.1.5. PALB2 Mutation Prevalence

According to the AACR Project GENIE, PALB2 mutations are present in only 1.52% of all malignant solid tumors (AACR Project GENIE Consortium, 2017). The MSK-IMPACT clinical sequencing cohort exhibits a similar overall prevalence at 1.3% (Zehir et al., 2017). The GENIE

consortium includes total sample counts for non–small cell lung cancer (n=2,985), colorectal cancer (n=2,081), and melanoma (n=785). In addition, there are approximate sample counts for other relevant tumor types from the Figure Landscape Overview of GENIE Dataset including breast (n=2,200), bladder (n=700), esophagogastric (n=600), and pancreatic (n=500) cancers. THE MSK-IMPACT dataset includes total sample counts for non–small cell lung (n=1,668), colorectal (n=1,007), melanoma (n=365), breast (n=1,324), bladder (n=423), esophagogastric (n=341), and pancreatic (n=502) cancers. Table 5 reflects the prevalence of PALB2 across different tumor types in the AACR GENIE and MSK-IMPACT datasets.

Table 5. PALB2 Mutation Prevalence by Tumor Type

Tumor type	AACR GENIE PALB2 mutation prevalence	MSK-IMPACT PALB2 mutation prevalence
Endometrial Carcinoma	3.66%	2.75%
Melanoma	3.48%	2.19%
Urothelial Carcinoma	3.05%	3.55%
Gastroesophageal junction	2.49%	Not available
Colorectal Adenocarcinoma	2.33%	2.18%
Non-small cell lung carcinoma	1.57%	1.74%
Head And Neck Squamous Cell Carcinoma	1.4%	2.15%
Breast	1.28%	1.59%
Ovarian	1.19%	0.89%
Prostate adenocarcinoma	1.12%	1.58%
Pancreatic carcinoma	0.97%	0.40%

Note: the prevalence can be affected by the number of cases and testing rates per indication.

2.2. Background on PARP Inhibitors and Niraparib

Due to their broad applicability across cancer types, distinct biomarkers, and demonstration of clinical efficacy, PARPi have emerged as a promising treatment option in the precision oncology space. PARPi are a distinctive group of antineoplastic agents which target the DNA repair/damage pathways to promote cytotoxicity in cancer cells. In combination with other agents or underlying genetic mutations, PARPi lead to extensive DNA damage and consequently cell death. This synergy between cellular defect and drug-induced effect has been referred to as synthetic lethality (Kaelin, 2005), and has been harnessed to apply PARPi as antitumor agents in a variety of cancers (Rose et al., 2020).

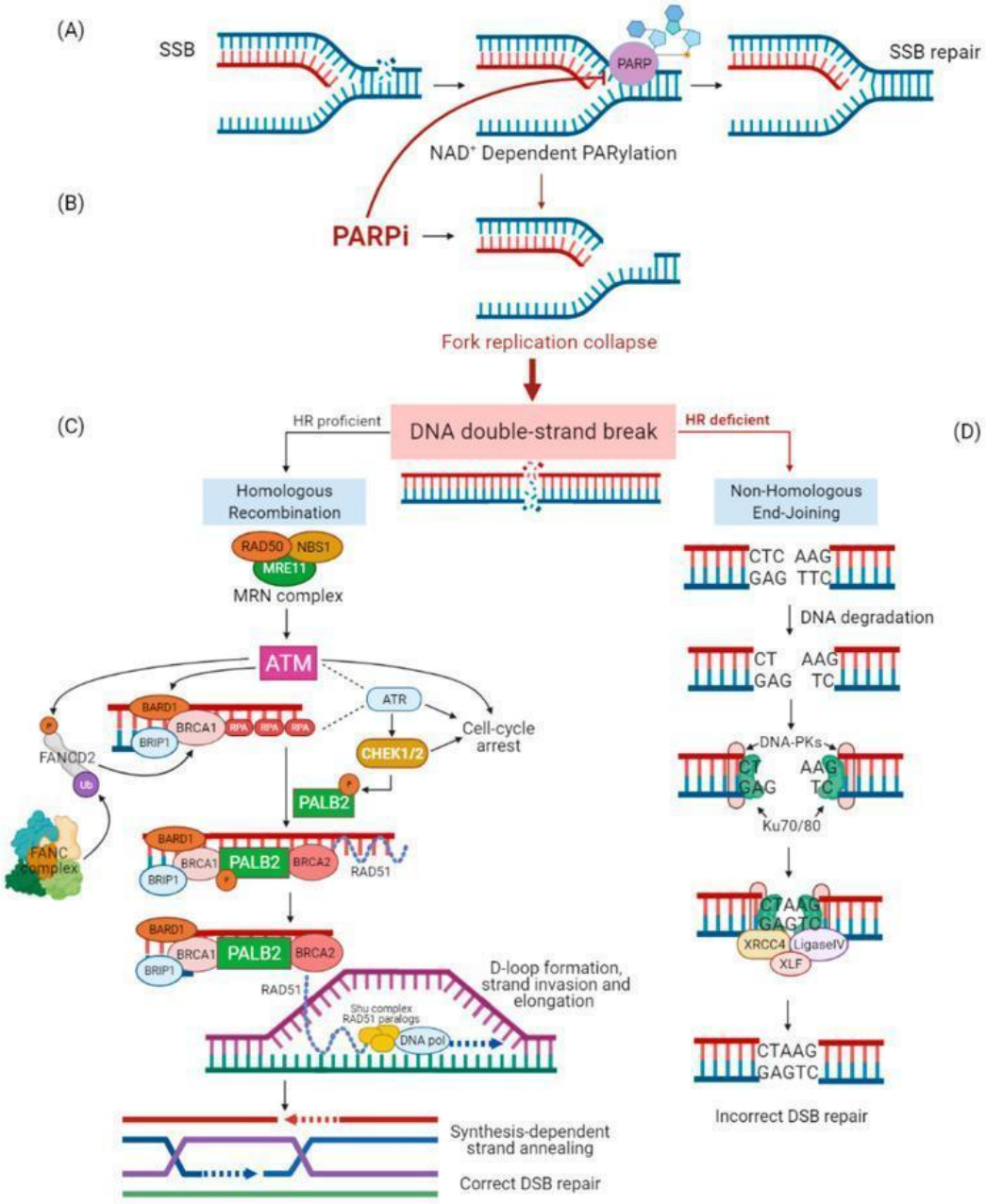
2.3. PARPi Mechanism of Action

DNA repair is accomplished by several mechanisms in healthy cells, including but not limited to HRR, non-homologous end joining (NHEJ), and base excision repair (BER) (Dantzer et. al., 1999 & Dantzer et al., 2000). Some cells are incapable of HRR due to the inactivation of genes such as BRCA1 or BRCA2. In the absence of HRR, these cells must rely on alternative DNA repair mechanisms such as pathways regulated by PARP-1 and PARP-2. PARP-1 and PARP-2 are zinc-finger DNA-binding proteins that detect damaged DNA and promote DNA repair by several mechanisms. For example, after detecting DNA damage, PARP activates the BER pathway via an intracellular signaling mechanism (Hanzlikova et al, 2017).

By preventing PARP-1 and PARP-2 from activating the BER pathway, PARPi block DNA repair. Thus, PARP inhibition in cells incapable of HRR leads to irreparable double-strand DNA breaks, collapsed replication forks, and an increased use of the NHEJ pathway (Sun et. al., 2020). These disruptions result in genomic instability and, ultimately, cell death. Treatment with PARPi represents an opportunity to selectively kill cancer cells with deficiencies in HRR and other DNA repair mechanisms (Cortesi et al., 2021). Figure 2 illustrates PARPi function in HRR-proficient versus HRR-deficient pathways.

Figure 2: DNA Double-strand Break Repair Mechanisms and PARPi Function (Cortesi et al., 2021)

(A) PARP-dependent DNA repair mechanisms are activated at DNA single-strand breaks (SSB). (B) PARPi stop PARP recruitment to DNA SSB and PARP-dependent DNA repair systems. This results in DNA fork replication collapse and DNA double-strand breaks (DSB). (C) In HRR-proficient cells, the DSB is repaired via the 'error-free' HRR system of proteins, including PALB2 - the BRCA2 localizer. (D) In HRR-deficient cells, the DSB is repaired via 'error-prone' non-homologous end-joining mechanisms and leads to incorrect DSB repair.



2.3.1. Biomarkers of PARPi Response

The rationale for employing PARPi to selectively eliminate cancer cells is supported by nonclinical ex vivo and in vivo experiments demonstrating that PARPi are more potent cytotoxicity inducers in tumors with homozygous inactivation of BRCA1 or BRCA2 than in BRCA-replete counterparts. Germline and somatic BRCA1/2 mutations are well-defined biomarkers for PARPi response in a number of cancer types, including breast, ovarian, pancreatic, and prostate cancer (Tung & Garber, 2018). Multiple studies examining PARPi have demonstrated promising results in the treatment of BRCA-mutated breast and ovarian cancer, and PARPi have been studied both as monotherapy and in combination with cytotoxic therapy or radiotherapy (Hu et al., 2020 & Swisher et al., 2021).

Recently, however, HRR-related mutations besides BRCA1/2 have also shown promise as treatment-directing biomarkers for PARPi therapy. For example, a recent study of the PARPi olaparib demonstrated an increased PFS in patients with tumors harboring PALB2 mutations. In TBCRC 048, a Phase II study of olaparib for metastatic breast cancer and mutations in HRR somatic or germline genes, patients received olaparib until progression or unacceptable toxicity. The data showed that patients with germline PALB2 mutations had an ORR of 82% (9/11) and a median PFS of 13.3 months (Tung et al., 2020).

2.3.2. Niraparib Preclinical Data

Niraparib is an orally available, potent, highly selective PARP-1 and PARP-2 inhibitor. Niraparib co-crystallizes with the human PARP-1 catalytic domain and has been shown to inhibit PARP-1 and PARP-2 activity in vitro with a half-maximal inhibitory concentration (IC50) of 3.8 and 2.1 nM, respectively. In cultured cells, niraparib inhibited PARP-dependent PARylation stimulated by DNA damage with an IC50 of 4 nM and a 90% inhibitory concentration (IC90) of 40 nM.

Niraparib demonstrated a 25- to 200-fold increased cytotoxicity against cancer cell lines that were engineered to be HRD via BRCA1 or BRCA2 silencing or that carried BRCA1 or BRCA2 mutations, as compared to control cell lines capable of homologous recombination. Treatment of xenograft-bearing mice with clinically relevant doses resulted in tumor regression in BRCA- and ATM-mutant tumor models. At the doses used in these studies, 90% PARP inhibition was observed in tumors for up to 24 hours after a single dose. Additionally, PARP inhibition in tumor tissue was greater and more durable than PARP inhibition in the corresponding PBMCs, where inhibition levels were ≤50% 24 hours after dosing.

Niraparib has also been evaluated in more than 30 ovarian cancer patient-derived xenograft and tumor cell line-derived xenograft models. Tumor regression has been observed in BRCA1- and BRCA2-mutant xenografts and in HRD-positive, wild-type BRCA models. Additionally, tumor

growth inhibition was observed in some models that were HRD negative as defined by the Myriad myChoice HRD test.

For more information on preclinical data, please refer to the Investigator's Brochure.

2.3.3. Niraparib Safety Data

In addition to the preclinical data described above, numerous clinical trials have led to FDA approvals of niraparib over the past decade. A total of 20 clinical studies investigating the safety and efficacy of niraparib have been conducted, ranging from Phase I to Phase III. From these studies, 2,244 patients have received at least one dose of niraparib. Most of these patients (n=1,606) participated in ovarian cancer studies, and the remaining 638 participated in non-ovarian studies. Niraparib's safety and efficacy has been studied as a single agent, as well as in combination with other agents, and adverse events (AEs) related to the treatment have been assessed extensively in both contexts.

The well-established AE profile of niraparib consists of AEs that are commonly managed in the patient population of advanced cancer. The key safety concerns included hematological toxicities, hypertension, and potential risks of MDS/AML and secondary malignancies. Common AEs, including Grade 3 and higher, were generally manageable with dose modification and clinical treatment. Furthermore, most AEs were resolved without discontinuation of niraparib. Additional information on safety data can be referenced in the Investigator's Brochure.

2.3.4. Niraparib Approved Indications and Registrational Trial Overviews

Niraparib was initially approved in 2017 for the maintenance of patients with recurrent ovarian, fallopian, or primary peritoneal carcinoma who have had a complete/partial response to chemotherapy, regardless of BRCA mutational status (Mirza et al., 2016). The approval was expanded in 2019 for the treatment of patients with HRD-positive, advanced ovarian, fallopian, or primary peritoneal carcinomas after 3 or more prior lines of therapy, independent of sensitivity to prior chemotherapy (Moore et al., 2019). Most recently in 2020, use of niraparib was further expanded as maintenance therapy for patients with advanced ovarian, fallopian, or primary peritoneal carcinomas that have shown prior complete/partial response to chemotherapy, regardless of mutational status (Gonzalez-Martin et al., 2019). These approved indications for niraparib were based mainly on data from the NOVA, PRIMA, and QUADRA trials.

The NOVA study explored the efficacy of niraparib as maintenance treatment in patients with platinum-sensitive, recurrent ovarian cancer in a randomized, double-blind, placebo-controlled Phase III trial. It also characterized the importance of biomarker-based patient selection for maintenance treatment with PARPi in this patient population. The PFS was significantly longer for participants who received niraparib compared to those who received placebo in both cohorts. Within the gBRCA-mutated cohort, the median PFS was 21.0 months with niraparib versus 5.5

months with placebo (HR: 0.27; 95% CI:0.173 to 0.410; p<0.001). In the non-gBRCA-mutated cohort, the median PFS was 9.3 months with niraparib versus 3.9 months with placebo (HR: 0.45; 95% CI: 0.338 to 0.607; p<0.001). In the HRD group of the non-gBRCA-mutated cohort, PFS was also significantly longer with niraparib than with placebo (median: 12.9 months versus 3.8 months; HR: 0.38; 95% CI: 0.243 to 0.586; p<0.001). The findings from this non-gBRCA-mutated, HRD-positive population support the exploration of non-BRCA HRR-related mutations as markers of PARPi treatment eligibility.

