TITLE PAGE

Protocol Title:	A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study Comparing Niraparib Plus Pembrolizumab Versus Placebo Plus Pembrolizumab as Maintenance Therapy in Participants Whose Disease has Remained Stable or Responded to First-Line Platinum-Based Chemotherapy with Pembrolizumab for Stage IIIB/IIIC or IV Non-Small Cell Lung Cancer (ZEAL-1L)
Protocol Number:	213400 / Amendment 05
Compound Name:	Niraparib (GSK3985771)
Brief Title:	Placebo-controlled Study Comparing Niraparib Plus Pembrolizumab Versus Placebo Plus Pembrolizumab as Maintenance Therapy in Participants with Advanced/Metastatic Non-Small Cell Lung Cancer
Study Phase:	Phase 3
Sponsor Name and Legal Registered Address:	GlaxoSmithKline Research & Development Limited 980 Great West Road Brentford Middlesex, TW8 9GS UK
Sponsor Signatory:	Gavin Chiu, MD Medical Director, Oncology Clinical Development, GSK
Medical Monitor Name and Contact Information:	PPD PPD PPD
Regulatory Agency Identification Numbers:	IND Number 134,426 EudraCT Number 2020-002202-20 EU CT number: 2023-508443-40
Approval Date:	06 Nov 2024

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Table 1: Document History

Document	Date	Document Number
Amendment 05	06 Nov 2024	TMF-19100280
Amendment 04 EU-1	05 August 2024	TMF-19637278
Amendment 04	12 January 2023	TMF-14939396
Amendment 03	08 December 2021	TMF-13996966
Amendment 02	16 March 2021	TMF-11871953
Amendment 01	01 December 2020	2020N436270_01
Original Protocol (Version 1.0)	13 May 2020	2020N436270_00

Amendment 05 (06 Nov 2024)

Overall Rationale for the Amendment

Amendment 05 is a global amendment to CCI [redacted]
Other changes in management of participants and clarifications in study conduct are also included, as well as minor editorial and typographical changes as part of this amendment.

A general description of the key changes in the protocol and brief rationales for the changes are provided in Table 2 below. Where applicable, the synopsis was updated to align with the changes in the main protocol body.

Table 2: Summary of Changes for Amendment 05

Section(s) Affected	Description of Change	Brief Rationale
Headers, title page, abbreviations, Protocol Amendment Summary of Changes, List of Abbreviations and Definitions of Terms, References, and throughout	Headers and title page were updates with new document number and amendment information; Protocol Amendment Summary of Changes section was updated to include rationale for this amendment (previous changes moved to Appendix); editorial revisions for administrative changes, consistency with Sponsor's ways of working, template, definitions included, minor corrections and formatting adjustments, and to add clarifications and remove discrepancies.	Editorial and administrative changes to align with the Sponsor's standard protocol template, style guide and ways of working, and for accuracy, clarify, conformity, flow, consistency between synopsis and main protocol text (as necessary), and typographical error correction.

Section(s) Affected	Description of Change	Brief Rationale
1.2 Schemas, Figure 1A 2.4 Rationale for Current Study 3. Study Objectives and Endpoints 8.1.1. Primary Efficacy Endpoints 8.1.2.1 PFS in the ITT Population 8.1.2.2. OS in the CR/PR Population and in the ITT Population 8.1.3.4. Patient Reported Outcomes 9.1. Statistical Hypotheses (including Figure 4 update) 9.2. Sample Size Determination 9.3. Analysis Populations, Table 15 9.4.2. Primary Endpoints 9.4.3. Secondary Endpoints 9.4.3.1. Key secondary Endpoints 9.4.3.2. Other Secondary Endpoints 9.4.4. Exploratory Endpoints 9.5. Analysis Timing Appendix 10. PFS Event and Censoring Rules, Table 26	CCI • Some additional text added to rationale for the study.	CCI

Section(s) Affected	Description of Change	Brief Rationale
1.3. Schedule of Activities (SoA), Table 3 footnote 4.1. Overall Design 6.2.3.1. Niraparib/Placebo 6.2.3.2. Pembrolizumab 7.1. Discontinuation from Study Treatment 8.1.1.1. Radiographic Evaluation of Tumor Response, Table 12 9.4.4. Exploratory Endpoints Appendix 10. PFS Event and Censoring Rules, Table 26 (footnote)	• Previously permitted pembrolizumab administration past 35 cycles, adjusted throughout indicating this may no longer be permitted. • Adjusted text surrounding visit frequency post-35 cycles for those only on niraparib/placebo, including text surrounding niraparib dispensing following discontinuation of pembrolizumab; with footnote addition to Table 3. • Added wording surrounding imaging for those in follow-up who reach 35 cycles and continue pembrolizumab alone and clarification added for PFS exploratory endpoints regarding subsequent anticancer therapy for these participants.	Clarification that participants may no longer be approved for >35 cycles of pembrolizumab to mitigate potential study integrity risk due to potential imbalance of extended pembrolizumab used between active and control arms. Clarification included for those that discontinue pembrolizumab treatment and handling and frequency of visits for those continuing only on niraparib to reduce patient visit burden.
4.1. Overall Design 4.5. End of Study 6.3.2. Blinding and Breaking the Blind 6.7. Continued access to study intervention after the end of the study	• Updated proportion of participants needed for survival follow-up prior to end of study to align with approximate proportion from statistical assumptions/projections and final analysis. • Clarifications and section added regarding access to treatment post-end of study including details for unblinding of participants post-final analysis and management of participants until end of study is reached.	Survival approximation updated in line with statistical projections for final analysis. Details included regarding participants access to treatment after the end of study in alignment with Sponsor template and study requirements.
6.1. Study Treatment(s) Administered (Table 9)	• Updated table to align with Sponsor template and regulatory requirements for IMPs/non-IMPs and alignment/clarifications added to remaining text.	Clarification to align with regulatory requirements.
1.3. Schedule of Activities (SoA) (footnote) 7.3. Participant Discontinuation/Withdrawal from the Study 7.4. Lost to Follow-up	• Survival follow-up language updated	Clarification to align with Sponsor's templated protocol language.
7.1.1. Liver Chemistry Stopping Criteria 7.1.2. Rechallenge	• Updated liver chemistry stopping criteria figures • Added section on rechallenge indicating it is not permitted in this study.	Updated to align with Sponsor template and requirements for liver safety monitoring for this study to date.
8.2.6. Laboratory Assessments, Table 13	• Footnote added regarding PT/INR not required for NOAC.	To relieve participant burden and perform blood tests in alignment with current literature/recommendation for non-Vitamin K NOACs [Salmonson, 2017].

Section(s) Affected	Description of Change	Brief Rationale
8.1.5. Patient-Reported Outcome Measures 8.3.2. Method of Detecting AEs and SAEs	• Text adding regarding free-text fields in questionnaires are not reviewed as safety data and should not be used to report AEs.	Clarification for study conduct that freely reported symptoms on PRO-CTCAE are being provided to GSK for information on tolerability of the drug, and are not being reviewed by study staff as safety data for AE reporting.
8.3.8. Participant Card	• Added details regarding participant card used in the study.	To align with template and align with expected conduct during the study.
8.3.4. Regulatory Reporting Requirements for SAEs Appendix 1: Regulatory, Ethical, and Study Considerations Appendix 2: Adverse Events and Serious Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting Appendix 3: Contraceptive Guidelines Appendix 12: Country-specific Requirements (new)	• Additional changes per template to align with required Sponsor template updates, including suspected unexpected serious adverse reactions (SUSAR) statement, informed consent process, recruitment strategy, data protection, committees structure, dissemination of clinical study data, data quality assurance, source documents, site termination • Additional definitions and reporting details included for AE/SAEs • Definitions updated in contraceptive guidelines. • New appendix outlining specific requirements for certain countries/regions	Alignment with Sponsor template, including addition of regulatory requirements, and new appendix to consolidate country-regional-specific requirements in the global protocol.
Appendix 7: Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM)	• Separate subsection added for new lesions and minor text edits. • Footnote added to Table 24	Clarifications and correction as new lesions information erroneously included under non-target lesion section.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1. PROTOCOL SUMMARY

1.1. Synopsis

Name of Sponsor/Company: GlaxoSmithKline Research & Development Limited

Name of Investigational Product: Niraparib and pembrolizumab

Name of Active Ingredient: Niraparib and pembrolizumab

Title of Study: A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study Comparing Niraparib Plus Pembrolizumab Versus Placebo Plus Pembrolizumab as Maintenance Therapy in Participants Whose Disease has Remained Stable or Responded to First-Line Platinum-Based Chemotherapy with Pembrolizumab for Stage IIIB/IIIC or IV Non-Small Cell Lung Cancer (213400; ZEAL1L)

Study Center(s): Multicenter

Planned Duration (Projected):	**Phase of development:**
Estimated date first participant enrolled: Q3 2020 CCI [redacted]	Phase 3

Objectives:

Primary Objective:

- To compare progression-free survival (PFS) as assessed by Blinded Independent Central Review (BICR) using Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) of niraparib plus pembrolizumab versus placebo plus pembrolizumab as maintenance therapy in best response to standard of care (SoC) induction chemotherapy with complete and partial response (CR/PR) Population

Key Secondary Objectives:

- To compare PFS as assessed by BICR using RECIST v1.1 of niraparib plus pembrolizumab versus placebo plus pembrolizumab as maintenance therapy in the ITT Population
- To compare overall survival (OS) of niraparib plus pembrolizumab versus placebo plus pembrolizumab as maintenance therapy in the best response to SoC induction chemotherapy with CR/PR Population
- To compare OS of niraparib plus pembrolizumab versus placebo plus pembrolizumab as maintenance therapy in the overall population

CCI [redacted]

Secondary Objectives:

- To evaluate PFS as assessed by the Investigator using RECIST v1.1
- To evaluate CNS-PFS as assessed by BICR using RANO-BM
- To evaluate PFS as assessed by BICR using RECIST v1.1 and OS by programmed cell death-ligand 1 (PD-L1) status (PD-L1 tumor cells [TCs] <1% versus ≥1%)

- To evaluate and compare time to deterioration (TTD) in lung symptoms, defined as time from randomization to meaningful deterioration on single and composite endpoints of dyspnea, chest pain, and cough, from the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire 13-item lung cancer-specific module (EORTC QLQ-LC13)
- To evaluate changes from baseline in health-related quality of life (HRQoL), functioning, and symptoms as assessed by the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire 30-item Core module (EORTC QLQ-C30) and the EORTC QLQ-LC13 total and domain scores
- To evaluate safety and tolerability in participants treated with niraparib plus pembrolizumab compared to placebo plus pembrolizumab
- To describe the exposure of niraparib when given in combination with pembrolizumab

CCI

[redacted]

Methodology:

This is a multicenter, randomized, double-blind, placebo-controlled study of niraparib plus pembrolizumab versus placebo plus pembrolizumab in participants with advanced or

metastatic non-small cell lung cancer (NSCLC) who have stable disease (SD), partial response (PR), or complete response (CR) following completion of standard of care (SoC) first-line (1L) platinum-based induction chemotherapy with pembrolizumab.

In order to be a candidate for this study, participants must have SD, PR, or CR, as assessed by the Investigator per RECIST v1.1 criteria, following 4 to 6 cycles of induction treatment. To support the transition from 1L induction to 1L maintenance therapy, a transition period that is 6 weeks, in duration, starting from the last dose of 1L induction therapy should occur (up to 7 weeks may be permitted with Sponsor approval). This transition period allows for recovery from chemotherapy-related hematological toxicity before initiating treatment with niraparib/placebo. During this transition period, pembrolizumab administration in the absence of chemotherapy should occur in the cycle immediately following the last cycle of 1L induction therapy (ie, 21 [±3] days after the last cycle of induction). If a transition period with administration of pembrolizumab only is not in accordance with standard prescribing directions and/or a pembrolizumab dose delay is needed that is greater than 3 weeks then the delay must be discussed with the Sponsor and reasons for the delay should be documented in the eCRF.

In addition, a tumor specimen must be submitted for central PD-L1 testing and stratification. Tumor specimen collected prior to initiating cytotoxic or radiation therapy (ie, tumor specimen collected at the time of diagnosis) is preferred. If available, a formalin-fixed, paraffin-embedded (FFPE) tissue block should be provided; if not available, freshly cut, unstained slides (<30 days from the date of sectioning) are acceptable. Participants whose submitted tissue for PD-L1 status that were not done by the study's central laboratory because the submitted tissue is not evaluable or any other reason may be eligible to participate in the study and will be stratified to the PD-L1 staining in TCs (TC <1%/Not Evaluable [NE]) group. Information on oncologic surgery, induction therapy and regimen, any changes to treatment and regimen, and histology at diagnosis/staging will be collected CCI [redacted]

Participants who have achieved SD, PR, or CR following SoC induction treatment and who meet all eligibility criteria will be randomized in a 1:1 ratio to receive niraparib plus pembrolizumab or placebo plus pembrolizumab as maintenance therapy. The proportion of participants with SD will be carefully monitored at the time of randomization, and a cap will be applied at SD enrollment threshold of 50% of total sample size to prevent the proportion of participants entering the study to differ significantly from the proportions observed in the KEYNOTE-189 and KEYNOTE-407 studies (approximately 35% to 40%) [Gadgeel, 2020; Paz-Ares, 2018].

Participants will continue to receive their assigned treatment until radiographic progressive disease (PD) is documented per RECIST v1.1 and verified by BICR, unacceptable toxicity, death, withdrawal of consent, or becoming lost to follow-up, whichever comes first.

Treatment with pembrolizumab will continue for up to a total maximum of 35 cycles from the beginning of SoC induction therapy (ie, approximately 92 weeks from randomization). Treatment with pembrolizumab may extend beyond 2 years (>35 cycles) in countries where continued pembrolizumab use is approved in accordance with SoC per label and upon Sponsor approval. As of November 16, 2023, the Sponsor may no longer approve new requests for pembrolizumab treatment beyond 35 cycles. Treatment with niraparib/placebo will continue until radiographic PD is documented per RECIST v1.1 and verified by BICR or other treatment discontinuation criterion is met. After completing 35 cycles of pembrolizumab, or if the participant has discontinued pembrolizumab for another reason, participants may receive a 6-week supply of niraparib/placebo and return for clinic visits on an every other cycle basis to collect assessments. In such instances where a 6-week supply of niraparib/placebo is provided, these dispensing visits should be planned to coincide with visits in which PROs are

administered at the site (Table 3); laboratory samples required for the skipped visits should be done and can be performed at a local laboratory.

CCI [redacted]

Randomization may occur up to 3 days prior to Cycle 1/Day 1 on study if all eligibility criteria are met. Administration of pembrolizumab will continue every 21 (±3) days.

Clinic visits will occur as indicated in Table 3. 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 8 weeks of the study treatment period. If participants are unable to attend the clinic visits on Cycle 1/Day 8, Cycle 2/Day 15, and Cycle 3/Day 8 for medical reasons or due to circumstances outside their control, alternative means of performing study assessments may be implemented by the Sponsor that may include deploying trained staff to the participant's home to perform protocol-required assessments.

Approximately 650 participants are expected to be randomized in the study.

Participants will be stratified by:

- histology (squamous versus non-squamous),
- PD-L1 status (TC <1%/NE versus ≥1%), and
- best response to SoC induction chemotherapy (PR/CR versus SD).

The proportion of participants with PR/CR versus SD will be monitored and the total amount of participants with SD will be capped at approximately 50%.

Imaging will be collected/conducted as follows. Baseline imaging for all participants will include the chest, abdomen, CNS, and other sites as clinically indicated. Additional details are provided in Section 8.1.1.1.

- Baseline: Eligibility scan(s) conducted within 28 days prior to randomization
- On Study: Every 6 weeks (every 42 [±7] days) from the date of randomization for a total of 48 weeks or until radiographic PD is documented per RECIST v1.1 and verified by BICR. From Week 49 on, subsequent imaging for participants who remain on treatment will be performed every 12 weeks (every 84 [±7] days), or more frequently if clinically indicated, until radiographic PD is documented per RECIST v1.1 and verified by BICR.
- In Follow-up: For participants who reach the 35 cycle limit and choose to stop all study treatment but continue pembrolizumab alone (through means outside the study), imaging should continue to be sent as per the study schedule until radiographic PD is documented per RECIST v1.1 and verified by BICR, death, withdrawal of consent, or becoming lost-to-follow-up, whichever comes first.