In the Phase III, double-blind, randomized, placebo-controlled PRIMA study, niraparib was tested in patients with ovarian, fallopian tube, or primary peritoneal cancer at high risk for progressive disease after response to first-line platinum-based chemotherapy. The data from PRIMA indicated a reduced hazard of death or disease progression and prolonged median PFS in participants who received niraparib compared to those who received placebo. Median PFS based on RECIST (version 1.1) was 21.9 months in the niraparib arm and 10.4 months in the placebo arm (HR 0.43 [95% CI: 0.310 to 0.588]; p<0.0001). Overall survival was also shown to be favorable in the niraparib arm (HR 0.70 [95% CI: 0.442 to 1.106]; p=0.1238).

Additionally, the QUADRA study examined the efficacy and safety of niraparib in participants with advanced ovarian cancer treated with 3 or more prior chemotherapy regimens. Overall, the results indicated clinical benefit as reflected by clinical and molecular biomarkers. The highest response rates were observed among participants with tumors that were HRD-positive and platinum-sensitive or BRCA-mutated regardless of platinum sensitivity status. Within the biomarker-defined population of 98 participants with 3 or more prior lines of treatment, the ORR was 25.5%, and median DoR was 8.3 months. The findings suggest that ORR was higher than the expected ORR associated with approved chemotherapy in late-line disease setting, including for participants with BRCA-mutated disease regardless of platinum sensitivity (ORR: 28.6%; median DoR: 9.2 months) and participants with non-BRCA-mutated/HRD-positive, platinum-sensitive disease (ORR: 20%; median DoR: 6.6 months)

2.3.5. Niraparib Clinical Trials Outside of Approved Indications

Niraparib is currently being developed as a monotherapy agent or in combination with cytotoxic/radiotherapy/biologic agents to treat other solid tumors, including triple-negative breast cancer (TNBC), non-small cell lung cancer, and prostate cancer.

The TOPACIO study evaluated the efficacy of niraparib in combination with pembrolizumab from 47 evaluable participants with advanced or metastatic TNBC. The ORR was 21% (90% CI: 12% to 33%) with a disease control rate (DCR) of 49% (90% CI: 36% to 62%). In 15 evaluable participants with tumor BRCA mutations, ORR was 47% (90% CI: 24% to 70%), DCR was 80% (90% CI: 56% to 94%), and median PFS was 8.3 months (95% CI: 2.1 months to not estimable). In 27 evaluable participants with BRCA-wild-type tumors, ORR was 11% (90% CI: 3% to 26%),

DCR was 33% (90% CI: 19% to 51%), and median PFS was 2.1 months (95% CI: 1.4 to 2.5 months). Another study in breast cancer, BRAVO, supported niraparib as an active agent for the treatment of patients with gBRCA-mutated metastatic breast cancer, and for the TNBC subpopulation.

The GALAHAD study, which is an ongoing open-label Phase II study, is examining niraparib in patients with metastatic castration-resistant prostate cancer (mCRPC) and DNA-repair gene defects (DRD) with disease progression on taxane and androgen receptor-targeted therapy. The results at the interim analysis have pointed at clinical activity and durable responses in patients with treatment-refractory mCRPC, specifically in biallelic BRCA mutation carriers. At the time of the interim analysis, 165 patients were enrolled and median follow-up in the BRCA- and non-BRCA-mutated groups was 7.3 and 6.4 months, respectively. In the BRCA-mutated subpopulation, ORR was 41%, CRR was 63%, and median DoR was 5.5 months (range: 3.5–9.2). Median radiographic PFS and OS in the BRCA-mutated group were 8.2 and 12.6 months, respectively. In the non-BRCA-mutated population, objective response was noted in 2/22 patients and CRR was 17%; DoRs were 3.8 and 6.5 months, respectively (Smith et al., 2019).

There are currently no approved therapies specifically targeting PALB2. Based on its well-understood safety profile and demonstrated efficacy in numerous tumor types, however, we hypothesize that niraparib may offer greater clinical benefit over existing options in this population of advanced or metastatic cancer patients harboring germline or somatic PALB2 mutations. In addition to the niraparib data summarized above, the totality of data across PARPi datasets also serves as evidence for the possible favorable benefit/risk profile, particularly in the PALB2-mutated population.

2.3.6. Other Approved PARPi

Olaparib (Lynparza) was the first PARPi approved by the FDA and EMA in 2014 as a monotherapy for the treatment of advanced, gBRCA-mutated ovarian cancer (Kaufman et al., 2015). In 2017, this was extended to include maintenance therapy of recurrent ovarian, fallopian, and primary peritoneal tumors, regardless of BRCA mutational status (Pujade-Lauraine et al., 2017; Friedlander et al., 2018). In addition, olaparib was approved for the treatment of gBRCA1/2-mutated HER2-negative breast cancer and metastatic pancreatic cancer in 2018 and 2019, respectively (Moore et al., 2018; Golan et al., 2019; Robson et al., 2019). In 2020, olaparib was approved for the treatment of HRD-positive mCRPC (de Bono et al., 2020).

Other PARPi, namely rucaparib (Rubraca) and talazoparib (Talzenna), have been approved in similar tumor types. In 2016, rucaparib was granted an accelerated approval for the treatment of germline or somatic BRCA1/2-mutated advanced ovarian carcinomas after patients received multiple chemotherapy treatments (Oza et al., 2017). Later, rucaparib maintenance therapy was approved in 2018 for recurrent ovarian, fallopian, and primary peritoneal cancers, regardless of

BRCA mutational status (Coleman et al., 2017). In 2020, rucaparib gained FDA approval for the treatment of BRCA1/2-mutated mCRPC (Abida et al., 2019).

2.3.7. Clinical Trials of PARPi in PALB2-mutated Tumors

Recent studies have demonstrated that patients with metastatic breast, melanoma, and pancreatic cancers with germline and/or somatic PALB2 mutations benefit from treatment with PARPi. Accordingly, PARPi have been studied as a subsequent line of therapy in breast cancer and melanoma. For TBCRC 048, a Phase II study of olaparib for metastatic breast cancer and mutations in HRR-related somatic or germline genes, patients received no prior PARPi nor progressed on a platinum-based therapy. All patients received olaparib until progression or unacceptable toxicity. As stated above, the data showed that patients with PALB2 mutations had an ORR of 82% (9/11) and a median PFS of 13.3 months (Tung et al., 2020). Additionally, a Phase II trial in gPALB2-mutated advanced and heavily pretreated breast cancers showed talazoparib monotherapy was associated with single-agent activity. For the 5 patients with gPALB2 mutations, all 5 had a reduction in target lesions > 20% and 3 of 5 achieved a RECIST 1.1 response (Gruber, et al., 2019). In melanoma, a case report of a patient with metastatic melanoma and an sPALB2 mutation who failed immunotherapy demonstrated an ongoing partial response at 6 months with olaparib (Lau, Menzies & Joshua, 2021).

Efficacy data for PARP inhibition in PALB2-mutated tumors also exists in the maintenance setting. In a Phase II study of rucaparib as maintenance therapy in advanced pancreatic cancer with germline or somatic pathogenic variants, patients with gPALB2 achieved an ORR of 3 out of 6 (50%) and the median PFS was 14.5 months (Reiss et al., 2021).

2.4. Benefit / Risk Assessment

2.4.1. Chemotherapy Agents Approved for Use in Advanced Cancers

Chemotherapy offers limited efficacy and significant toxicity in patients with advanced solid tumors and PALB2 mutations who have progressed on at least one systemic therapy. Aggregate data in advanced solid tumors demonstrates ORRs with single-agent chemotherapeutics in the 15% range and DoRs generally less than 6 months. Table 6 demonstrates representative data regarding on-label responses and time to progression (TTP) or PFS following single-agent chemotherapy that is FDA approved for advanced/metastatic tumors (Cancer.gov, 2021). The data in the table below reflect various solid tumor types which can harbor PALB2 mutations.

Table 6. Single-Agent Chemotherapy ORR, TTP or DoR by Tumor Type

Tumor type	Chemotherapy agent	ORR %	TTP or DoR
Breast Cancer	Capecitabine Paclitaxel Eribulin	25.6% (13.5, 41.2) (95% C.I.) 22%, 28% 11% (95% CI: 8.6%, 14.3%)	154 (63-233) days DoR 3, 4.2 mo TTP 4.2 months (95% CI: 3.8, 5.0 months) mDoR
Non-small Cell Lung Cancer	Docetaxel	5.7% (2.3, 11.3)	8.3 weeks (7.0, 11.7) TTP
Colon Cancer	Irinotecan Capecitabine	18% 21% (16-26) (%, 95% C.I.)	4.2 mo TTP 128 days (120-136) TTP
Pancreatic Cancer	Gemcitabine	0%	2.1 months (95% CI;1.9, 3.4) TTP
Melanoma	Dacarbazine	Not available	Not available
Urothelial Cancer (Bladder)	Cisplatin Doxorubicin	Not available	Not available
Esophageal Cancer	Not available	Not available	Not available

Abbreviations: ORR=overall response rate; TTP=time to progression; DoR=durations of response

2.4.2. Benefit of PARPi in PALB2-mutated cancers

Patients with advanced solid tumors and PALB2 mutations are a rare population who can potentially derive benefit from niraparib. While these patients may carry various mutations differing across and within histologies, their shared feature of PALB2 alterations confers a homogeneous molecular profile that can guide therapy selection. Data surrounding the use of PARPi in PALB2-mutated cancers is described in Section 2.3.7. These aggregate data support that PARPi could deliver a benefit for a variety of PALB2-mutated solid tumors and expand the population of patients who may benefit from PARPi. However, the limited sample sizes of PALB2-positive patients in the metastatic breast (n=11), advanced breast (n=5), melanoma (n=1), and advanced pancreatic cancer (n=6) groups from these studies indicate a need for further investigation.

2.4.3. Risk Assessment

More detailed information about the known and expected benefits and risks, as well as the reasonably expected AEs of niraparib may be found in the current version of the Investigator's Brochure.

Table 7. Summary of Risks and Mitigations for the Product

Risks of Clinical Significance (Identified or Potential)	Summary of Data / Rationale for Risk	Mitigation Strategy
Thrombocytopenia Anemia Leukopenia Neutropenia Pancytopenia	Based on nonclinical and clinical observations as well as identified risk with PARPi, niraparib	Protocol has inclusion criteria that participants must have adequate organ and bone marrow function; randomization and treatment may be delayed up to 3 weeks to allow for these criteria to be met. Protocol provides guidelines for monitoring hematologic labs and adverse reactions. Protocol provides Investigator guidance for the clinical management of these events. Protocol provides guidance for dose modification (Appendix 10) and discontinuation of study (Section 7.1).
Hypertension, Including Hypertensive Crisis	Cases reported with niraparib	Protocol provides monitoring and stopping criteria for discontinuation of study treatment. Protocol includes exclusion criteria for participants who have systolic BP >140 mmHg or diastolic BP >90 mmHg that has not been adequately treated or controlled.
Second Primary Malignancy Myelodysplastic Syndrome / Acute Myeloid Leukemia Embryofetal Toxicity	Based on nonclinical and clinical observations as well as identified with PARPi, niraparib	Protocol provides monitoring and stopping criteria for discontinuation of study treatment. Protocol excludes participants that are pregnant or breastfeeding and provides detailed guidance on contraception.

Posterior Reversible Encephalopathy Syndrome (PRES)	Cases reported with niraparib	Protocol provides monitoring and stopping criteria for discontinuation of study treatment.

Abbreviation: PARP=poly (adenosine diphosphate-ribose) polymerase.

There have been rare reports of niraparib-treated patients developing signs and symptoms that are consistent with Posterior Reversible Encephalopathy Syndrome (PRES), a treatable acute neurologic illness characterized by rapid onset headache, visual disturbance, altered consciousness, seizures, hypertension, and imaging findings of white matter, parietal, and posterior occipital vasogenic edema. In patients developing PRES, treatment of specific symptoms including control of hypertension is recommended, along with discontinuation of niraparib.

2.4.4. Overall Benefit/Risk Conclusion

Based on the available clinical data, the benefit/risk profile of niraparib is anticipated to be favorable in the populations targeted in this study with utilization of the risk mitigation strategies as outlined in the study protocol. The goal of this trial is to determine whether niraparib treatment will demonstrate a favorable therapeutic index for this rare subset of tumor-agnostic patients. There is a vast amount of efficacy and safety data for PARPi and, specifically, niraparib in many indications. Overall, niraparib has a favorable benefit/risk profile when assessing the current landscape of single-agent chemotherapeutic options. By targeting pathogenic or likely pathogenic tPALB2 mutations in this population of advanced cancer patients, niraparib may offer greater clinical benefit over existing options.

3. STUDY OBJECTIVES AND ENDPOINTS

Table 8. Objectives and Endpoints for Study TMPS-101

Objectives	**Endpoints**
Primary	
To evaluate ORR as assessed by ICR using RECIST v1.1	ORR is defined as the proportion of participants who have a partial or complete response to therapy and will be assessed by ICR using the RECIST v.1.1 criteria.

Secondary	
To evaluate DOR as assessed by ICR using RECIST v1.1	DOR is defined as the time between initial response to therapy and subsequent disease progression or relapse and will be assessed by ICR using the RECIST v.1.1 criteria.
To evaluate PFS as assessed by ICR using Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1)	PFS is defined as the time from first dose to the date of first radiographic progression or death from any cause in the absence of progression, whichever occurs first. Progression will be assessed by ICR using the RECIST v.1.1 criteria.
To evaluate ORR as assessed by Investigator using RECIST v1.1	ORR is defined as the proportion of participants who have a partial or complete response to therapy and will be assessed by Investigator.
To evaluate DOR as assessed by Investigator using RECIST v1.1	DOR is defined as the time between initial response to therapy and subsequent disease progression or relapse and will be assessed by Investigator using the RECIST v.1.1 criteria.
To evaluate PFS as assessed by Investigator using RECIST v1.1	PFS is defined as the time from first dose to the date of first radiographic progression or death from any cause in the absence of progression, whichever occurs first. Progression will be assessed by Investigator using the RECIST v.1.1 criteria.
To evaluate CBR as assessed by ICR and Investigator	CBR is defined as the percentage of participants who have achieved complete response, partial response and stable disease, and will be assessed by ICR and Investigator.
To evaluate Intracranial ORR and PFS in participants with untreated measurable CNS lesions as assessed by ICR and Investigator using RECIST v1.1	ORR is defined as the proportion of participants who have a partial or complete intracranial response to therapy as assessed by ICR and Investigator using RECIST v1.1. PFS is defined as the time from first dose to the date of first radiographic progression or death from any cause in the absence of progression, whichever occurs first, and will be assessed by ICR and Investigator using RECIST v1.1

To evaluate safety and tolerability per the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 (NCI-CTCAE v5.0)	Assess the incidence of AEs, SAEs, and AESIs
To evaluate OS	OS is a secondary efficacy endpoint in this study is defined as the time from first dose to the date of death by any cause. Participants who are alive will be censored at the date of last contact. OS includes the following: death attributable to any cause, including primary cancer, secondary cancer, or unknown cause.
Exploratory	
To evaluate health-related quality of life (HRQoL) and symptoms as assessed by EORTC QLQ-C30 and the EuroQol EQ-5D-3L	The EORTC QLQ-C30 and EuroQol EQ-5D-3L will be analyzed descriptively by changes from baseline in overall score, sub scores, and individual items when applicable.
To evaluate exploratory biomarkers in tumor and/or blood that may be predictive of response including clinical factors	Blood and tissue samples for the evaluation of exploratory biomarkers will be obtained at screening. The incidence of biomarkers will be summarized using descriptive statistics. Comparisons of efficacy endpoints between biomarker subpopulations may be performed.
To evaluate niraparib concentration or PK	Plasma concentrations or PK parameters of niraparib, as data permit.

4. STUDY DESIGN

4.1. Overall Design

This is a multicenter study of niraparib in participants with locally advanced or metastatic solid tumors and a confirmed pathogenic or likely pathogenic tPALB2 mutation. Participants must have received all standard therapies appropriate for their tumor type and stage of disease or, in the opinion of the Investigator, the patient would be unlikely to tolerate or derive clinically meaningful benefit from appropriate standard of care therapy, or the participant has no satisfactory alternative treatments.

To participate in this study, participants eligibility will be confirmed via scan(s) conducted within 28 days prior to enrollment. While on-study, imaging will be performed every 8 weeks (every 56 [±7] days) from the date of enrollment until disease progression. If at any time radiographic PD is documented per RECIST v1.1 the participant will come off study.

Complete blood count (CBC) will be monitored weekly for the first 4 weeks of the treatment period, and blood pressure (BP) and heart rate will be monitored weekly for the first 2 months of the treatment period. Patient-reported outcomes (PROs) will be collected in a coordinated fashion with imaging while participants remain on study treatment. For participants who discontinue all study treatment, all PROs should be collected at the End-of-Treatment (EOT) Visit.

Each participant will have an EOT Visit at the time of discontinuation from study treatment, Safety Follow-up Visits at 30 (±7) days, and Survival Follow-up Assessments which may be conducted via telephone, email, in person visits to the clinic or back-up contacts every 90 (±14) days for 1 year after last dose and then every 180 (±14) days that will continue until death or the end of study data collection.

4.2. Number of Participants

Approximately 110 participants will be enrolled based on approximately 140 participants screened.

4.3. Dose Justification

Niraparib monotherapy has demonstrated efficacy in the homologous recombination deficiency (HRd) and homologous recombination proficient (HRp) cancer populations at both the fixed starting dose of 300 mg or an individualized starting dose of 200 or 300 mg based on baseline weight and platelet count in ovarian cancer (Gonzalez-Martin et al., 2019). Therefore, the individualized starting dose regimen is expected to be suitable for a population of patients with PALB2 mutations as PALb2 is a Homologous Recombination Repair gene. Pathogenic mutations in PALB2 result in a HRd state within the tumor (Nyugen et al., 2020).

Niraparib has a demonstrated acceptable benefit/risk ratio across tumor types when prescribed as an individualized starting dose regimen across tumor types. In this study, the dosing regimen for niraparib is the approved individualized starting dose regimen, which is 300 mg of niraparib in participants with a baseline body weight ≥77 kg AND baseline platelet count ≥150,000/μL or 200 mg in participants with a baseline body weight <77 kg OR baseline platelet count <150,000/μL, given once daily (QD), in participants with normal hepatic function or mild hepatic impairment.

Retrospective exploratory statistical multivariable analysis of data from the NOVA trial (Study 213356) identified baseline body weight and platelet counts as predictors of adverse events that required dose modification in patients treated with niraparib at 300 mg QD. Participants with a body weight <77 kg or platelet counts <150,000/μL at baseline had higher rates of Grade 3 thrombocytopenia (35% versus 12%) and were more likely to require dose modification to 200 mg within the first two months of treatment, with only 17% of participants with these baseline characteristics remaining on 300 mg by Month 4. In prospective evaluation in the PRIMA study in advanced ovarian cancer patients (Study 213359), the individualized starting dose regimen allowed participants to achieve comparable efficacy to a fixed starting dose of 300 mg, with a substantially lower incidence of thrombocytopenia and anemia, and this individualized starting dose regimen is approved for first-line maintenance treatment in advanced ovarian cancer.

4.4. Dose Adjustment Criteria

4.4.1. Niraparib

To manage adverse reactions, Investigators may consider interruption of treatment, dose reduction, or discontinuation, consistent with the following guidance.

Niraparib dose interruption is allowed for up to 28 days. Participants should be placed back on study therapy within 28 days of the scheduled interruption, unless otherwise discussed with the Sponsor. In this case, the medical monitor, in agreement with the sponsor, can allow delays of greater than 28 days. If, in the opinion of the investigator, a participant cannot safely restart therapy within 28 days, they will be discontinued from the study. 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).

For participants whose initial dose is 300 mg/day, dose reductions to 200 mg/day and subsequently to 100 mg/day will be allowed. No further dose reduction will be allowed.

For participants whose initial dose is 200 mg/day, dose reduction to 100 mg/day will be allowed. No further dose reduction will be allowed.

4.5. End of Study

The end of the study is defined as the date of the last scheduled procedure shown in the SoA for the last participant in the study. A participant is considered to have completed the study if he/she has completed all study assessments, including the last scheduled procedure as reflected in the SoA (including survival assessment).

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

4.6. Study Conduct

4.6.1. Procedures by Visit

Prior to participation, all participants must sign the main study ICF. Baseline and on-study imaging for all participants will include the chest, abdomen, pelvis, CNS as applicable, and other sites as clinically indicated. Imaging studies performed prior to informed consent as part of routine clinical management are also acceptable for use as initial imaging if they are of diagnostic quality, meet the protocol imaging requirements, and are performed within 28 (± 7) days prior to enrollment. Note that source documents must clearly identify the standard of care tests/procedures that are used for study Screening and the results of these tests/procedures must be entered in the eCRF (documentation of study-related procedures and study data will be captured in the eCRFs).

5. STUDY POPULATION

5.1. Participant Inclusion Criteria

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

1. Participants must be ≥18 years of age.
2. Participants must have a histologically or cytologically confirmed diagnosis of locally advanced or metastatic solid tumor(s). This study will enrich for lung, breast, and colon cancers; targeting approximately 10 participants for each of these cancer types.
3. Participants must have tested positive for a pathogenic or likely pathogenic tPALB2 mutation using a CLIA-certified laboratory as defined in the NGS Laboratory Manual.
4. Participants who have stable and asymptomatic CNS disease must be receiving a stable (for at least 7 days) or decreasing corticosteroid dose at the time of study entry.
5. Participants must submit fresh or archived (collected within 24 months of enrollment) FFPE tumor sample to the central laboratory for post-enrollment confirmation of tPALB2 status.
6. Participants must have received all standard therapies appropriate for their tumor type and stage of disease or, in the opinion of the Investigator, the patient would be unlikely to tolerate or derive clinically meaningful benefit from appropriate standard of care therapy, or the participant has no satisfactory alternative treatments.
7. Participants must have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
8. Participants must have a life expectancy of at least 12 weeks.
9. Participants must have adequate organ and bone marrow function defined below. Treatment may be delayed up to 3 weeks from enrollment to allow for these criteria to be met.

Table 9. Organ/Bone Marrow Function Inclusion Criteria

Absolute neutrophil count:	≥1,500/μL
Platelets:	≥100,000/μL
Hemoglobin:	≥9 g/dL or 5.6 mmol/L
Creatinine clearance (CLCr):	>30 mL/min as estimated by the Cockcroft-Gault equation
Total bilirubin*:	≤1.5×upper limit of normal (ULN) (except in participants with Gilbert's syndrome. Participants with Gilbert's syndrome: isolated bilirubin >1.5×ULN is acceptable if bilirubin is fractionated, and direct bilirubin is <35%).

Aspartate aminotransferase (AST) and alanine aminotransferase (ALT)*:	≤ 2.5×ULN (unless liver metastases are present, in which case they must be ≤5×ULN)

Note: CBC test should be obtained without transfusion or receipt of colony-stimulating factors within 4 weeks prior to obtaining sample.

*Participants with mild to moderate hepatic impairment are allowed in the study.

Mild hepatic impairment is defined as total bilirubin ≤1.5×upper limit of normal (ULN), any aspartate aminotransferase (AST); and an alanine aminotransferase (ALT) ≤2.5×ULN.

Moderate impaired hepatic function is defined as total bilirubin >1.5× and ≤3×ULN, any level of AST; and an ALT ≤2.5×ULN.

10. Participants must be able to swallow and retain orally administered study treatment.
11. A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:
    - Is not a woman of childbearing potential (WOCBP).

      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, during the intervention 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 (either a highly sensitive urine or a serum pregnancy test as required by local regulations) within 72 hours before the first dose of study treatment.
    - If a highly sensitive urine test cannot be confirmed as negative (eg, 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.
    - 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.
12. Male participants are eligible to participate if they agree to the following during the intervention period and for at least 90 days after the last dose of study treatment:
    - Refrain from donating sperm

      plus, either:

    - Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent

      or

    - Must agree to use contraception/barrier as detailed below:

- Agree to use a male condom (and should also be advised of the benefit for a female partner to use a highly effective method of contraception as a condom may break or leak) when having sexual intercourse
- Participants must be able to understand the study procedures and agree to participate in the study by providing written informed consent. Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent to participate in the study.

5.2. Participant Exclusion Criteria

Participants will be excluded from study entry if any of the following criteria are met:

1. Participants have other active concomitant malignancy that warrants systemic, biologic, or hormonal therapy.
2. Participants who have ovarian or prostate cancer.
3. Participants who have variants of undetermined significance (VUS), but not pathogenic variants of tPALB2, at the time of screening.
4. Participants who relapsed while receiving platinum based therapy in the adjuvant/curative setting.
5. Participants progressing within 14-18 weeks while receiving platinum based therapy in the metastatic setting.
6. Participants who have received PARP inhibitor(s) in prior lines of treatment.
7. Participants with leptomeningeal disease, carcinomatous meningitis, symptomatic brain metastases, or radiologic signs of CNS hemorrhage.
8. Participants with germline or somatic BRCA1 or BRCA2 mutations.
9. Participant has systolic BP >140 mmHg or diastolic BP >90 mmHg, despite optimal medical therapy.
10. Participants who have any clinically significant gastrointestinal abnormalities that may alter absorption such as malabsorption syndrome or major resection of the stomach and/or bowels.
11. Participants with current active liver or biliary disease are excluded (with the exception of Gilbert's syndrome or asymptomatic gallstones, liver cancer/metastases, or otherwise stable chronic liver disease per Investigator assessment).
12. Participants who are receiving chronic systemic steroids (prednisone >20 mg per day). Participants with asthma who require intermittent use of bronchodilators or inhaled steroids; or with medical conditions who require topical, local steroid application or injections, would not be excluded from the study.
13. Participants have previously or are currently participating in a treatment study of an investigational agent within 3 weeks of the first dose of therapy preceding the study.
14. Participants have received prior systemic cytotoxic chemotherapy, biological therapy, or hormonal therapy for cancer, or received radiation therapy within 3 weeks of the first dose therapy preceding the study.

15. Participants with toxicity from prior cancer therapy must have recovered to Grade 1. (A participant with Grade 2 neuropathy or Grade 2 alopecia is an exception to this criterion and qualify for this study.)
16. Participants have known hypersensitivity to the components of niraparib or their formulation excipients.
17. Participants have undergone major surgery within 4 weeks of starting the first dose of study treatment or have not recovered from any effects of any major surgery.
18. Participants have other active concomitant malignancy that warrants systemic, biologic, or hormonal therapy.
19. Participants have received a live vaccine within 30 days of study enrollment.
20. Participants have current active pneumonitis or any history of pneumonitis requiring steroids (any dose) or immunomodulatory treatment within 90 days of planned start of the study.
21. Participants who have any clinically significant concomitant disease or condition (such as transfusion-dependent anemia or thrombocytopenia) that could interfere with, or for which the treatment might interfere with, the conduct of the study or that would, in the opinion of the Investigator, pose an unacceptable risk to the participants in this study.
22. Participants who have any psychological, familial, sociological, or geographical condition potentially hampering compliance with the study requirements and/or follow up procedures. Those conditions should be discussed with the participants before study entry.
23. Participants have high medical risk due to a serious, uncontrolled medical disorder; nonmalignant systemic disease; or active, uncontrolled infection (including COVID-19). Examples include, but are not limited to, uncontrolled ventricular arrhythmia, recent (within 90 days) myocardial infarction, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, active uncontrolled coagulopathy, bleeding disorder, or any psychiatric disorder that prohibits obtaining informed consent.
24. Participants who are pregnant, breastfeeding, or expecting to conceive children while receiving study treatment and/or for up to 180 days after the last dose of study treatment.
25. Participants have presence of hepatitis B surface antigen or a positive hepatitis C antibody test result at screening or within 3 months prior to first dose of study treatment. Participants with presence of hepatitis B core antibody should also be excluded.
26. Participants have a known history or current diagnosis of myelodysplastic syndrome (MDS), acute myeloid leukemia (AML) or posterior reversible encephalopathy syndrome (PRES).
27. Participant is immunocompromised. Participants with splenectomy are allowed. Participants with known human immunodeficiency virus (HIV) are allowed if they meet the following criteria:

- Cluster of differentiation 4 ≥350/μL and viral load <400 copies/mL.
- No history of acquired immunodeficiency syndrome-defining opportunistic infections within 12 months prior to enrollment.
- No history of HIV-associated malignancy for the past 5 years.