Overall disease progression will be assessed using RECIST v1.1 by BICR (for the primary endpoint) and Investigator (for a secondary endpoint) to measure PFS. BICR-assessed progression will also be utilized separately in the CNS, per RANO-BM criteria, CCI [redacted]

CCI [redacted]

Each participant will have an End-of-Treatment (EOT) Visit at the time it is decided to discontinue study treatment. Safety Follow-up Visits are conducted at 30 (±3) days and 90 (±3) days after the EOT Visit, and Survival Follow-up Visits every 90 (±14) days continue until death or the end of study data collection (provided this allows the opportunity for completion

of all 90-day follow-up assessments). Information regarding subsequent anticancer treatments (including regimen and number of cycles), as well as the date of any subsequent PD (ie, for PFS2 determination), will be collected during these Safety and Survival Follow-up visits.

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 EOT Visit, and the EORTC QLQ-C30, EORTC QLQ-LC13, and CCI [redacted] should be collected at the 30- and 90-day Safety Follow-up Visits, as described in Table 3.

An Independent Data Monitoring Committee (IDMC) will be established to provide independent review and assessment of the efficacy and safety data in a systematic manner and to safeguard the interest and safety of the study participants. An interim safety analysis will be assessed by the IDMC when approximately 120 participants total across both treatment arms have completed at least 2 cycles of maintenance therapy. IDMC periodic safety data reviews will be performed as specified in the IDMC charter.

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.

CCI [redacted]

The exposure of niraparib in combination with pembrolizumab will also be evaluated.

CCI [redacted]

Number of Participants (Planned): Approximately 650.

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.

   Note: Participants in Korea are eligible if they are ≥19 years of age at the time informed consent is obtained.
2. Participants must have a histologically or cytologically confirmed diagnosis of NSCLC without known targetable driver alteration (either non-squamous or squamous histology; mixed histology is allowed) for which an approved targeted therapy is available in the 1L induction/maintenance therapy setting.

3. Participants must have advanced (Stage IIIB or Stage IIIC, not amenable to definitive chemoradiotherapy [CRT]) or metastatic (Stage IV) NSCLC as defined by the American Joint Committee on Cancer (AJCC) 8th Edition Staging Manual.
4. Participants must have completed at least 4 but no more than 6 cycles of SoC 1L platinum-based induction chemotherapy with pembrolizumab (according to SoC defined by National Comprehensive Cancer Network [NCCN] and/or European Society for Medical Oncology [ESMO] Clinical Practice Guidelines for NSCLC).

   Note: To support the transition from 1L induction to 1L maintenance therapy, a transition period that is 6 weeks, in duration, starting from the last dose of 1L induction therapy should occur (up to 7 weeks may be permitted with Sponsor approval). This transition period allows for recovery from chemotherapy-related hematological toxicity before initiating treatment with niraparib/placebo. During this transition period, pembrolizumab administration in the absence of chemotherapy should occur in the cycle immediately following the last cycle of 1L induction therapy (ie, 21 [±3] days after the last cycle of induction). If a transition period with administration of pembrolizumab only is not in accordance with standard prescribing directions and/or a pembrolizumab dose delay is needed that is greater than 3 weeks then the delay must be discussed with the Sponsor and reasons for the delay should be documented in the eCRF.
5. Participants must have SD, PR, or CR of their NSCLC per Investigator's assessment after completion of 4 to 6 cycles of SoC 1L platinum-based induction chemotherapy with pembrolizumab.

   Note: Baseline imaging may be done as part of the SoC 1L induction period so long as imaging is within 28 days of randomization. If baseline imaging falls outside of this 28-day window, then new imaging will be needed (computed tomography [CT, preferred] or magnetic resonance imaging [MRI] scan [if clinically indicated] of the chest and abdomen, and MRI [preferred; CT if MRI not possible] of the brain).

   Note: For participants with only non-measurable/non-target disease at the onset of platinum-based induction therapy with pembrolizumab, a RECIST v1.1 response of non-CR/non-PD is consistent with SD as an overall response.
6. Participants must have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
7. Participants must have a life expectancy of at least 12 weeks.
8. Participants must have adequate organ and bone marrow function defined as:

Absolute neutrophil count:	≥1,500/µL
Platelets:	≥100,000/µL
Hemoglobin:	≥9 g/dL or 5.6 mmol/L
Creatinine clearance (CL_{Cr}):	>30 mL/min as estimated by the Cockcroft-Gault equation (Appendix 11)
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 current active liver or biliary disease are excluded (with the exception of Gilbert's syndrome or asymptomatic

gallstones, liver metastases, or otherwise stable chronic liver disease per Investigator assessment).

9. Participants must submit FFPE tumor specimens preferably collected after being diagnosed with metastatic disease and prior to initiating SoC induction therapy (chemotherapy or radiation) [ie, collected at time of diagnosis of advanced (Stage IIIB/IIIC) or metastatic (Stage IV) NSCLC], from location(s) not irradiated prior to biopsy. If available, a FFPE tissue block should be provided; if not available, freshly cut, unstained slides (<30 days from the date of sectioning) are acceptable.
10. Participants with toxicity from SoC induction therapy must have recovered to a level of organ and bone marrow function as defined by Inclusion Criterion #8 and there is no ongoing toxicity of CTCAE Grade ≥3.
11. Participants must be able to swallow and retain orally administered study treatment.
12. 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, as described in Appendix 3 of the protocol, 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 relationship 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.
    - Additional requirements for pregnancy testing during and after study treatment are described in Section 6.6.2.
    - 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.

13. 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 sexual activity as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent

      or

- Must 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)

14. 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 mixed small cell lung cancer or sarcomatoid variant NSCLC.
2. Participants have received prior PARP inhibitor(s) in prior lines of treatment.
3. Participant has systolic BP >140 mmHg or diastolic BP >90 mmHg.
4. Participants have any clinically significant gastrointestinal abnormalities that may alter absorption such as malabsorption syndrome or major resection of the stomach and/or bowels.
5. Participants have leptomeningeal disease, carcinomatous meningitis, symptomatic brain metastases, or radiographic signs of CNS hemorrhage.

   Note: Participants with asymptomatic brain metastases (ie, off corticosteroids and anticonvulsants for at least 7 days) are permitted.
6. Participants have received colony-stimulating factors (eg, granulocyte macrophage colony-stimulating factor or recombinant erythropoietin) within 4 weeks prior to the first dose of study treatment.
7. Participants have active or previously documented autoimmune or inflammatory disorder, including:
   a. Active infection
   b. Known diagnosis of immunodeficiency (including known history of human immunodeficiency, human immunodeficiency virus [HIV], or infection) or is receiving chronic systemic steroid therapy (eg, >30 days) or any other form of immunosuppressive therapy within 7 days prior to the first dose of study treatment
   c. Active autoimmune disease that has required systemic treatment in the past 2 years (ie, with use of disease-modifying agents, corticosteroids, or immunosuppressive drugs). Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment.
   d. History of organ transplant
8. Participants are receiving chronic systemic steroids (prednisone >20 mg per day). Participants with asthma who require intermittent use of bronchodilators, inhaled steroids, or local steroid injections would not be excluded from the study.
9. Participants have previously or are currently participating in a treatment study of an investigational agent within 4 weeks of the first dose of SoC 1L induction therapy preceding the study.
10. Participants have received prior systemic cytotoxic chemotherapy (intravenous [IV] or intraperitoneal), biological therapy (including checkpoint inhibitor), or hormonal therapy for cancer, or received thoracic radiation therapy of >30 Gy within 6 months of the first dose of the start of SoC 1L induction therapy.

11. Participants have received live vaccine within 30 days of planned start of study randomization.
12. Participants have known hypersensitivity to the components of niraparib, placebo, or pembrolizumab or their formulation excipients.
13. Participants have undergone major surgery within 4 weeks of starting the first dose of study treatment or has not recovered from any effects of any major surgery.
14. Participants have other active concomitant malignancy that warrants systemic, biologic, or hormonal therapy.
15. Participants 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.
16. Participants 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.
17. Participants have high medical risk due to a serious, uncontrolled medical disorder; nonmalignant systemic disease; or active, uncontrolled infection. 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.
18. Participant is 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.
19. 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. For potent immunosuppressive agents, participants with presence of hepatitis B core antibody should also be excluded.
20. Participants have a known history or current diagnosis of myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML).
21. Participants have a known history of active tuberculosis.
22. Participants have current active pneumonitis within 90 days of planned start of the study or a known history of interstitial lung disease, drug-related pneumonitis, or radiation pneumonitis requiring steroid treatment.

Investigational Product, Dosage, and Mode of Administration:

CCI

[redacted]

Pembrolizumab:

Pembrolizumab will be administered in accordance with the product's standard prescribing instructions at a dose of 200 mg as an IV infusion over approximately 30 minutes on Day 1 (±3 days beyond Cycle 1) of each 21-day cycle for up to a maximum total of 35 cycles from the beginning of SoC induction therapy (ie, approximately 92 weeks from randomization). Treatment with pembrolizumab may extend beyond 2 years (>35 cycles) in countries where

continued pembrolizumab use is approved in accordance with SoC per label and upon Sponsor approval. As of November 16, 2023, the Sponsor may no longer approve new requests for pembrolizumab treatment beyond 35 cycles. Any participant who is still receiving pembrolizumab through the study will need to acquire the drug through means outside of the study.

CCI [redacted] 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 study treatments 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 their assigned treatment until radiographic PD is documented per RECIST v1.1 and verified by BICR, unacceptable toxicity, death, withdrawal of consent, or becoming lost to follow-up, whichever comes first.

Treatment with pembrolizumab will continue for up to a total maximum of 35 cycles from the beginning of SoC induction therapy (ie, approximately 92 weeks from randomization). As of November 16, 2023, the Sponsor may no longer approve new requests for pembrolizumab treatment beyond 35 cycles. Treatment with niraparib/placebo will continue until radiographic PD is documented per RECIST v1.1 and verified by BICR or another study treatment discontinuation criterion is met. Participants with evidence of disease at 3 years who, in the opinion of the treating physician may derive further benefit from continuation of study treatment, may be treated beyond 3 years. After completing 35 cycles of pembrolizumab, or if the participant has discontinued pembrolizumab for another reason, participants may receive a 6-week supply of niraparib/placebo and return for clinic visits on an every other cycle basis to collect assessments. Participants continuing niraparib treatment at the time of final analysis may be offered the option to continue niraparib under an extension study, managed access, or other program, as applicable. Any participant who is still receiving pembrolizumab through the study will need to acquire the drug through means outside of the study.

Criteria for Evaluation:

Efficacy Analysis

Primary Efficacy Endpoint

The primary efficacy endpoint is PFS in the CR/PR Population. PFS is defined as the time from the date of randomization to the date of first radiographic progression as determined by BICR or death from any cause in the absence of progression, whichever occurs first. Progression will be assessed by BICR using the RECIST v.1.1 criteria.

Key Secondary Efficacy Endpoint

The following key secondary efficacy endpoint will be evaluated:

- PFS in the ITT Population; as defined for the CR/PR Population
- OS in the CR/PR Population (OS is defined as the time from randomization to the date of death due to any cause.)
- OS in the ITT Population; as defined above for the CR/PR Population

- CCI [redacted]

Secondary Efficacy Endpoints

The following secondary efficacy endpoints will be evaluated:

- PFS as assessed by the Investigator using RECIST v1.1
- CNS-PFS as assessed by BICR using RANO-BM
- PFS, per RECIST v1.1 based on BICR, and OS by PD-L1 status (PD-L1 TC <1% and NE versus ≥1%)
- TTD, defined as the time from randomization to meaningful deterioration on single and composite endpoints of dyspnea, chest pain, and cough, on the EORTC QLQ-LC13
- Change from baseline in the EORTC QLQ-C30 and EORTC QLQ-LC13 domain scores, and individual items, when applicable

Safety Analysis (Secondary and Exploratory Endpoints)

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).

An interim safety analysis will be assessed by the IDMC when approximately 120 participants total across both treatment arms have completed at least 2 cycles of maintenance therapy.

PK Analysis (Secondary Endpoint)

To evaluate niraparib exposure, blood samples for niraparib pharmacokinetics (PK) will be collected at the time points specified in Table 3 for all study participants with sparse PK sampling.

CCI [redacted]

CCI

Analysis Populations:

- The All Screened Population will consist of all participants who sign 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 will consist of all randomized participants whether or not randomized treatment was administered. This population will be based on the treatment and strata to which the participant was randomized and will be the primary population for the analysis of efficacy data. Any participant who receives a treatment randomization number will be considered to have been randomized. Efficacy analyses in the CR/PR Population will be conducted in patients with best response to SoC induction chemotherapy with CR/PR in the ITT Population.
- The Response Evaluable Population – RECIST will consist of all randomized participants with evidence of disease at baseline per RECIST v1.1.
- The Response Evaluable Population – RANO-BM will consist of all randomized participants with evidence of disease at baseline per RANO-BM BICR assessment.
- The Safety Population will consist of all randomized participants who take at least 1 dose of study treatment. Participants will be analyzed according to the intervention they actually received.
- The PK Population will consist of those participants in the Safety Population from whom at least 1 PK sample has been obtained and analyzed. This population will be the primary population for PK analyses.

Primary Efficacy Analysis

The primary efficacy analysis will be based on the CR/PR population. The distribution of PFS in the CR/PR Population for each treatment arm will be estimated using the Kaplan-Meier method and will be compared between the 2 treatment arms using log-rank test stratified by the

stratification factors used for randomization. PFS will be assessed by BICR using RECIST v1.1.

Key Secondary Efficacy Analysis

PFS in the ITT Population, and OS in the CR/PR and ITT Populations will be analyzed following a similar approach as for PFS CR/PR.

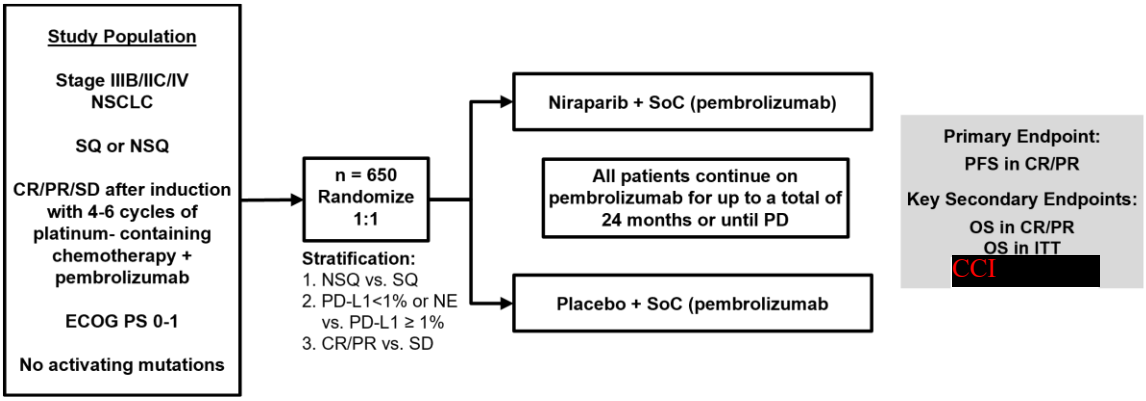
CCI

[redacted]