- Concurrent antiretroviral therapy as per the most current National Institutes of Health (NIH) Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV [NIH, 2021] started <4 weeks prior to study enrollment.

5.3. Lifestyle Considerations

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

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demographics, screen failure details, eligibility criteria, any protocol deviations, and any SAEs.
A participant that has previously screen failed may be rescreened for the study. Participants who are rescreened are required to sign a new ICF. Rescreened participants should be assigned a new participant number for every Screening/Rescreening event.

6. STUDY TREATMENT(S) AND CONCOMITANT THERAPY

6.1. Study Treatment(s) Administered

Table 10. Investigational Product Details

Product name	Niraparib
Dosage form	Capsules
Unit dose	100 mg
Route of administration	Oral
Physical description	Capsules will be packaged in high-density polyethylene bottles
Manufacturer	GlaxoSmithKline

6.1.1. Niraparib

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

Niraparib will be supplied as 100-mg capsules. The starting dose will be based upon the participant's baseline body weight and/or baseline platelet count.

Participants with a baseline body weight ≥77 kg and baseline platelet count ≥150,000 μL will be administered niraparib 300 mg daily. Participants with a baseline body weight <77 kg or baseline platelet count <150,000 μL will be administered niraparib 200 mg daily.

6.2. Preparation/Handling/Storage/Accountability

6.2.1. Study Drug Packaging and Labeling

Niraparib capsules will be packaged in high-density polyethylene bottles with child-resistant closures. Participants will be provided enough capsules to accommodate 28 days of dosing with up to +3 days for visit flexibility.

The label text of the study treatments will comply with Good Manufacturing Practice and national legislation to meet the requirements of the participating countries.

6.2.2. Study Drug Storage

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

The Investigator shall take responsibility for and shall take all steps necessary to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

6.2.3. Niraparib Administration

Niraparib will be taken orally once a day, continuously throughout the 28-day cycle starting on Cycle 1/Day 1. Two capsules of 100-mg strength (200 mg/day) or 3 capsules of 100-mg strength (300 mg/day), based on baseline body weight and/or platelet count, will be taken at each dose administration. Participants will be instructed to take their niraparib dose in the morning at approximately the same time each day, except on clinic visit days. On these days, participants will be instructed to hold their niraparib dose until their visit; it will be administered at the site. Niraparib may be taken with or without food or water. Participants must swallow and not chew the capsules. If a participant vomits or misses a dose of niraparib, a replacement dose should not be taken. Bedtime administration may be a potential method for managing nausea.

Niraparib will be dispensed to participants on Day 1 of every cycle (every 28 days) thereafter until radiographic PD is documented per RECIST v1.1 or other treatment discontinuation criterion is met. The niraparib product guidelines document contains descriptions of the packaging of niraparib and instructions for administration of niraparib.

Complete instructions for collection, processing, shipping, and handling are described in the Manual.

Table 11. Niraparib Dosing Criteria

Baseline Criteria	Starting Dose
Weight <77 kg or platelets <150,000/µL, or both	200 mg daily (two 100-mg capsules)
Weight ≥77 kg and platelets ≥150,000/µL	300 mg daily (three 100-mg capsules)

6.2.4. Study Drug Accountability

The Investigator or designee is responsible for maintaining accurate dispensing records of the study treatments throughout the clinical study.

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

The Pharmacist will dispense study treatment for each participant according to the protocol and Study Manual.

6.2.5. Study Drug Handling and Disposal

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label. Receipt and dispensing of study treatment must be recorded by an authorized person at the study site. Refer to the niraparib product guidelines document for full niraparib handling precautions.

The Investigator is responsible for keeping accurate records of the clinical supplies received from the Sponsor or designee, the amount dispensed to and returned by the participants, and the amount remaining at the conclusion of the study.

Clinical supplies may not be used for any purpose other than that stated in the protocol. At the end of study, when all participants have stopped protocol treatment, complete drug reconciliation per batch should be available at the site for verification in order to allow drug destruction or return procedure. After receiving Sponsor approval in writing, the investigational site is responsible for destruction of study treatment according to local regulations. If a site does not have the capability for onsite destruction, the Sponsor will provide a return for destruction service through 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 treatment provided for this study is to be used only as indicated in this protocol and only for the participants entered in this study.

6.3. Study Treatment Compliance

Compliance with inclusion and exclusion criteria will be assessed as outlined in Sections 5.1 and 5.2.

Study treatment will be administered by site personnel at study sites as detailed in Section 6.2.3.

When participants are dosed at the site, they will receive study intervention directly from the Investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

When participants self-administer study intervention at home, compliance with niraparib will be assessed by direct questioning or counting returned capsules during the site visits and recording in the source document and relevant forms. Deviation(s) from the prescribed dosage regimen should be recorded.

A record of the quantity of study treatment dispensed to and administered by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions will also be recorded.

Study treatment accountability will be monitored with a patient dosing diary.

6.4. Treatment of Overdose

For this study, a dose of niraparib greater than indicated in this protocol within the specified administration window will be considered an overdose.

In the event of an overdose, the Investigator should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for AE/SAE and laboratory abnormalities until the investigational product can no longer be detected systemically.
3. 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.

6.5. Concomitant Therapy

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

At Screening, 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.

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the course of this study. All treatment interventions that the Investigator considers medically necessary for a participant's wellbeing may be administered at the discretion of the Investigator in keeping with the community standards of practice. If there is a clinical indication

for any medication or vaccination specifically prohibited during the study, discontinuation of study treatment may be required. The final decision on any supportive medications or vaccination is the responsibility of the Investigator and/or the participant's primary physician. The decision to continue the participant on the study treatment schedule requires the mutual agreement of the Investigator, the Sponsor, and the participant.

6.5.1. Prohibited Medications

Known prior medications that exclude a participant from participating in the study are described in the exclusion criteria.

Participants are prohibited from receiving the following therapies during the Screening and Treatment phase of this study:

- Systemic anticancer or biological treatment
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than niraparib
- Prophylactic cytokines (eg, GCSF) should not be administered in the first cycle of the study but may be administered in subsequent cycles according to local guidelines.
- Live vaccines within 30 days prior to the first dose of study treatment and while participating in this clinical study
- Chronic systemic steroids (prednisone >20 mg per day)

The data on niraparib in combination with cytotoxic medicinal products are limited. Therefore, caution should be taken if niraparib is used in combination with vaccines, immunosuppressant agents or with other cytotoxic medicinal products.

No other anticancer treatment is permitted during the course of the study treatment for any participant. Palliative radiotherapy (excluding palliative radiotherapy encompassing >20% of the bone marrow within 1 week of the first dose of study treatment) is allowed for pre-existing small areas of painful bone metastases that cannot be managed with local or systemic analgesics, as long as no evidence of disease progression is present.

The niraparib safety profile includes risk for thrombocytopenia; therefore, participants should be advised to use caution when taking anticoagulants (eg, warfarin) and antiplatelet drugs (eg, aspirin).

Caution is recommended when niraparib is combined with active substances the metabolism of which is cytochrome P450 enzyme (CYP)3A4-dependent and, notably, those having a narrow therapeutic range (eg, cyclosporine, tacrolimus, alfentanil, ergotamine, pimozide, quetiapine, and halofantrine).

Caution is recommended when niraparib is combined with active substances the metabolism of which is CYP1A2-dependent and, notably, those having a narrow therapeutic range (eg, clapzine, theophylline, and ropinirole). Caution is then recommended when niraparib is combined with substrates of breast cancer resistance protein (eg, rosuvastatin, simvastatin, atorvastatin, and methotrexate).

Niraparib is an inhibitor of multidrug and toxin extrusion transporter (MATE)1 and MATE2 with a half maximal inhibitory concentration of 0.18 μM and ≤0.14 μM, respectively. Increased plasma concentrations of coadministered medicinal products that are substrates of these transporters (eg, metformin) cannot be excluded.

Caution is recommended when niraparib is combined with active substances that undergo an uptake transport by organic cation transporter 1 (eg, metformin).

Physicians should follow the current versions of the niraparib Investigator's Brochure for information on the general management of the participants receiving this therapy.

6.5.2. Contraception

Niraparib is known to have properties that require participants to use contraception. For details on niraparib, refer to the current niraparib Investigator's Brochure.

Based on its mechanism of action, niraparib may cause teratogenicity and/or embryo-fetal death when administered to a pregnant woman.

Participants 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. 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 effective contraception, or be of non-childbearing potential.

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 participant will not reliably comply with the requirements for contraception, that participant should not be enrolled in the study.

Male participants must use an adequate method of contraception and not donate sperm starting with the first dose of study treatment through 90 days after the last dose of study treatment. Abstinence is acceptable if this is the established and preferred contraception for the participant.

Table 12. Timing of Contraception and Sperm Donation

Parameter	Timeframe
Contraception use, female participants	Starting with the Screening visit through 180 days after the last dose of study treatment
Contraception use, male participants	Starting with the first dose of study treatment through 90 days after the last dose of study treatment
Sperm donation	Starting with the first dose of study treatment through 90 days after the last dose of study treatment

6.5.3. 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.

7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation from Study Treatment

Participants may be discontinued from study treatment at any time. Participants who discontinue from study treatment or from the study will not be replaced. Participants who discontinue from study treatment will attend the EOT Visit within 7 days after the last dose of study treatment, Safety Follow-up Visits at 30 (±7) days, and Survival Follow-up assessments which may be conducted via telephone, email, in person visits to the clinic or back-up contacts every 90 (±14) days for 1 year after last dose and then every 180 (±14) days that will continue until death or the end of study data collection (provided that this allows the opportunity for completion of all 90-day follow-up assessments).

Specific reasons for discontinuing study treatment include the following:

- AE
  - If a participant has any treatment-related NCI-CTCAE v5.0 Grade 3 or 4 AEs that have not reverted to NCI-CTCAE v5.0 Grade 1 or better within 28 days.
  - If upon re-challenge with study treatment at the lowest allowable dose any NCI-CTCAE v5.0 Grade 3 or 4 AEs recur, the participant must be discontinued from niraparib treatment.
- Liver chemistry stopping criteria are met per Appendix 4: Liver Safety Required Actions and Follow-up Assessments
- Thrombocytopenia, if the platelet count has not returned to ≥100,000/µL within 28 days of dose interruption
- Neutropenia, if the neutrophil counts has not returned to ≥1,500/mcL within 28 days of dose interruption
- Anemia, if the hemoglobin has not returned to ≥9 g/dL within 28 days of dose interruption
- MDS, AML or PRES
- New primary malignancy other than MDS or AML
- Risk to the participant as judged by the Investigator, Sponsor, or both
- Severe non-compliance with protocol as judged by the Investigator, Sponsor, or both
- Pregnancy
- Withdrawn consent
- Lost to follow-up
- Death
- PD as indicated by radiographic evidence per RECIST v1.1

Treatment with niraparib will continue until radiographic PD is documented per RECIST v1.1 or another treatment discontinuation criterion is met.

If a participant discontinues treatment for any reason other than radiographic PD per RECIST v1.1, then tumor assessment scans should continue at the specified intervals until radiographic PD is documented per RECIST v1.1 or until the start of subsequent anticancer treatment.

Participants who discontinue from study treatment will continue to receive follow-up assessments as part of the study unless they are discontinued from the study. During follow-up, contact to assess survival may be made via another form of communication (eg, telephone, email).

7.2. Withdrawal of Consent

Participants may withdraw consent at any time. If a participant withdraws consent, the Investigator is to determine whether the participant is willing to be followed up for subsequent procedures in the safety and survival follow-up periods and for OS. Such participants will be required to indicate whether they agree to continue these procedures as well as whether they agree to the collection of their disease history information until the end of the study and to the use of the blood and tumor samples they provided for the study for research purposes; this information will be recorded on the appropriate eCRF page.

Documentation of participant consent for further research will be captured in the eCRFs. Any specimens for which such an informed consent cannot be verified will be destroyed, as will those requested to be destroyed at time of consent withdrawal.

7.3. Participant Discontinuation/Withdrawal from the Study

Specific reasons for discontinuing from the study include the following:

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

A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, or compliance reasons. This is expected to be uncommon.

At the time of discontinuing from the study, if possible, an EOT Visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of study discontinuation and follow up and for any further evaluations, including survival status, that need to be completed.

If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

A participant may choose to stop receiving study treatment and still be involved in the study. In this case, study staff may contact the participant (or other representatives [eg, caregiver, doctor] if the participant cannot be reached directly) by telephone or email (every 90 days for 1 year after last dose and then every 180 days) to make health inquiries, which may help to inform long-term effects of the study treatment.

7.4. Lost to Follow-Up

A participant will be considered lost to follow-up if he or she repeatedly 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 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, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Regarding collection of date for death/survival status, a back-up contact, if documented by the participant, or public databases can be used to provide the information.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

7.4.1. Further Research Maintaining Confidential Participant Information

The Sponsor will conduct further research on specimens collected during this study. This research may include genetic/genomic, proteomic, metabolomic, and transcriptional analyses. The data generated may be combined with clinical and histological image analysis. Such research helps to address emergent questions not described in the protocol and will only be conducted on specimens from properly consented participants.

In an effort to optimize the research that can be conducted with further research specimens, it is essential to link study participant clinical study data with further research test results. The clinical study data allow specific analyses to be conducted. Knowing participant characteristics like gender, age, medical history, treatment type, and treatment outcomes are critical to understanding the clinical context of further research analytical results.

To maintain privacy of information collected from specimens obtained for further research, the Sponsor has developed secure policies and procedures. All specimens will be single coded per International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E15 guidelines, "Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories".

At the clinical study site, unique codes will be placed on the further research specimens for transfer to the storage facility. This first code is a random number that does not contain any personally identifying information embedded within it in order to maintain participant privacy. The link (or key) between participant identifiers and this first unique code will be held at the study site. No personal identifiers will appear on the specimen tube.

Participants may withdraw their consent for further research and have their specimens and all derivatives destroyed. Participants may withdraw consent at any time by contacting the Investigator.

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Screening and Critical Baseline Assessments

8.1.1. Baseline Assessments at Screening

Refer to the Schedule of Activities (Table 3 and Table 4) for the full list of assessments collected during Screening. Tumor characteristics to be collected during Screening include, but are not limited to, histologic tumor type, tumor grade, tumor stage (both clinical and pathologic staging as per the American Joint Committee on Cancer (AJCC) and response to chemotherapy (as applicable). Primary pathology reports will be collected from biopsy.