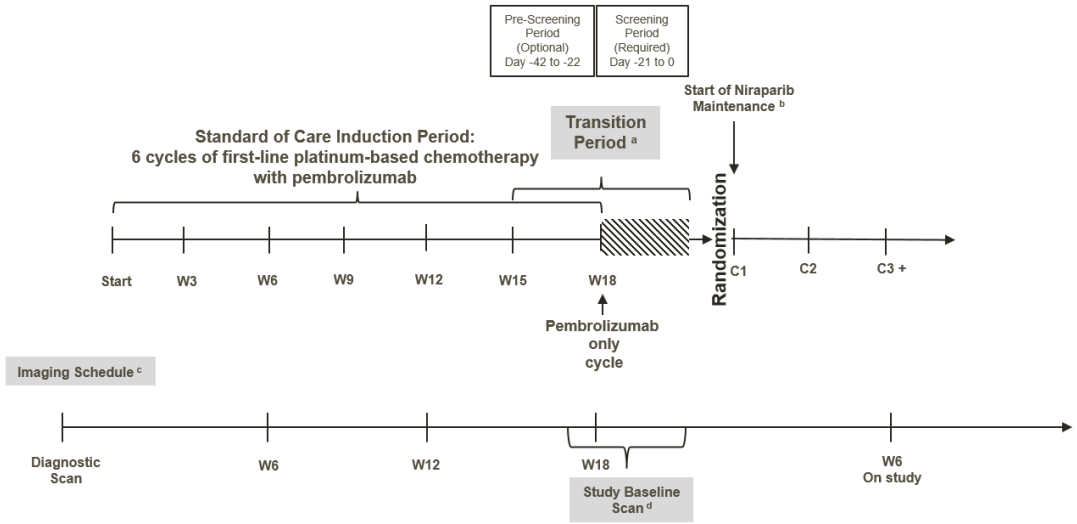
1.2. Schemas

Figure 1: Overall Study Schemas

(A)



(B)



Abbreviations: BICR=Blinded Independent Central Review; C=Cycle; CNS=central nervous system; CR=complete response; CTCAE=Common Terminology Criteria for Adverse Events; ECOG=Eastern Cooperative Oncology Group; EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire 30-item Core module; EORTC QLQ-LC13=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire 13-item lung cancer-specific module; CCI ; HRQoL=health-related quality of life; NE=not evaluable; NSCLC=non-small cell lung cancer; NSQ=non-squamous; OS=overall survival; PD=progressive disease; PD-L1=programmed cell death-ligand 1; PFS=progression-free survival; PR=partial response; PS=performance scale; QoL=quality of life; SD=stable disease; SQ=squamous; W=week.

[a] To support the transition from 1L induction to 1L maintenance therapy, a transition period that is 6 weeks, in duration, starting from the last dose of 1L induction therapy should occur (up to 7 weeks may be permitted with Sponsor approval). This transition period allows for recovery from chemotherapy-related hematological toxicity before initiating treatment with niraparib/placebo. During this transition period, pembrolizumab administration in the absence of chemotherapy should occur in the cycle immediately following the last cycle of 1L induction therapy (ie, 21 [±3] days after the last cycle of induction). If a transition period with administration of pembrolizumab only is not in accordance with standard prescribing directions and/or a pembrolizumab dose delay is needed that is greater than 3 weeks then the delay must be discussed with the Sponsor and reasons for the delay should be documented in the eCRF.

[b] Niraparib/placebo must start and pembrolizumab must continue on C1D1.
[c] Imaging during the SoC induction period is conducted according to local SoC. Imaging on study will be submitted to a central imaging vendor and assessed by BICR. On study imaging should be performed every 6 weeks (every 42 [±7] days) for 48 weeks; from Week 49 on, scans are performed every 12 weeks (every 84 [±7] days).
[d] Regularly scheduled scans may be used as the Study Baseline Scan if taken within 28 days of randomization; scans performed outside of the 28-day window will not be accepted as a Study Baseline Scan, and a new scan must be performed.

1.3. Schedule of Activities (SoA)

The schedule of activities (SoA) for this study is presented in Table 3.

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

	Maintenance Treatment Cycles														End-of-Treatment Phase		Survival Follow-Up
Cycle[a]	**Pre-Screening (Optional)[w]**	**Screening (Required)**	**C1**			**C2**			**C3**		**C4**	**C5**	**C6**	**C7[z], etc**	**EOT[b]**	**Safety Follow-Up Visits**	**Survival Follow-Up Visit 1 and Beyond**
Day	**-42 to -22**	**-21 to 0**	**1**	**8[c]**	**15**	**1**	**8**	**15[c]**	**1**	**8[c]**	**1**	**1**	**1**	**1**			
Scheduling Window (Days)	**NA**	**NA**	**NA**	**±1**	**±1**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**Within 7 days of Study Treatment Discontinuation Decision**	**30 and 90 (±3) Days After EOT Visit**	**Every 90 (±14) Days After the last Safety FU Visit**
Procedure																	
Pre-screening informed consent	X																
Main study informed consents		X															
Inclusion/exclusion criteria review		X															
Demographics		X															
Medical, surgical, disease, and medication history		X															
NSCLC history		X															
Randomization			X														
Vital signs, height, and weight[d]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Physical examination		X[x]	X	X	X	X	X	X	X	X	X	X	X	X			
ECOG performance status		X	X[e]			X			X		X	X	X	X	X	X	
Serum/plasma chemistry[f]		X	X[e]			X[g]			X[g]		X[g]	X[g]	X[g]	X[g]	X	X	
CBC with differential[h]		X	X[e]	X	X	X[g]	X[g]		X[g]		X[g]	X[g]	X[g]	X[g]	X	X	

Table 3: Schedule of Activities (Continued)

	Maintenance Treatment Cycles														End-of-Treatment Phase		Survival Follow-Up
Cycle[a]	**Pre-Screening (Optional)[w]**	**Screening (Required)**	**C1**			**C2**			**C3**		**C4**	**C5**	**C6**	**C7[z], etc**	**EOT[b]**	**Safety Follow-Up Visits**	**Survival Follow-Up Visit 1 and Beyond**
Day	**-42 to -22**	**-21 to 0**	**1**	**8[c]**	**15**	**1**	**8**	**15[c]**	**1**	**8[c]**	**1**	**1**	**1**	**1**			
Scheduling Window (Days)	**NA**	**NA**	**NA**	**±1**	**±1**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**Within 7 days of Study Treatment Discontinuation Decision**	**30 and 90 (±3) Days After EOT Visit**	**Every 90 (±14) Days After the last Safety FU Visit**
Procedure																	
Coagulation[i]		X	X[e]			X[g]			X[g]		X[g]	X[g]	X[g]	X[g]	X	X	
Thyroid panel[j]		X				Every 2 cycles from C2/D1[g]									X	If clinically indicated	
Urinalysis		X															
Serum or urine pregnancy test[k]		X	X			X			X		X	X	X	X			
HIV test[l]		X															
HBV/HCV test[l]		X															
Blood sample for niraparib PK[m]			X		X	X					X			X	X		
Blood sample for biomarkers[n]		X				X							X		X		
CCI																	
FFPE tumor tissue for PD-L1 and biomarker testing	X[o]																
Concomitant medications		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[p]
Adverse event monitoring		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[q]	X[q]

Table 3: Schedule of Activities (Continued)

	Maintenance Treatment Cycles														End-of-Treatment Phase		Survival Follow-Up
Cycle[a]	**Pre-Screening (Optional)[w]**	**Screening (Required)**	**C1**			**C2**			**C3**		**C4**	**C5**	**C6**	**C7[z], etc**	**EOT[b]**	**Safety Follow-Up Visits**	**Survival Follow-Up Visit 1 and Beyond**
Day	**-42 to -22**	**-21 to 0**	**1**	**8[c]**	**15**	**1**	**8**	**15[c]**	**1**	**8[c]**	**1**	**1**	**1**	**1**			
Scheduling Window (Days)	**NA**	**NA**	**NA**	**±1**	**±1**	**±3**	**± 3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**Within 7 Days of Study Treatment Discontinuation Decision**	**30 and 90 (±3) Days After EOT Visit**	**Every 90 (±14) Days After the last Safety FU Visit**
Procedure																	
Oral niraparib/placebo dispensed/collected[z]			X			X			X		X	X	X	X	X		
IV pembrolizumab administered[r]			X			X			X		X	X	X	X[r]			
CT/MRI for RECIST v.1.1 and RANO-BM assessment[s] **Note: IV contrast-enhanced CT (preferred) or MRI scans of chest and abdomen plus IV contrast-enhanced MRI (preferred) or CT of brain**	X[s]	X[s]	Every 6 weeks (every 42 [±7] days) from the date of randomization for 48 weeks; from Week 49 on, every 12 weeks (every 84 [±7] days) until radiographic PD documented per RECIST v1.1 and verified by BICR[s]												X[s]		
EORTC QLQ-C30, EORTC QLQ-LC13[t]			X			X			X		X	X	Every 2 cycles from C5/D1		X	X[t]	
CCI [redacted]																	

Table 3: Schedule of Activities (Continued)

	Maintenance Treatment Cycles														End-of-Treatment Phase		Survival Follow-Up
Cycle[a]	**Pre-Screening (Optional)[w]**	**Screening (Required)**	**C1**			**C2**			**C3**		**C4**	**C5**	**C6**	**C7[z], etc**	**EOT[b]**	**Safety Follow-Up Visits**	**Survival Follow-Up Visit 1 and Beyond**
Day	**-42 to -22**	**-21 to 0**	**1**	**8[c]**	**15**	**1**	**8**	**15[c]**	**1**	**8[c]**	**1**	**1**	**1**	**1**			
Scheduling Window (Days)	**NA**	**NA**	**NA**	**±1**	**±1**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**Within 7 days of Study Treatment Discontinuation Decision**	**30 and 90 (±3) Days After EOT Visit**	**Every 90 (±14) Days After the last Safety FU Visit**
Procedure																	
CCI [redacted]																	
Subsequent anticancer treatments[u]															X	X	X
Survival assessment[v]																X	X

Abbreviations: AE=adverse event; AESI=adverse event of special interest; C=cycle; CBC=complete blood count; CNS=central nervous system; CT=computed tomography; D=day; DNA=deoxyribonucleic acid; ECOG=Eastern Cooperative Oncology Group; EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire 30-item Core module; EORTC QLQ-LC13=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire 13-item lung cancer-specific module; EOT=End-of-Treatment; CCI [redacted]; FFPE=formalin-fixed, paraffin-embedded; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; IV=intravenous; MRI=magnetic resonance imaging; NA=not applicable; NSCLC=non-small cell lung cancer; PD=progressive disease; PD-1=programmed cell death protein 1; PD-L1=programmed cell death-ligand 1; CCI [redacted]; PK=pharmacokinetic(s); PRO=patient-reported outcome; CCI [redacted] RANO-BM=Response Assessment in Neuro-Oncology Brain Metastases; RECIST v1.1=Response Evaluation Criteria in Solid Tumors version 1.1; SAE=serious adverse event; TC=tumor cell.

[a] Treatment cycles are 21 days long. On Cycle 1/Day 1, the first dose of niraparib/placebo and the first dose of on-study pembrolizumab will be administered. Randomization may occur up to 3 days prior to Cycle 1/Day 1 if all eligibility criteria are met. Administration of pembrolizumab will continue every 21 (±3) days.

[b] All participants will undergo an EOT Visit within 7 days of the decision to discontinue all study treatment for any reason. If a participant discontinues all study treatment for any reason other than Investigator-assessed PD per RECIST v1.1, which has been verified by BICR, then scans should continue at the specified intervals until radiographic PD is documented per RECIST v1.1 and verified by BICR or until the start of subsequent anticancer treatment. Also, clinically stable participants should not be discontinued from study treatment until radiographic PD is documented per RECIST v.1.1 and verified by BICR.

[c] If participants are unable to attend the clinic visits on Cycle 1/Day 8, Cycle 2/Day 15, and Cycle 3/Day 8 for medical reasons or due to circumstances outside their control, alternative means of performing study assessments may be implemented by the Sponsor that may include deploying trained staff to the participant's home to perform protocol-required assessments.

[d] Height will be measured only at Screening.

[e] Screening assessments completed within 10 days of the first dose do not need to be repeated.

[f] Serum/plasma chemistry parameters that will be measured are listed in Section 8.2.6.

[g] After Cycle 1, clinical laboratory samples may be collected within 3 days prior to each visit. Serum/plasma chemistry and CBC need to be performed and results evaluated prior to dosing.

[h] If dose interruption or modification is required at any point on study because of hematologic toxicity, weekly blood draws for CBC will be monitored until the AE resolves, and to ensure safety of the new dose, weekly blood draws for CBC will also be required for an additional 4 weeks after the AE has been resolved to the specified levels, after which monitoring every 4 weeks may resume. See Section 8.2.6 for specific parameters to be measured.

[i] Specific coagulation factors to be evaluated are presented in Section 8.2.6.

[j] Includes thyroid-stimulating hormone, triiodothyronine or free triiodothyronine, and free thyroxine.

[k] A serum pregnancy test must be performed for women of childbearing potential within 72 hours prior to the first dose of study treatment and then starting with Cycle 2, on Day 1 of every cycle for the duration of the treatment period. Test result must be available and negative before the first dose of study treatment. If serum pregnancy test results are not available before dosing, highly sensitive urine pregnancy test may be performed. Additional pregnancy testing may be necessary if required by local practices or regulations or if potential pregnancy is suspected.

[l] See Section 8.2.7 for guidance regarding HIV, HBV, and HCV testing. Testing should be done for hepatitis B surface antigen (or equivalent) and HCV ribonucleic acid.

[m] Blood samples for PK analysis will be collected on Cycle 1/Day 1, Cycle 1/Day 15, 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) as long as participants continue on niraparib/placebo treatment. 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. On days of pembrolizumab infusion, niraparib/placebo will be taken upon completion of the infusion. See the Laboratory Manual for additional details.

[n] To be collected predose when collected on dosing days for evaluation of circulating tumor DNA burden from baseline and on-treatment and exploration of potential resistant mechanisms.

[o] Participants must submit an FFPE tumor specimen preferably collected prior to initiating SoC induction therapy (chemotherapy or radiation) [ie, collected at time of diagnosis of advanced (Stage IIIB/IIIC) or metastatic (Stage IV) NSCLC] from location(s) not irradiated prior to biopsy, for central PD-L1 testing and CCI [redacted] If available, a FFPE tissue block should be provided; if not available, freshly cut, unstained slides (<30 days from the date of sectioning) are acceptable. Participants whose submitted tissue is not evaluable for PD-L1 status may be eligible to participate in the study and will be stratified to the PD-L1 staining in TCs (TC <1% and NE) group. Note: Tumor specimens obtained from non-irradiated body regions can be obtained after the induction period

for advanced/metastatic NSCLC. Tumor specimens should not be from bone metastasis, as the likelihood of no invasive primary tumor cells or insufficient quantity of invasive primary tumor cells is high with bone tumor sampling.

[p] After Survival Follow-up Visit 1, only medications taken for SAEs and AESIs need to be recorded.

[q] All AEs and 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. Study treatment-related SAEs and AESIs will be collected and reported until study closeout. Any pregnancies that occur within 180 days post-treatment discontinuation are to be reported.

[r] Pembrolizumab will be administered at a dose of 200 mg over an approximately 30-minute IV infusion on Day 1 of each treatment cycle after all procedures and assessments have been completed, for up to a maximum total of 35 cycles from the beginning of SoC induction therapy (ie, approximately 92 weeks from randomization).

[s] A baseline scan (performed within 28 days prior to randomization) via CT (preferred) or MRI (if clinically indicated) of the chest, abdomen, CNS (MRI preferred; CT if MRI not possible), and other sites as clinically indicated is required (eg, CT scan of bone for participants known to have bone metastasis). On-study imaging must be performed every 6 weeks (every 42 [±7] days) from the date of randomization for 48 weeks. From Week 49 on, imaging must be performed every 12 weeks (every 84 [±7] days) until radiographic PD is documented per RECIST v1.1 and verified by BICR. Imaging should follow calendar days and should not be adjusted for delays in cycle starts. Scans may be performed more frequently, if clinically indicated. The same imaging method and anatomical coverage should be used throughout the study. If a participant discontinues treatment for any reason other than Investigator assessed PD per RECIST v1.1, which has been verified by BICR, then scans should continue at the specified intervals until radiographic PD is documented per RECIST v1.1 and verified by BICR or until the start of subsequent anticancer treatment. For participants who discontinue study treatment due to BICR-verified progression, additional imaging assessment is not required at EOT; for participants who begin a subsequent anticancer treatment prior to BICR-verified progression, imaging assessment must be performed within 4 weeks of the date of study treatment discontinuation. Refer to Section 8.1.1.1 for additional details.