8.1.2. Biomarker Testing for PALB2 and Translational Research

Screening Testing

An individual must have a PALB2 somatic or germline mutation to be eligible for enrollment. Results from local NGS testing from tissue and/or blood performed by a CLIA-certified laboratory as described in the NGS Laboratory Manual will be used to meet molecular eligibility.

If an individual is enrolled based on local testing, tissue and blood samples must be submitted for retrospective confirmation of PALB2 status (where applicable), diagnostic development, and biomarker research. 30 FFPE slides or 1 block equivalent of tumor tissue collected from the most recent biopsy (sample collected within the past 24 months of enrollment) must be provided. For participants with only germline PALB2 mutations, archival tissue from a primary or metastatic tumor may be provided. For participants with somatic PALB2 mutations, a metastatic tissue sample is requested; if not available, a primary tumor sample may be provided and a new biopsy will be requested, though optional, so that a metastatic disease sample may be submitted for testing. To obtain the new biopsy sample a core or needle biopsy may be performed; however, more invasive procedures should not be utilized for the purpose of this trial.

In addition, a total of 3 tubes with stabilization solution of peripheral blood, ~ 30 mL, will be collected for biomarker testing in accordance with Table 3.

Longitudinal Testing

Additional blood samples (2 tubes with stabilization solution, ~ 20 mL, of peripheral blood) for exploratory biomarker testing will be collected at the time points specified in the SoA to evaluate

genomic, gene expression, proteomic, or other signatures to investigate predictive biomarkers for response and mechanisms of resistance as well as for exploratory research.

If a participant discontinues study treatment for any reason other than disease progression per RECIST v1.1, death, withdrawal of consent, or loss to follow-up, then biomarker blood sample collection should continue at the specified intervals until disease recurrence is confirmed.

8.1.3. Baseline CT/MRI

A CT scan of the chest, and IV contrast-enhanced CT of the abdomen, and pelvis will be conducted within 28 (± 7) days prior to randomization. An IV contrast-enhanced MRI of the abdomen and pelvis plus noncontrast CT of the chest should only be conducted if clinically indicated (eg, if the participant is sensitive to IV CT contrast). For participants with CNS lesions, brain MRI will also be conducted within 28 (± 7) days prior to randomization. The same imaging modality, method, and anatomical coverage should be used throughout the study.

8.2. Assessment of Efficacy

8.2.1. Primary Efficacy Endpoint

This study has the efficacy endpoint ORR, which is defined as the proportion of participants who have a partial or complete response to therapy and will be assessed by ICR.

8.2.2. Radiographic Evaluation of Tumor Response

Images of the chest, abdomen, pelvis, CNS as applicable, and other sites as clinically indicated will be used to determine extent of disease. The same imaging method and anatomical coverage should be used throughout the study.

The preferred method used for chest, abdomen and pelvis assessments is cross-sectional imaging by CT scan. CT scans should be performed with IV contrast, unless contraindicated for medical reasons, in which case MRIs are acceptable. MRI of the chest should not be substituted for CT of the chest, even if IV contrast is contraindicated. In such a case, CT will be performed without IV contrast to evaluate the lung parenchyma. Premedication (including steroids) is permitted prior to CT scans for participants with a documented history of IV contrast allergy.

Imaging of the CNS (brain only, unless otherwise clinically indicated) will be performed for all participants with documented CNS disease by MRI at baseline and all CNS assessments throughout the study. However, CT is acceptable if MRI is not possible.

Participants who are known to have bone metastasis or who display clinical or laboratory signs (eg, serum alkaline phosphatase >1.5×ULN) of bone metastasis may undergo additional imaging (eg, radionuclide bone scan, CT scan, MRI, PET scan, Xray) as clinically indicated, in the judgment of the Investigator.

Overall progression will be assessed by the Investigator per RECIST v1.1 and verified by ICR to measure PFS.

Imaging will be collected/conducted per Table 13.

Table 13. Overview of Imaging Requirements by Visit

Imaging Visit	Description
Baseline	● Performed within 28 [±7] days prior to randomization ● Performed by CT of chest, abdomen, and pelvis. MRI of the brain is necessary for imaging participants with CNS lesions. ● Assessed by ICR and Investigator per RECIST v1.1 ● Imaging assessment conducted prior to consent as part of routine care may be used if it is performed within the 28 (± 7)-day window
Treatment Period	● Performed every 8 weeks (every 56[±7] days) from the date of study start ● Participants with either a PR or CR should have an additional set of scans to confirm the response at least 28 (+7) days after scans showing the PR or CR ● Performed more frequently if clinically indicated ● Brain scan required for participants with documented CNS disease every 8 weeks (every 56[±7] days) from the date of study start to assess intracranial ORR and PFS in participants with untreated measurable CNS lesions (all scans must be the same as the initial scan type) ● Assessed by ICR and Investigator per RECIST v1.1
EOT	● For participants who discontinue study treatment due to ICR-verified progression, additional imaging assessment is not required at EOT ● For participants who begin a subsequent anticancer treatment prior to ICR-verified progression, EOT imaging assessment must be performed within 4 weeks of the date of study treatment discontinuation
Post-Treatment Follow-Up	● Participants who discontinue study treatment for any reason other than radiographic PD per RECIST v1.1 should continue monitoring disease status by tumor imaging every 8 weeks (every 56 [±7] days) until radiographic PD is documented per RECIST v1.1 or until the start of subsequent anticancer treatment.

Abbreviations: ICR= independent central review; CNS=central nervous system; CR=complete response; CT=computed tomography; EOT=End-of-Treatment; MRI=magnetic resonance imaging; PD=progressive disease; PR=partial response; RECIST v1.1=Response Evaluation Criteria in Solid Tumors version 1.1; SD=stable disease; TTP=time to progression.

Tumor assessments and timing should occur according to this schedule regardless of treatment interruptions. Imaging should not be delayed due to delays in cycle starts or extension.

All imaging will be submitted to the imaging vendor for ICR. Two independent radiologists (along with an adjudicator, as necessary) will conduct reads using RECIST v1.1 criteria for the determination of response.

8.2.3. Secondary Efficacy Endpoints

This study has the following secondary efficacy endpoints: ORR, DOR, PFS, CBR and OS.

ORR is defined as the proportion of participants who have a partial or complete response to therapy and will be assessed by Investigator as a secondary efficacy endpoint.

DOR is defined as the time between initial response to therapy and subsequent disease progression or relapse and will be assessed by ICR and Investigator using the RECIST v.1.1 criteria.

PFS is defined as the time from first dose to the date of first radiographic progression or death from any cause in the absence of progression, whichever occurs first. Progression will be assessed by ICR and Investigator using the RECIST v.1.1 criteria.

CBR is defined as the percentage of participants who have achieved complete response, partial response, and stable disease, and will be assessed by ICR and Investigator.

Intracranial ORR and PFS in participants with untreated measurable CNS lesions as assessed by ICR and Investigator using RECIST v1.1.

OS is a secondary efficacy endpoint in this study is defined as the time from first dose to the date of death by any cause. Participants who are alive will be censored at the date of last contact. OS includes the following: death attributable to any cause, including primary cancer, secondary cancer, or unknown cause.

8.2.4. Patient-Reported Outcome Measures

Summaries of the PRO instruments for EORTC QLQ-C30 and EQ-5D-3L are provided in Appendix 7.

The PRO questionnaires should be conducted in the clinic, on the day of study treatment administration, prior to dosing or clinical procedures during the Treatment Period. They may be administered by telephone in follow up if the participant is no longer actively returning to the site.

The questionnaires will be administered to participants based on the availability of translated versions.

Participants will be instructed on the completion of the questionnaires by site personnel who have been trained on their implementation.

8.2.5. Pharmacokinetic Sample Collection

Blood samples for niraparib PK will be collected at the time points specified in Table 4 for all study participants with sparse PK sampling. Each PK sample must be collected as close as possible to the planned time relative to the dose administered to the participant on PK sampling

days.

Plasma prepared from the blood samples will be analyzed for niraparib concentrations for PK

Evaluation.

Complete instructions for collection, processing, shipping, and handling of PK samples are detailed in a study-specific Laboratory Manual.

8.3. Assessment of Safety

8.3.1. Safety Parameters

Safety parameters will include the incidence of AEs, SAEs, and AESIs, the incidence of treatment discontinuations, dose interruptions, and dose reductions due to AEs, SAEs, or AESIs, changes in ECOG performance status, changes in clinical laboratory results (hematology, chemistry and urinalysis), vital sign measurements, observations during physical examination, and use of concomitant medications.

8.3.2. 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, smoking status (nonsmoker, former smoker, and current smoker), and sex. Medical history will include disease history, medical and surgical history, previous and concomitant medications, and any other relevant information. Information regarding standard of care induction chemotherapy and cancer history will also be collected.

8.3.3. Physical Examination

Physical examinations and symptom-directed physical examinations will be performed in accordance with the standard of care for oncology patients and in accordance with local-regional standards of practice.

A full physical examination will include, at a minimum, assessments of respiratory, cardiovascular, gastrointestinal, and neurological systems.

Symptom-directed, targeted physical examinations will include, at a minimum, assessments of the skin, heart, lungs, and abdomen (including liver and spleen), along with a neurological assessment. Investigators should pay special attention to clinical signs related to previous serious illness and to emerging AEs. Abnormal findings should be reassessed at subsequent visits.

Any physical examination or vital sign abnormalities assessed as clinically significant should be recorded as an AE or SAE. If SAE criteria are met or the abnormality is an AESI, the finding should be recorded and reported according to the SAE reporting process.

8.3.4. Vital Signs, Height, and Weight

Vital signs, including BP, temperature, heart rate, respiratory rate, weight, and height will be measured. 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 AESI, the event should be recorded and reported according to the SAE reporting process. Height will be measured at Screening only. Weight will be measured at Screening and at every visit indicated in the schedule. Heart rate and BP must be monitored weekly for the first 2 months, then on Day 1 of each subsequent cycle. Blood pressure and heart rate collection methodology can occur during on-site scheduled clinic visits, at a local laboratory/clinic, or may also be reported to the site by a home nurse, or by another method deemed by the investigator and sponsor to be reliable. Three readings of BP and heart rate should be performed at a clinic visit. The first reading should be rejected and the second and third averaged to give the measurement to be recorded in the CRF.

8.3.5. Laboratory Assessments

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

Any abnormal laboratory value assessed as clinically significant should be recorded as an AE. Evaluation by Investigators should be given to clinically significant laboratory values that begin before the start of study treatment but after obtaining main study ICF for determination regarding whether values should be recorded as medical history/current medical conditions. If SAE criteria are met or if the laboratory abnormality is an AESI, the event should be recorded and reported according to the SAE reporting process.

Hematologic, blood chemistry and coagulation factor testing may occur more frequently than is specified, if medically indicated per Investigator judgment or if the event meets the criteria for study treatment dose modification. Additional tests may be performed at a laboratory facility other than the study site, but the test results must be reported to the study site, the study 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 reported while a participant is receiving treatment or followed for post-treatment assessments must be referred for evaluation to a local hematologist to perform bone marrow aspirate and biopsy as per local practice. The study 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. Report 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. If a diagnosis of MDS/AML is confirmed by a hematologist, the participant must permanently discontinue study treatment.

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.

Table 14. Laboratory Assessments

Hematology	**Coagulation Factors**[a]	**Chemistry**	**Chemistry**	**Urinalysis**	**Other**
WBC – total and differential	PT/INR	Sodium	Calcium	Specific gravity	Serum β-hCG[b]
Hemoglobin	PTT/aPTT	Potassium	Magnesium	Blood	FT4
Hematocrit		Chloride	Phosphorus	Glucose	
Platelet count[c]		CO_2 or bicarbonate[d]	Albumin	Ketones	
Absolute neutrophil count		BUN or urea[e]	Total Protein	Protein	
Absolute lymphocyte Count		Uric acid	Alkaline phosphatase	Nitrite	
		Creatinine	ALT	Leukocyte esterase	
		Glucose	AST	Urobilinogen	
			Amylase	Bilirubin	
			Total Bilirubin	Microscopic exam, if abnormal results are noted	
				Urine pregnancy test	

Abbreviations: β-hCG=beta-human chorionic gonadotropin; ALT=alanine aminotransferase; aPTT=activated partial thromboplastin time; AST=aspartate aminotransferase; BUN=blood urea nitrogen; CO_2=carbon dioxide; FT4=free thyroxine; INR=international normalized ratio; PT=prothrombin time; PTT=partial thromboplastin time; WBC=white blood cell.

[a] Coagulation factors (PT/INR and aPTT/PTT) should be tested as part of the screening procedures for all participants. Any participant receiving anticoagulant therapy should have coagulation factors monitored closely throughout the study.

[b] Perform β-hCG on women of childbearing potential only. Urine pregnancy test is preferred. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

[c] Mean platelet volume is optional but encouraged, especially for participants with high-grade thrombocytopenia.

[d] If CO_2 or bicarbonate in the chemistry panel are not done as part of standard of care in your region, then these tests do not need to be performed.

[e] BUN is preferred; if not available, urea may be tested.

8.3.6. HIV, Hepatitis B, and Hepatitis C Testing

HIV, hepatitis B virus, and hepatitis C virus testing will be done at Screening and performed consistent with local regulations, where applicable.

8.3.7. ECOG Performance Status

Performance status will be assessed using the ECOG scale in Appendix 8. The same observer should assess ECOG performance status each time.

8.4. Adverse Events (AEs), Serious Adverse Events (SAEs), and Other Safety Reporting

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally appointed representative).

The Investigator and any qualified designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE, SAE, or AESI according to CTCAE v5.0 and remain responsible for following up all events.

8.4.1. Time Period and Frequency for Collecting AE and SAE Information

- All AEs and SAEs will be collected from the signing of the main study ICF until 30 days after the last dose of study treatment at the time points specified in Table 4. However, any SAEs assessed as related to study participation (eg, study treatment, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to study treatment will be collected and reported until study closeout as specified in Table 4.
- AESIs will be collected and reported from the signing of the main study ICF until study closeout at the time points specified in Table 4 and as described in 8.4.6.
- Adverse Events that begin before the start of study treatment but after obtaining informed consent will be recorded as Medical History/Current Medical Conditions.
- All SAEs will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours. The Investigator will submit any updated SAE data to the Sponsor or designee within 24 hours of it being available.
- Investigators are not obligated to actively seek information on AEs or SAEs after the conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the Investigator must promptly notify the Sponsor.