[t] PROs will be collected electronically on site on the day of study treatment administration, prior to dosing and clinical procedures (including collection of AEs). On-treatment PROs will continue until radiographic PD is documented by RECIST v1.1 and verified by BICR or end of study treatment. Follow-up PROs will be conducted for the EORTC QLQ-C30, QLQ-LC13, and CCI at the 30- and 90-day Safety Follow-up Visits. PROs may be administered by telephone if the participant is no longer actively returning to the clinic. CCI is not collected on Cycle 1/Day 1.

[u] CCI [redacted]

[v] After documented PD or start of new anticancer treatment; contact will be every 90 days by telephone. In addition to survival, this assessment includes outcomes for subsequent anticancer treatment, including any new malignancy information. The sponsor may request that updated survival data be collected on all participants outside the protocol window noted in the SoA. At the time of the request, the site will determine survival status for each participant by the method agreed with the participant (as allowed per local regulations), unless the participant has not given or has withdrawn consent for survival follow-up. See Section 7.3 and Section 7.4 for additional details.

[w] Pre-screening period is optional and based on site need. If a participant can be fully screened within the required 21-day Screening period, including collection of archival tissue, then the Prescreening period is not needed and all Pre-screening assessments should occur between -21 to 0 days (ie, the Screening period).

[x] Full physical examination required at Screening, only. All other physical examinations will be symptom-directed (refer to Section 8.2.3).

[y] CCI [redacted]

[z.] After completing 35 cycles of pembrolizumab, or if the participant has discontinued pembrolizumab for another reason, participants may receive a 6-week supply of niraparib/placebo and return for clinic visits on an every other cycle basis to collect assessments. In such instances, these dispensing visits should be planned to

coincide with visits in which PROs are administered at the site. Laboratory samples required for the skipped visits should be done and can be performed at a local laboratory.

2. INTRODUCTION

2.1. Lung Cancer

Lung cancer is the most common cause of cancer mortality globally, and the second most common cancer in both men and women. About 12.9% of all new cancers are lung cancers in the United States (US) and have a 5-year survival rate of 19.4%. Patients who are diagnosed with metastatic or distant lung cancer have a 5.2% OS at 5 years. In the US, approximately ~228,820 new cases of lung and bronchus cancer (inclusive of both men and women) are estimated to occur in 2020 [Siegel, 2020]. Lung cancer was the most common cause of death from cancer in the European Union (EU) in 2018 in both men and women [Ferlay, 2019]. About 11.1% of all new cancers are lung cancers in the EU with a mortality rate of 20% [Bray, 2018].

There are 2 major forms of lung cancer: small cell and non-small cell lung cancer. NSCLC is a heterogeneous disease that consists of adenocarcinoma, large-cell carcinoma, and squamous cell carcinoma, and comprises approximately 80% to 85% of all lung cancers [Torre, 2016]. Despite advances in early detection and standard treatment, NSCLC is often diagnosed at an advanced stage with inoperable disease and carries a poor prognosis [Siegel, 2020]. Squamous cell carcinoma of the lung accounts for 20% to 30% of NSCLC [Siegel, 2020]. Patients with squamous NSCLC rarely have epidermal growth factor receptor (EGFR), BRAF V600E, anaplastic lymphoma kinase (ALK), receptor tyrosine kinase-1 (ROS-1), or NTRK gene alterations in their tumors. Molecular testing is not routinely performed for this NSCLC histology.

Decline in tobacco use and advances in treatment (eg, molecularly targeted therapies and immunotherapies) have contributed to declines in lung cancer mortality rates; however, there remains a high unmet medical need for improved treatment in patients with advanced/metastatic NSCLC.

2.2. Treatment Options for Patients with Stage III or Stage IV NSCLC

The backbone of first-line (1L) treatment for patients with advanced or recurrent (Stage IIIB or Stage IIIC, not amenable to definitive chemoradiotherapy) or metastatic (Stage IV) NSCLC without molecular therapy targets was platinum-based chemotherapy.

The KEYNOTE-024 and KEYNOTE-042 studies demonstrated the benefit of pembrolizumab monotherapy over platinum-containing chemotherapy in previously untreated patients with metastatic NSCLC (regardless of histology) in patients whose tumors expressed PD-L1. This led to the approval of pembrolizumab as a single agent for the 1L treatment of patients with advanced or recurrent (Stage IIIB not amenable to definitive chemoradiotherapy) or metastatic (Stage IV) NSCLC expressing PD-L1 (Tumor Proportion Score [TPS] ≥1%) with no EGFR or ALK genomic tumor aberrations in the US. In the EU, pembrolizumab as a single agent for the 1L treatment of patients with advanced or recurrent (Stage IIIB not amenable to definitive chemoradiotherapy) or metastatic (Stage IV) NSCLC is limited to patients with tumors expressing PD-L1 (TPS ≥50%) [ESMO Guidelines, 2019].

The randomized Phase 3 KEYNOTE-189 and KEYNOTE-407 studies studied participants with previously untreated metastatic non-squamous and squamous NSCLC, respectively, and demonstrated that the addition of pembrolizumab to standard chemotherapy prolonged PFS and OS when compared to chemotherapy alone regardless of PD-L1 status [Gandhi, 2018; Paz-Ares, 2018]. This led to the approval of the combination in the US and EU and shifted the treatment paradigm to establish pembrolizumab in combination with platinum-based chemotherapy as a new standard of practice in patients with previously untreated metastatic non-squamous NSCLC and pembrolizumab in combination with chemotherapy (carboplatin + paclitaxel or carboplatin + nab-paclitaxel) as a new standard of practice in advanced/metastatic squamous NSCLC [NCCN, 2020].

Maintenance therapy regimens such as non-platinum cytotoxic agents (eg, pemetrexed) or molecularly targeted agents (eg, bevacizumab, a vascular endothelial growth factor inhibitor) after frontline platinum-based chemotherapy have been primarily replaced with pembrolizumab in frontline practice, despite existing indications [Hanna, 2020].

2.3. Niraparib

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 CR or PR to platinum-based chemotherapy. Niraparib was approved by the FDA on 23 October 2019 for patients with advanced ovarian, fallopian tube, or primary peritoneal cancer treated with 3 or more prior chemotherapy regimens and whose cancer is associated with HRD-positive status. Additionally, the FDA approved the Myriad myChoice® CDx test (PMA P190014) as a companion diagnostic for determination of tumor HRD status to select patients for treatment with niraparib in the late-line setting. A supplemental NDA (NDA 208447-S017) based on results of the PRIMA study, which evaluated the efficacy of niraparib in participants with newly diagnosed advanced ovarian cancer after a response to 1L platinum-based chemotherapy, is currently under real-time oncology review (RTOR) with the FDA.

Niraparib has shown an acceptable clinical and nonclinical safety profile. The evaluation of niraparib plus pembrolizumab as maintenance therapy for NSCLC is based on nonclinical and clinical data showing synergy of immune checkpoint and PARP inhibitors.

In the TOPACIO/KEYNOTE-162 study, the combination of niraparib plus pembrolizumab provided promising antitumor activity in both advanced or metastatic triple-negative breast cancer, with numerically higher response rates in those with tumor breast cancer susceptibility gene (*BRCA*) and recurrent ovarian cancer [Konstantinopoulos, 2019; Vinayak, 2019]. The combination therapy was safe with a

tolerable safety profile. In the Phase 2 JASPER study (Study 3000-02-001), data provided further support of the safety of the combination of niraparib and pembrolizumab in NSCLC. The combination of niraparib with pembrolizumab in this 1L treatment setting showed antitumor activity, with the highest response rate observed in participants with high PD-L1 expression.