8.4.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

8.4.3. Follow-Up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs and SAEs will be followed until the event is resolved, stabilized, or otherwise explained; until the participant is lost to follow-up; or until the participant has died.

Regulatory Reporting Requirements for SAEs

- Prompt notification by the Investigator to the Sponsor and GSK of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and Investigators.
- An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) as applicable and in accordance with regional reporting requirements. Sponsor policy and applicable provision to Investigators as necessary should also apply.

8.4.4. Pregnancy

- Details of all pregnancies in female participants and female partners of male participants who receive study treatment will be collected after the start of study treatment and until 180 days after the last dose of study treatment in female participants and 90 days after the last dose of study treatment for female partners of male participants.
- If a pregnancy is reported, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the pregnancy of the female participant or female partner of male participant (after obtaining the necessary signed informed consent from the female partner). While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The participant/pregnant female partner will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the

participant/pregnant female partner and the neonate, and the information will be forwarded to the Sponsor.

- Any post-study pregnancy-related SAE considered reasonably related to the study treatment by the Investigator will be reported to the Sponsor. While the Investigator is not obligated to actively seek this information in former study participants/pregnant female partners, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study treatment.

8.4.5. Cardiovascular and Death Events

For any cardiovascular (CV) events detailed in Appendix 2 and all deaths, whether or not they are considered SAEs, specific sections of the eCRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

The CV-related eCRFs are presented as queries in response to reporting of certain CV Medical Dictionary for Regulatory Activities (MedDRA) terms. The CV information should be recorded in the specific cardiovascular section of the eCRF within 1 week of receipt of a CV Event data query prompting its completion.

The death-related eCRF is provided immediately after the occurrence or outcome of death is reported. Initial and follow-up reports regarding death must be completed within 1 week of when the death is reported.

8.4.6. Adverse Events of Special Interest (AESIs)

Selected non-serious AEs and SAEs are also known as Adverse Events of Special Interest (AESI). Serious AESIs must be recorded as such on the eCRF and reported to the Sponsor within 24 hours of the Investigator becoming aware of them.

The AESIs for niraparib should be reported as follows:

- MDS or AML, along with other secondary cancers (new malignancies other than MDS or AML), should be reported to the Sponsor until death or loss to follow up.

9. STATISTICAL CONSIDERATIONS

ORR is the only endpoint for which a formal statistical test will be performed according to the Bayesian Optimal Phase 2 (BOP2) design, for all other endpoints the statistical analyses will be descriptive only.

Continuous data will be summarized for the overall population using descriptive statistics (number, mean, standard deviation [Std], minimum, median and maximum). Categorical data will be summarized by treatment group using frequency tables (number and percentage). Where appropriate 95% CI will be calculated and presented in addition to the point estimates.

9.1. Statistical Hypotheses

The primary efficacy endpoint ORR will be assessed using the BOP2 design (Zhou, Lee and Yuan, 2017). Based on historical data the expected ORR in this population is assumed to be at best 15% under standard of care (SOC). Niraparib would be considered promising in this population if an ORR=30% would be achieved. Therefore, if p_{eff} denotes the ORR, the null hypothesis is $H_0: p_{eff} \leq 0.15$, under which the treatment is deemed as not promising and unacceptable and the alternative hypothesis $H_1: p_{eff} \geq 0.3$, where the treatment is considered promising. These hypotheses will be tested at a one-sided α=0.025 with about 90% power.

9.2. Sample Size Determination

The primary efficacy endpoint ORR will be assessed using the Bayesian Optimal Phase 2 (BOP2) design (Zhou, Lee and Yuan, 2017). Specifically, let n denote the interim sample size and N denote the maximum sample size. Let p_{eff} denote the ORR and define the null hypothesis $H_0: p_{eff} \leq 0.15$, under which the treatment is deemed as not promising and unacceptable. The trial will stop enrolling participants and claim that the treatment is unacceptable if

$$Pr(p_{eff} > 0.15 | data) < \lambda \left(\frac{n}{N}\right)^{\alpha},$$

where λ =0.96 and α =1 are design parameters optimized to maximize power under the alternative hypothesis $H_1: p_{eff} = 0.3$, (i.e., the probability of correctly claiming that the treatment is acceptable under H_1), while controlling the type I error rate (i.e., the probability of incorrectly claiming that the treatment is acceptable under H_0) at 0.024. This optimization is performed assuming a vague prior Beta (0.15,0.85) for p_{eff}. The above decision rule leads to the following stopping boundaries and yields a statistical power of 0.932 under H_1 when 90 participants are included as evaluable participants for ORR described in Table 2.

Based on Table 2, the interim analysis will be performed when a total of 40 participants have completed their efficacy assessment on ORR. If 5 or less responders are observed in these 40 participants, the study could be stopped for futility. If 6 or more responders are observed among the 40 participants, the study could continue to enroll a total of 90 participants. At the end of the study the null hypothesis would be rejected and concluded that the treatment is promising if at least 21 responders are observed in the total of 90 participants; otherwise, it will be concluded that the treatment is not promising in the overall population. The go/no-go criteria in Table 2 are

non-binding. In order to achieve 90 evaluable participants a total of approximately 110 participants will be treated.

In Table 15 the operating characteristics of the design are presented for different response rates using the BOP2 web application (BOP2 V1.4.8.0), which is available at http://www.trialdesign.org.

Table 15. Operating characteristics

Scenario	Response Rate	Early Stopping (%)	Claim Promising (%)	Average Sample Size
1	0.150	43.25	2.36	68.4
2	0.175	27.60	9.53	76.2
3	0.200	16.13	24.68	81.9
4	0.225	8.69	46.04	85.7
5	0.250	4.33	67.53	87.8

9.3. Analysis Populations

- All Screened Population: all participants who signed the main study ICF to participate in the clinical study. Participants in this population will be used for screen failure summary.
- The Intent-to-Treat (ITT) Population: all participants who were enrolled in the study and who received at least one dose of study treatment. This population will be the secondary population for the analysis of efficacy data. Any participant who receives a treatment number will be considered to have been enrolled.
- The Response Evaluable Population: –all participants who received at least one dose of study treatment, who have an adequate baseline tumor assessment and at least one follow-up tumor assessment will be considered evaluable for anti-tumor efficacy using RECIST version 1.1 criteria. Participants who are treated and removed from study prior to on-study tumor assessment because of disease progression will be considered evaluable for efficacy and counted as failures. This population will be considered the primary population for the analysis of efficacy data.
- The Safety Population will consist of all participants who took at least 1 dose of study treatment.

9.4. Statistical Analyses

9.4.1. General Considerations

All statistical analysis will be performed using SAS® version 9.4 or later, unless otherwise stated.

Descriptive statistics (i.e., mean, standard deviation, median, minimum, maximum, etc.) will be provided for all continuous variables; frequencies and percentages will be tabulated for incidence and categorical variables and 95% CIs based on the Clopper-Pearson exact method provided as appropriate. For parameters measured over time, observed values and changes from baseline will be described for each time point. For time to event endpoints Kaplan-Meier estimates will be provided.

The study will be monitored on an ongoing basis to permit the early decision to proceed to the end of the study. The formal futility decision will be made at the pre-specified interim analysis with less than 6 responders out of 40 patients.

A Statistical Analysis Plan (SAP) describing statistical analyses in detail will be provided as a separate document. The SAP will be finalized prior to major analyses of the study.

9.4.2. Primary Endpoints

The primary endpoint ORR is defined as the proportion of participants with a confirmed CR or confirmed PR according to RECIST version 1.1 definitions, as assessed by the ICR. Confirmed responses are those that persist on repeat tumor assessments for at least 4 weeks after initial documentation of response. Otherwise, the participant will be counted as a non-responder in the assessment of ORR. The frequency and proportion of participants with ORR will be summarized for the response evaluable population as well as the safety population and 95% CI be calculated. Rates for CR and PR will also be presented in addition to ORR. As a secondary analysis the ORR based on non-confirmed responses will be presented as well.

- Sensitivity analyses for ORR will be defined in the SAP to account for intercurrent events which can affect the availability of data for the ORR analysis or affect the interpretation of the results.

9.4.3. Secondary Endpoints

The first secondary endpoint considered is DOR as assessed by ICR and is defined as the time from the first documentation of objective tumor response (CR or PR) that is subsequently confirmed to the first documentation of objective tumor progression or to death due to any cause, whichever occurs first. Participants with ongoing response will be censored at time of data cut-off for the analysis. Kaplan-Meier estimates will be provided along with 95% CIs for the median DOR. These analyses will be presented for the ICR assessments as well as the investigator assessments.

For other secondary endpoints measured as frequencies and percentages will be presented as well with 95% CIs for the response evaluable population as well as the safety population for the following endpoints:

- ORR as assessed by the investigator
- CBR as assessed by ICR and investigator, defined as CR+PR+SD at 6- and 12 months
- Intracranial response and control in participants with untreated measurable CNS lesions as assessed by ICR and investigator

PFS is defined as the time from the first dose to the first progression of disease (PD) or death for any reason in the absence of documented PD. PFS will be summarized in the safety analysis set. PFS data will be censored on the date of the last tumor assessment on study for participants who do not have objective tumor progression and who do not die while on study. Participants lacking an evaluation of tumor response after enrollment will have their PFS time censored on the date of first dose with a duration of 1 day. Participants who are treated and removed from study prior to on-study tumor assessment because of disease progression will be considered evaluable for efficacy and counted as an event at the time of progression. Additionally, participants who start a new anti-cancer therapy prior to documented PD will be censored at the date of the last tumor assessment prior to the start of the new therapy. PFS (in months) will be calculated as (date of progression or death − date of first dose +1)/30.4. PFS will be summarized for the response evaluable population as well as the safety population and 95% CI be calculated. This analysis will be performed separately based on ICR assessment as well as the investigator assessment. Kaplan-Meier estimates for PFS will be provided including median PFS, 6- and 12 months PFS together with 95% CIs.

Sensitivity analyses will be defined in the SAP to account for intercurrent events which can affect the availability of data for the PFS analysis or affect the interpretation of the results.

OS is defined as the time from the date of first dose of study medication to the date of death due to any cause. OS (in months) is calculated as (date of death − date of first dose +1)/30.4. For participants still alive at the time of the analysis, for those who are lost to follow-up, and those who withdraw consent for additional follow-up, the OS will be censored on the last date that participants were known to be alive. Participants lacking data beyond the first dose will have their OS censored at the date of first dose. Kaplan-Meier estimates for OS will be provided including median OS, 6- and 12 months OS together with 95% CIs.

9.4.4. Exploratory Endpoints

The changes from baseline in health-related quality of life (HRQoL) and symptoms as assessed by EORTC QLQ-C30 and EuroQol EQ-5D-3L will be analyzed for each timepoint by presenting descriptive statistics as mean, standard deviation, median, minimum, maximum.

Exploratory statistical analyses of Biomarkers will be defined in the SAP.

Niraparib plasma concentration-time data will be plotted and summarized (if appropriate) by planned time point. Niraparib plasma concentration-time data may be combined with data from other studies and analyzed using a population PK approach. Summary exposure measures (e.g., maximum concentration [Cmax], area under the concentration-time curve [AUC]) may also be

computed. Results of this analysis may be provided in a separate report. If deemed appropriate and if data permit, exposure-response relationships between niraparib exposure (e.g., dose, Cmax, or AUC) and clinical activity and/or toxicity (e.g., response, safety event, biomarkers) may be explored using population methods.

9.4.5. Safety Analyses

The safety analyses are described in Table 16. All safety analyses will be performed on the Safety Population.

Table 16. Statistical Analytical Methods - Safety

Endpoint	Statistical Analysis Methods
Secondary	AEs: All AEs, whether serious or non-serious, will be reported from the start of treatment until 30 days after the last dose of study treatment, until the participant withdraws consent for study participation, or until the participant starts subsequent anticancer treatment, whichever occurs first. AEs will be recorded using standard medical terminology and graded according to the NCI-CTCAE v5.0. For AE reporting, the verbatim term used in the eCRF by Investigators to identify AEs will be coded using the latest version of MedDRA coding dictionary. AEs and SAEs will be summarized by frequency and proportion of total participants, by system organ class and preferred term. Separate summaries will be given for all AEs, common (>5%) AEs, and AESIs. The incidence of deaths and the primary cause of death will be summarized. Additional summaries will be provided for treatment-related AEs and AEs leading to dose reduction, interruption, an/or discontinuation of study treatment. AEs, if listed in the NCI-CTCAE v5.0, will be summarized by the maximum grade. Clinical laboratory evaluation: The evaluation of clinical laboratory tests will focus on selected laboratory analytes from the hematology and blood chemistry panel and will include the toxicity grading by NCI-CTCAE. The worst-case toxicity grade in hematology and chemistry result during the treatment will be summarized Descriptive statistics (mean, standard deviation, median, range) will be used to summarize change from baseline in observed value at each scheduled visit. Other Safety Measures: Data for ECG and vital signs will be summarized. For continuous variables, these summaries will include sample size, mean, median, standard deviation, minimum, and maximum. These summary statistics will be provided for absolute values as well as change from baseline. For categorical variables, the summaries will include frequencies and corresponding percentages. Details will be provided in the SAP.

Abbreviations: AE=adverse event; AESI=adverse event of special interest; eCRF=electronic case report form; NCI-CTCAE v5.0=National Cancer Institute - Common Terminology Criteria for Adverse Events version 5.0; SAE=serious adverse event; SAP=Statistical Analysis Plan.
Abbreviations: cum.=cumulative; HR=hazard ratio; IA=interim analysis; OS=overall survival; PFS=progression-free survival.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

The Regulatory and ethical considerations of the study are outlined in Appendix 1.

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12. APPENDICES

Appendix 1. REGULATORY, ETHICAL, AND STUDY CONSIDERATIONS

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

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable ICH Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations
- The protocol, protocol amendments, ICFs, Investigator's Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will comply with health authority requirements.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC
  - Notifying the IRB/IEC of SAE or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

Financial Disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the participant and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent which meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant.

TEMPUS (alone or working with others) may use participant's coded study data and samples and other information to carry out this study, understand the results of this study, learn more about the study treatments or about the study disease, publish the results of these research efforts, and work with government agencies or insurers to have the study treatments approved for medical use or approved for payment coverage.

The ICF contains a section that addresses the use of participant data and remaining samples for further research, as approved by the IRB. The Investigator or authorized designee will inform each participant of the possibility of further research not related to the study/disease. In accordance with the IRB approved ICF, participants may be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. The participant's decision to participate in further research will be indicated in the ICF.

Sponsor will notify GSK in the event consent is withheld by a participant.

Data Protection

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier.
- The participant must be informed that his/her 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, who will be required to give consent for their data to be used as described in the informed consent.
- The participant must be informed that his/her 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.

Secondary Use of Biospecimens

Tempus (or people or companies working with Tempus) will store the biomarker and exploratory research samples in a secure storage space with adequate measures to protect confidentiality. The samples will be retained while research on niraparib (or drugs of this class) or this disease and related conditions continues but may be destroyed 20 years after study completion. Some portion of samples may remain after their use in the study. Tempus may use or direct use of these residual samples for secondary use, such as validation, bridging studies, and other purposes to the extent permitted by applicable law.

Reporting Product Complaints for GSK Products

Any written, electronic or oral communication that alleges dissatisfaction related to manufactured clinical drug product with regards to its manufacturing, testing, labeling, packaging, or shipping, must be reported by the Sponsor Institution or qualified designee to GSK within 1 working day of first becoming aware of the possible defect to [redacted]. The product and packaging components in question, if available, must be stored in a secure area under specified storage conditions until it is determined whether the product is required to be returned for investigation of the defect. If the product complaint is associated with an SAE, the SAE must be reported separately in accordance with the protocol, and the SAE report should mention the product quality complaint.

Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Quality tolerance limits (QTLs) will be predefined in the Study Manual to identify systematic issues that can impact participant safety and/or reliability of study results. These pre-defined parameters will be monitored during the study and deviations from the QTLs and remedial actions taken will be summarized in the CSR.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy including definition of study critical data items and processes (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data. Detailed information about the study data collection and management process, including systems used, can be found in the study Data Management Plan.

- The Sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations [CROs]).
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 25 years from the issue of the final CSR/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.

Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Study and Site Start and Closure

First Act of Recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first site open and will be the study start date.

Study/Site Termination

Tempus 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 Tempus. 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 treatment 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 of participants (evaluated after a reasonable amount of time) by the Investigator
- If the study is prematurely terminated or 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 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

Publication Policy

- Subject to the terms of the applicable study agreement, the results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor in accordance with the terms of the applicable study agreement. Review allows the Sponsor to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.

Appendix 2. Adverse Events, Serious Adverse Events and Pregnancies: Definitions and Procedures for Recording, Evaluating, Follow Up, and Reporting

Definition of Adverse Event (AE)

AE Definition
• An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study treatment, whether or not considered related to the study treatment. NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study treatment.
Definition of Unsolicited and Solicited AE
• An unsolicited AE is an AE that was not solicited using a Participant Diary and that is communicated by a participant/LAR(s) who has signed the informed consent. Unsolicited AEs include serious and non-serious AEs. • Potential unsolicited AEs may be medically attended (ie, symptoms or illnesses requiring a hospitalization, or emergency room visit, or visit to/by a health care provider). The participant/LAR(s) will be instructed to contact the site as soon as possible to report medically attended event(s), as well as any events that, though not medically attended, are of participant/LAR(s) concern. Detailed information about reported unsolicited AEs will be collected by qualified site personnel and documented in the participant's records. • Unsolicited AEs that are not medically attended nor perceived as a concern by participants/(LAR(s) will be collected during interview with the participant/LAR(s) and by review of available medical records at the next visit. • Solicited AEs are predefined local and systemic events for which the participant is specifically questioned, and which are noted by the participant in their diary.
Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, electrocardiogram, radiographical scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition, including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected intervention- intervention interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. 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.

Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of Treatment-Emergent Adverse Event (TEAE)

TEAE Definition

- A TEAE is defined as any new AE that begins, or any pre-existing condition that worsens in severity, after at least 1 dose of study treatment has been administered.

Definition of Serious Adverse Event (SAE)

An SAE is defined as any SAE that, at any dose:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are considered AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent or significant disability/incapacity The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Other situations: Medical or scientific judgment should be exercised by the Investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions, or development of intervention dependency or intervention abuse.

Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:
Investigators will be required to fill out the specific CV event page of the eCRF for the following AEs and SAEs: • Myocardial infarction/unstable angina • Congestive heart failure • Arrhythmias • Valvulopathy • Pulmonary hypertension • Cerebrovascular events/stroke and transient ischemic attack • Peripheral arterial thromboembolism • Deep venous thrombosis/pulmonary embolism • Revascularization

Recording and Follow-Up of AEs and SAEs

AE and SAE Recording
• When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g. hospital progress notes, laboratory, and diagnostics reports) related to the event. • The Investigator will then record all relevant AE/SAE information on the AE/SAE eCRF. • It is not acceptable for the Investigator to send photocopies of the participant's medical records to Sponsor/CROin lieu of completion of the Sponsor/CRO required form. • There may be instances when copies of medical records for certain cases are requested by Sponsor/CRO. In this case, all participant identifiers, except for the participant number, will be redacted on the copies of the medical records before submission to Sponsor/CRO. • The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Pregnancy Recording
• The primary mechanism for recording and reporting pregnancies will be done via the paper pregnancy notification and pregnancy follow-up forms and should be emailed to Sponsor/CRO. • Contacts for pregnancy reporting can be found in the Study Manual.
Assessment of Intensity
The severity of AEs will be graded according to National Cancer Institute-Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v5.0): 27 November 2017; National Institutes of Health (NIH). The NCI-CTCAE v5.0 severity Grades 1 through 5 provide unique clinical descriptions of severity of each AE. The NCI-CTCAE v5.0 is available on the NCI/NIH website.
Assessment of Causality
The Investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE. • A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. • The Investigator will use clinical judgment to determine the relationship. • Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated. • The Investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in his/her assessment. • For each AE/SAE, the Investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality. • There may be situations in which an SAE has occurred, and the Investigator has minimal information to include in the initial report to the Sponsor/CRO. However, it is very important that the Investigator always makes an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor/CRO. • The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment. • The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE
• The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor or delegate to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • New or updated information will be recorded in the originally submitted documents. • The Investigator will submit any updated SAE data to Sponsor/CRO within 24 hours of receipt of the information.

Reporting of SAE to GSK

SAEs and Pregnancy Reporting to GSK
• The primary mechanism for reporting SAEs to the Sponsor/CRO and GSK will be EDC. The Sponsor/CRO will report all SAEs to GSK within 1 business day of receipt from the site. • Any updated SAE data should be reported to GSK within 1 business day of receipt from site. • The primary mechanism for reporting pregnancies to the Sponsor/CRO and GSK will be via paper pregnancy notification and pregnancy follow-up forms. • The Sponsor/CRO will report all pregnancy notifications to GSK within 1 business day of first becoming aware of the pregnancy from the site by forwarding the completed paper pregnancy notification form. • The Sponsor/CRO will report all pregnancies outcomes to GSK within 1 business day of first becoming aware of the pregnancy outcome from the site by forwarding the completed paper pregnancy follow-up form. • Any follow-up questions from GSK will be directed to Sponsor/CRO. • Contacts for SAE reporting can be found in the Study Manual.

Appendix 3. CONTRACEPTION GUIDELINES

Definitions

A woman in either of the following categories is considered a woman of childbearing potential (WOCBP) (fertile):

1. Following menarche
2. From the time of menarche until becoming post-menopausal unless permanently sterile (see below)

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 hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
- Females on HRT and whose menopausal status is in doubt will be required to use one 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.

Permanent sterilization methods (for the purpose of this study) include:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), Investigator discretion should be applied to determining study entry.

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of study treatment, additional evaluation should be considered.

Contraception Guidance

Table 17. 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.)*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
• IUD
• IUS[c]
• 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 woman of childbearing potential 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.
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 – intravaginal – transdermal – injectable
• Progestogen-only hormone 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: CTFG=Clinical Trial Facilitation Group; IUD=intrauterine device; IUS=intrauterine hormone-releasing system; LAM=lactational amenorrhea method.
Note: Periodic abstinence (calendar, sympto-thermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and LAM are not acceptable methods of contraception for this study. Male condom and female condom should not be used together (due to risk of failure with friction).
[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] Male condoms must be used in addition to hormonal contraception. If locally required, in accordance with CTFG guidelines, acceptable contraceptive methods are limited to those that inhibit ovulation as the primary mode of action.

Appendix 4. LIVER SAFETY REQUIRED ACTIONS AND FOLLOW-UP ASSESSMENTS

Phase III to IV liver chemistry stopping, and increased monitoring criteria have been designed to assure participant safety and evaluate liver event etiology (in alignment with the United States Food and Drug Administration's premarketing clinical liver safety guidance: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf).

Table 18. Phase III-IV Liver Chemistry Stopping Criteria and Required Follow-up Assessments

Liver Chemistry Stopping Criteria –Liver Stopping Event Participant with entry criteria ALT≤2.5×ULN	
ALT-absolute	ALT ≥8×ULN
ALT Increase	ALT ≥5×ULN but <8×ULN persists for ≥2 weeks ALT ≥3×ULN but <5×ULN persists for ≥4 weeks
Bilirubin[a,b]	ALT ≥3×ULN and bilirubin ≥2×ULN (>35% direct bilirubin)
INR[b]	ALT ≥3×ULN and INR >1.5, if INR measured
Cannot Monitor	ALT ≥5×ULN but <8×ULN and cannot be monitored weekly for ≥2 weeks ALT ≥3×ULN but <5×ULN and cannot be monitored weekly for ≥4 weeks
Symptomatic[c]	ALT ≥3×ULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity
Liver Chemistry Stopping Criteria – Liver Stopping Event Including participants with documented liver metastases/tumor infiltration at baseline and entry criteria ALT>2.5×ULN but ≤5×ULN	
ALT-absolute	Both ALT ≥8×ULN and ≥2×baseline value
ALT Increase	Both ALT ≥3×ULN and ≥1.5×baseline value that persists for ≥4 weeks
Bilirubin[a,b]	ALT ≥3×ULN and bilirubin ≥2×ULN (>35% direct bilirubin)
INR[b]	ALT ≥3×ULN and INR >1.5, if INR measured
Cannot Monitor	Both ALT ≥3×ULN and ≥1.5×baseline value and cannot be monitored weekly for ≥4 weeks
Symptomatic[c]	Both ALT ≥3×ULN and ≥1.5×baseline value associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

Table 19. Phase III-IV Liver Chemistry Stopping Criteria and Required Follow-up Assessments (Continued)

Required Actions and Follow up Assessments following Any Liver Stopping Event	
Actions	Follow Up Assessments
• Immediately discontinue study treatment • Report the event to Sponsor within 24 hours • Complete the liver event eCRF and complete an SAE data collection tool if the event also meets the criteria for an SAE[b] • Perform liver event follow up assessments • Monitor the participant until liver chemistries resolve, stabilize, or return to within baseline (see MONITORING below) • Do not restart/rechallenge participant with study treatment unless allowed per protocol and GSK Medical Governance approval is granted • If restart/rechallenge not allowed or not granted, permanently discontinue study treatment and may continue participant in the study for any protocol specified follow up assessments MONITORING: For bilirubin or INR criteria: • Repeat liver chemistries (include ALT, AST, ALP, bilirubin) and perform liver event follow up assessments within 24 hours • Monitor participants twice weekly until liver chemistries resolve, stabilize, or return to within baseline • A specialist or hepatology consultation is recommended For all other criteria: • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within 24 to 72 hours • Monitor participants weekly until liver chemistries resolve, stabilize, or return to within baseline	• Viral hepatitis serology[d] • Only in those with underlying chronic hepatitis B at study entry (identified by positive hepatitis B surface antigen) quantitative hepatitis B DNA and hepatitis delta antibody[e] • Blood sample for PK analysis, obtained within 3 hours (±15 minutes) after last dose[f] • Serum CPK and LDH • Fractionate bilirubin, if total bilirubin ≥2×ULN • Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form • Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications. • Record alcohol use on the liver event alcohol intake case report form For bilirubin or INR criteria: • Antinuclear antibody, antismooth muscle antibody, Type 1 antiliver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins). • Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week (James, 2009)). • Liver imaging (ultrasound, MRI, or CT) and/or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy eCRF forms.

Abbreviations: AE=adverse event; ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; CPK=serum creatine phosphokinase; eCRF=electronic case report form; CT=computed tomography; GSK=GlaxoSmithKline; HPLC=high performance liquid chromatography; IgG=immunoglobulin G; IgM=immunoglobulin M; INR=international normalized ratio; LDH=lactate dehydrogenase; MRI=magnetic resonance imaging; PCR=polymerase chain reaction; PK=pharmacokinetics; SAE=serious adverse event; SM=Study Manual; ULN=upper limit of normal.
a Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that participant if ALT ≥3×ULN and bilirubin ≥2×ULN. Additionally, if serum bilirubin fractionation testing is unavailable, record presence of detectable urinary bilirubin on dipstick, indicating direct bilirubin elevations and suggesting liver injury.
b All events of ALT ≥3×ULN and bilirubin ≥2×ULN (>35% direct bilirubin) or ALT ≥3×ULN and INR>1.5, if INR measured, which may indicate severe liver injury (possible “Hy’s Law”), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis); INR measurement is not required, and the threshold value stated will not apply to participants receiving anticoagulants.
c New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash, or eosinophilia).
d Includes: Hepatitis A IgM antibody, hepatitis B surface antigen, hepatitis B core antibody (IgM), hepatitis C RNA, cytomegalovirus IgM antibody, Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing), and hepatitis E IgM antibody.
e If hepatitis delta antibody assay cannot be performed, it can be replaced with a PCR assay of hepatitis D RNA virus (where needed) (Le Gal, 2005).
f Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the participant’s best approximation. If the date/time of the last dose cannot be approximated or a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM.

Table 20. Phase III-IV Liver Chemistry Increased Monitoring Criteria with Continued Therapy

Liver Chemistry Increased Monitoring Criteria – Liver Monitoring Event	
Criteria	Actions
Participant with entry criteria ALT≤2.5×ULN: ALT ≥5×ULN and <8×ULN and bilirubin <2×ULN without symptoms believed to be related to liver injury or hypersensitivity, and who can be monitored weekly for 2 weeks or ALT ≥3×ULN and <5×ULN and bilirubin <2×ULN without symptoms believed to be related to liver injury or hypersensitivity, and who can be monitored weekly for 4 weeks Participant with documented liver metastases/tumor infiltration at baseline AND entry criteria ALT >2.5×ULN but ≤5×ULN: ALT ≥3×ULN and ≥1.5×baseline value but ALT <8×ULN and 2×baseline value and bilirubin <2×ULN without symptoms believed to be related to liver injury or hypersensitivity, and who can be monitored weekly for 4 weeks	Notify the GSK medical monitor within 24 hours of learning of the abnormality to discuss participant safety Participant can continue study treatment Participant must return weekly for repeat liver chemistries (ALT, AST, ALP, bilirubin) until they resolve, stabilize or return to within baseline[a] If at any time participant meets the liver chemistry stopping criteria, proceed as described above For participant with entry criteria ALT≤2.5×ULN: If ALT decreases from ALT ≥5×ULN and <8×ULN to ≥3×ULN but <5×ULN, continue to monitor liver chemistries weekly If, after 4 weeks of monitoring, ALT <3×ULN and bilirubin <2×ULN, monitor participants twice monthly until liver chemistries normalize or return to within baseline For participants with documented liver metastases/tumor infiltration at baseline and entry criteria ALT >2.5×ULN but ≤5×ULN: If, after 4 weeks of monitoring, ALT <3×ULN and <1.5× baseline value, and bilirubin <2×ULN, monitor participants twice monthly until liver chemistries normalize or return to within baseline[a]

Abbreviations: ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; GSK=GlaxoSmithKline; ULN=upper limit of normal.

[a] For the purpose of these guidelines, "baseline" refers to laboratory assessments performed closest and prior to first dose of study treatment.

Appendix 5. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

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

Table 21. Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
β-hCG	beta-human chorionic gonadotropin
AE	adverse event
AESI	adverse event of special interest
AJCC	American Joint Committee on Cancer
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AML	acute myeloid leukemia
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ICR	independent central review
IgG	immunoglobulin G
IgM	immunoglobulin M
BM	brain metastases
BOP2	Bayesian Optimal Phase 2
BP	blood pressure
BRCA	breast cancer susceptibility gene
BUN	blood urea nitrogen
CBC	complete blood count
CI	confidence interval
CL_{Cr}	creatinine clearance
CNS	central nervous system
CO2	carbon dioxide
CPK	serum creatine phosphokinase
CR	complete response
CRF	case report form
CRO	Contract Research Organization
CSR	Clinical Study Report
CT	computed tomography

CTCAE	Common Terminology Criteria for Adverse Events
CV	cardiovascular event
CYP	cytochrome P450
DOR	duration of response
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire 30-item Core module
EOT	End-of-Treatment
EQ-5D-3L	European Quality of Life 5-Dimensions 3-Level Scale
EU	European Union
FDA	(United States) Food and Drug Administration
FFPE	formalin-fixed, paraffin-embedded
FT4	free thyroxine
GCP	Good Clinical Practice
GSK	GlaxoSmithKline
HR	hazard ratio
HRD (pos)	homologous recombination deficiency (positive)
HRQoL	health-related quality of life
HPLC	high performance liquid chromatography
IA	interim analysis
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IgG4	immunoglobulin G4
IMP	investigational medicinal product
INR	international normalized ratio
IRB	Institutional Review Board
ITT	Intent-to-Treat
IV	intravenous
LDH	lactate dehydrogenase
mAb	monoclonal antibody
MDS	myelodysplastic syndrome

MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
NA	not applicable
NCCN	National Comprehensive Cancer Network
NCI-CTCAE	National Cancer Institute - Common Terminology Criteria for Adverse Events
NGS	Next Generation Sequencing
ORR	objective response rate
OS	overall survival
PARP	poly (adenosine diphosphate-ribose) polymerase
PALB2	partner and localizer of BRCA2
PCR	polymerase chain reaction
PD	progressive disease
PK	pharmacokinetics
PFS	progression-free survival
PR	partial response
PRES	Posterior Reversible Encephalopathy Syndrome
PRO	patient-reported outcome
PRO-CTCAE	Patient-Reported Outcomes version of the Common Term Criteria for Adverse Events
PT	prothrombin time
PTT	partial thromboplastin time
QoL	quality of life
RECIST v1.1	Response Evaluation Criteria in Solid Tumors version 1.1
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	stable disease
SM	Study Manual
SoA	Schedule of Activities
SOP	standard operating procedure
TEAE	treatment-emergent adverse event
tPALB2	tumor partner and localizer of BRCA2
TTP	time to progression
ULN	upper limit of normal

US	United States
WBC	white blood count
WOCBP	woman of childbearing potential

Appendix 6. RESPONSE EVALUATION CRITERIA IN SOLID TUMORS V1.1

Response Criteria by RECIST v1.1

Evaluation of Target Lesions

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

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

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

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Not Applicable (NA): No target lesions at baseline.

Not Evaluable (NE): Cannot be classified by one of the 5 preceding definitions.

Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Non-CR/Non-PD: Persistence of 1 or more non-target lesion(s).

Progressive Disease (PD): Appearance of 1 or more new lesions and/or unequivocal progression of existing non-target lesions. A modest ‘increase’ in the size of one or more non-target lesions is usually not sufficient to quality for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

NA: No non-target lesions at baseline.

NE: Cannot be classified by one of the 5 preceding definitions.

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression (taking as reference for PD the smallest measurements recorded since the treatment started). The participant's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Table 22. Evaluation of Response for Participants with Measurable Disease (ie, Target Disease)

Target Lesions	Non-Target Lesions	New Lesions[a]	Overall Response	Best Overall Response when Confirmation is Required
CR	CR or NA	No	CR	>4 weeks confirmation[b]
CR	Non-CR/Non-PD or NE	No	PR	>4 weeks confirmation[b]
CR	NE	No	PR	
PR	Non-CR/Non-PD/NE	No	PR	
SD	Non-CR/Non-PD/NE	No	SD	Documented at least once >4 weeks from baseline[b]
NE	Non-CR/Non-PD or NA	No	NE	
PD	Any	Yes or No	PD	No prior SD, PR, or CR
Any	PD	Yes or No	PD	
Any	Any	Yes	PD	

Abbreviations: CR=complete response; NA=not applicable; NE=not evaluable; PD=progressive disease; PR=partial response; RECIST v1.1=Response Evaluation Criteria in Solid Tumors version 1.1; SD=stable disease.
Note: Participants who are CR following standard of care induction treatment (at baseline) will be assigned a status of "no disease" or "NA," and evidence of any new lesion at a follow-up time point will constitute PD. 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 manuscript for further details on what is evidence of a new lesion.
[b] Only for non-randomized studies with response as primary endpoint.

Table 23. Evaluation of Response for Participants with Non-Measurable Disease (ie, Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
NE	No	not evaluated

Unequivocal PD	Yes or No	PD
Any	Yes	PD

Abbreviations: CR=complete response; NE=not evaluable; PD=progressive disease; SD=stable disease.
[a] "Non-CR/non-PD" is preferred over "stable disease" for non-target 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.

Duration of Response (DOR)

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or PD is objectively documented (taking as reference for PD the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that PD is objectively documented.

Appendix 7. PATIENT-REPORTED OUTCOMES

EORTC QLQ-C30

The EORTC QLQ-C30 was developed to assess the quality of life of patients with cancer, and it is the most widely used cancer-specific, health-related quality of life (HRQoL) instrument.

The EORTC QLQ-C30 is a 30-item questionnaire used to measure HRQoL in participants with cancer; it has been translated and validated in over 100 languages and has been used in more than 3,000 studies worldwide (http://groups.eortc.be/qol/eortc-qlq-c30). The EORTC QLQ-C30 is composed of both multi-item scales and single-item measures. These include 5 functional scales (Physical functioning, Role functioning, Emotional functioning, Cognitive functioning, and Social functioning), 3 symptom scales (Fatigue, Nausea and vomiting, and Pain), 6 single items (Dyspnea, Insomnia, Appetite loss, Constipation, Diarrhea, and Financial difficulties), and a global health status/HRQoL scale. The EORTC QLQ-C30 employs a 1-week recall period for all items and a 4-point scale for the functional and symptom scales/items with response categories of “Not at all,” “A little,” “Quite a bit,” and “Very much.” The 2 items assessing global health status/quality of life utilize a 7-point scale ranging from 1 (“Very Poor”) to 7 (“Excellent”) (Aaronson, 1993).

EuroQol Questionnaire (EQ-5D-3L)

The EQ-5D-3L is a standardized instrument for use as a measure of health utility. It is designed for self-completion or interview administration and is cognitively simple, taking only a few minutes to complete.

The EQ-5D-3L self-assessment questionnaire has 2 parts. The first part consists of 5 items covering 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Each dimension is measured by a 3-point Likert scale (no problems, some or moderate problems, and unable or extreme problems). Participants are asked to choose one level that reflects their "own health state today" for each of the 5 dimensions. Participants can be then classified into 1 of 243 distinct health states. The second part is a 20-cm visual analogue scale (EQ-VAS) that has endpoints labelled "best imaginable health state" and "worst imaginable health state" anchored at 100 and 0, respectively.

The EQ-5D-3L will provide data for use in economic models and analyses including developing health utilities or quality-adjusted life-years. The EQ-5D-3L will be completed by participants last after completing all other PRO assessments.

Appendix 8. EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS

Table 24. ECOG Performance Status Grading

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 (ie, 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
Dead	5

Source: (Oken, 1982)
Abbreviation: ECOG=Eastern Cooperative Oncology Group.

Appendix 9. ESTIMATION OF CREATININE CLEARANCE WITH THE COCKCROFT-GAULT FORMULA

The Cockcroft-Gault formula is a commonly used equation for calculating estimated creatinine clearance (CL_{Cr}) and employs creatinine measurements and a participant's weight (in kilograms) to predict the clearance (Cockcroft, 1976). As estimated by the Cockcroft-Gault equation, mild renal impairment is considered CLCr of 60 to 89 mL/min and moderate renal impairment is considered CL_{Cr} of 30 to 59 mL/min.

Table 25. Cockcroft-Gault Formula for Serum Creatinine Clearance

Serum Creatinine Units	Formula
mmol/L	(Q × (140 - age [years]) × actual body weight [kg][a]) ÷ (48816 × serum creatinine [mmol/L])
mg/dL	(Q × (140 - age [years]) × actual body weight [kg][a]) ÷ (72 × serum creatinine [mg/dL])

Note: Q=0.85 for females, Q=1.0 for males.
[a] Calculation of ideal body weight using the Devine formula (McCarron, 1974) as follows:
Male participants: 50.0 kg + (2.3 kg × each inch over 5 feet) or 50.0 kg + (0.906 kg × each cm over 152.4 cm)

Female participants: 45.5 kg + (2.3 kg × each inch over 5 feet) or 45.5 kg + (0.906 kg X each cm over 152.4 cm)

If a participant is below ideal body weight, use actual body weight in the calculation to estimate CL_{Cr}.

If a participant is obese (>30% over ideal body weight), use ideal body weight in the calculation to estimate CL_{Cr}. For example, for a male participant with actual body weight of 90.0 kg and height of 68 inches, the calculation is as follows:

Ideal body weight=50.0 kg + (2.3 kg × (68 - 60))=68.4 kg

This participant's actual body weight is >30% over ideal body weight. In this case, the participant's ideal body weight of 68.4 kg should be used in calculating estimated CL_{Cr}.

Appendix 10. DOSAGE ADJUSTMENTS FOR ADVERSE REACTIONS

Table 26. Recommended Dose Modifications for Adverse Reactions

Starting Dose Level	200 mg	300 mg
First dose reduction	100 mg/day[a] (one 100-mg capsule)	200 mg/day (two 100-mg capsules)
Second dose reduction	Discontinue niraparib.	100 mg/day[a] (one 100-mg capsule)

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

Table 27. Dose Modifications for Non-Hematologic Adverse Reactions

Non-hematologic CTCAE ≥Grade 3 adverse reaction that persists despite medical management	• Withhold niraparib for a maximum of 28 days or until resolution of adverse reaction. • Resume niraparib at a reduced dose per Table 26.
CTCAE ≥Grade 3 treatment-related adverse reaction lasting more than 28 days while patient is administered niraparib 100 mg/day	Discontinue niraparib.

CTCAE = Common Terminology Criteria for Adverse Events.

Table 28. Dose Modifications for Hematologic Adverse Reactions

Monitor complete blood counts weekly for the first month, monthly for the next 11 months of treatment, and periodically after this time.	
Platelet count <100,000/mcL	First occurrence: • Withhold niraparib for a maximum of 28 days and monitor blood counts weekly until platelet counts return to ≥100,000/mcL. • Resume niraparib at same or reduced dose per Table 26. • If platelet count is <75,000/mcL, resume at a reduced dose. Second occurrence: • Withhold niraparib for a maximum of 28 days and monitor blood counts weekly until platelet counts return to ≥100,000/mcL. • Resume niraparib at a reduced dose per Table 26. • Discontinue niraparib if the platelet count has not returned to acceptable levels within 28 days of the dose interruption period or if the patient has already undergone dose reduction to 100 mg once daily.[a]
Neutrophil <1,000/mcL or hemoglobin <8 g/dL	• Withhold niraparib for a maximum of 28 days and monitor blood counts weekly until neutrophil counts return to ≥1,500/mcL or hemoglobin returns to ≥9 g/dL. • Resume niraparib at a reduced dose per Table 26. • Discontinue niraparib if neutrophils and/or hemoglobin have not returned to acceptable levels within 28 days of the dose interruption period or if the patient has already undergone dose reduction to 100 mg once daily.[a]

Hematologic adverse reaction requiring transfusion	• For patients with platelet count ≤10,000/mcL, platelet transfusion should be considered. If there are other risk factors such as coadministration of anticoagulation or antiplatelet drugs, consider interrupting these drugs and/or transfusion at a higher platelet count. • Resume niraparib at a reduced dose.

[a] If myelodysplastic syndrome or acute myeloid leukemia (MDS/AML) is confirmed, discontinue niraparib.