Clinical data with niraparib has also supported the efficacy of niraparib in ovarian cancer in the maintenance therapy setting following a response to platinum-based chemotherapy, irrespective of BRCA status. In addition, clinical data on the efficacy of PARP inhibitors in both squamous and non-squamous NSCLC histologies support a study design that includes both histologies [Ramalingam, 2020; Ramalingam, 2021].

Refer to the current version of the niraparib Investigator's Brochure for more information.

2.4. Rationale for Current Study

Development of more efficacious treatment options for patients with NSCLC remains a high unmet need. Novel combination therapy regimens are needed with acceptable safety profiles that deliver clinically meaningful improvement in PFS and OS when administered in the maintenance setting for patients with advanced/metastatic NSCLC whose disease did not progress with frontline pembrolizumab/platinum-based therapy.

This study will evaluate the efficacy of niraparib in combination with pembrolizumab in comparison to pembrolizumab plus placebo as maintenance therapy in participants with Stage IIIB/IIIC, or IV NSCLC (both squamous and non-squamous histology) who have achieved SD, PR, or CR in response to standard of care (SoC) induction with 4 to 6 cycles of platinum-based chemotherapy and pembrolizumab. Patients with asymptomatic brain metastases (BM) will be allowed to enroll in this study given the high potential of lung cancer patients to have or develop BM during treatment. If the participant did not have a CNS magnetic resonance imaging (MRI) at the beginning of SoC induction therapy, the presence of BM at first screening scan will not be considered evidence of progression in the absence of other factors, such as new CNS symptoms.

Platinum sensitivity as a predictor of response to PARPi is well established in ovarian cancer. NSCLC patients sensitive to platinum-double treatment may be enriched for impaired DNA damaging response. Alterations in DNA damaging response are associated with genomic instability and augmented mutational burden, which could lead to increasing tumor immunogenicity through neoantigen load generation and leading to accumulation of incompletely repaired DNA damage with activation of the STING signaling pathway [Passiglia, 2021]. Treatment with PARPi may further enhance DNA damage levels promoting neoantigen release, as well as tumor PD-L1 expression, favoring the generation of a more susceptible tumor microenvironment.

Some NSCLC patients with DNA repair gene deficiencies (e.g., *ERCC1*, *BRCA1*, and *ATM*) have shown sensitivity to PARPi, suggesting that platinum sensitivity, linked to DNA repair defects, can serve as a potential predictive marker for PARPi activity in lung cancers [Fennell, 2022; Ahn, 2023; Hochmair, 2024]. It is therefore theorized that the

platinum sensitive CR/PR induction response cohort may benefit from addition of niraparib to immunotherapy.

The following aspects of the study design are discussed in more detail below:

- The inclusion of both squamous and non-squamous histologies
- The use of pembrolizumab in the control arm

2.4.1. Inclusion of Squamous and Non-squamous Histologies

It is hypothesized that both the squamous and non-squamous histologies may benefit from the addition of niraparib. There are limited clinical data with PARP inhibitors in NSCLC that would allow the comparison of efficacy between the 2 histologies. In the Phase 2 JASPER study (3000-02-001), which evaluated niraparib administered alone and in combination with a programmed cell death protein 1 (PD-1) inhibitor in participants with advanced and metastatic NSCLC, the sample size was too small to allow such a comparison (5 participants with squamous histology in each cohort).

In a Phase 2 study (N=158) assessing the efficacy and safety of adding veliparib to a carboplatin-paclitaxel regimen in unselected 1L NSCLC, an efficacy signal was observed for both histologies, with a suggestion of better efficacy in the squamous histology (PFS HR 0.54 versus 0.87; OS HR 0.73 versus 0.70). The authors suggested that participants in the arm receiving veliparib in non-squamous NSCLC were more likely to receive pemetrexed after veliparib, influencing OS results in favor of the veliparib arm [Ramalingam, 2017]. The authors interpreted this outcome as possibly related to the higher genomic instability of the squamous histology. However, the significance of this study remains limited by the selection of veliparib, a PARP inhibitor that demonstrates less efficacy compared to other PARP inhibitors (relatively decreased trapping and cytotoxic potency of veliparib), and the absence of participant selection based on platinum response, which is considered a predictive surrogate for response to PARP inhibition. The veliparib study did not select study participants based on prior response to platinum-based therapy, as enrolled participants had not received prior chemotherapy for advanced/metastatic disease.

Given the similar treatment regimens, the fact that all participants will be treated with 1L platinum-based therapy in this study prior to randomization, the stratification by histology, and by accounting for any differences in response for statistical assumptions, inclusion of participants with NSCLC with both squamous and non-squamous histology for evaluation in a single study is deemed appropriate.

The treatment of both squamous and non-squamous histologies of NSCLC have evolved in a parallel fashion. The current SoC for patients with advanced/metastatic squamous NSCLC histology is platinum-based chemotherapy in combination with pembrolizumab for 4 to 6 cycles, typically followed by pembrolizumab maintenance monotherapy [NCCN, 2020]. Similarly, in patients with advanced non-squamous NSCLC, pembrolizumab in combination with platinum-based chemotherapy is a preferred 1L SoC with different recommended options for maintenance therapy primarily dependent on what was given in the first line.

2.4.2. Use of Pembrolizumab in the Control Arm

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to PD-1 receptor, thus inhibiting its interaction with PD-L1 and PD-L2 ligands. Based on nonclinical in vitro data, pembrolizumab has high affinity and potent receptor-blocking activity for PD-1.

Based on the existing evolution of medical practice, pembrolizumab maintenance monotherapy is an acceptable control arm for both the squamous and non-squamous NSCLC histologies and is consistent with current SoC.

Refer to the CCI [redacted] prescribing information for more details.

2.5. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of niraparib may be found in the current version of the Investigator's Brochure. Risk minimization measures for this study (such as investigational medicinal product [IMP] dose reduction and IMP discontinuation) are discussed in Table 4 below, Section 4.4. (including Table 6, Table 7 and Table 8 therein), and Section 7.1. The SoA table in Section 1.3. also indicates Safety Follow-up Visits.

2.5.1. Risk Assessment

Table 4: 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 PARP inhibitor, niraparib	Protocol provides guidelines for monitoring hematologic labs and adverse reactions (Section 8.2.6) Protocol provides Investigator guidance for the clinical management of these events (Section 8.3 and Section 9.4.5) Protocol provides guidance for dose modification and discontinuation of study (Section 4.4)
Hypertension	Cases reported with niraparib	Protocol provides monitoring and stopping criteria for discontinuation of study treatment (Section 4.4 and Section 7.1)

Risks of Clinical Significance (Identified or Potential)	Summary of Data/Rationale for Risk	Mitigation Strategy
MDS or AML, along with other secondary cancers (new malignancies other than MDS or AML)	Based on nonclinical and clinical observations as well as identified with PARP inhibitor, niraparib	Protocol provides monitoring and stopping criteria for discontinuation of study treatment (Section 7.1)
Embryofetal Toxicity	Based on nonclinical observations and mechanism of action, niraparib is expected to exhibit embryo-fetal toxicity	Protocol excludes participants that are pregnant or breastfeeding and provides detailed guidance on contraception (Section 5.2)
Posterior Reversible Encephalopathy Syndrome (PRES)	Cases reported with niraparib	Protocol provides monitoring and stopping criteria for discontinuation of study treatment (Section 7.1)

Abbreviation: AML=Acute myeloid leukemia; MDS=Myelodysplastic syndrome; 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 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.

2.5.2. Benefit Assessment

The primary efficacy and safety data of niraparib as maintenance treatment in patients with platinum-sensitive, recurrent ovarian cancer are derived from a Phase 3 study (ENGOT-OV16/NOVA: Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer), which included a total of 546 niraparib- or placebo-treated patients at the time of the data cutoff. Niraparib, as a daily oral treatment, prolonged the effect of platinum-based chemotherapy, improved progression-free survival (PFS), and reduced the risk of recurrence or death in a broad population of patients.

In patients with germline *BRCA* mutations (g*BRCA*mut), median PFS was 21.0 months for those receiving niraparib versus 5.5 months in patients receiving placebo (hazard ratio [HR]: 0.27; 95% confidence interval [CI]: 0.173 to 0.410; p <0.0001). PFS was also significantly longer for niraparib-treated patients in the homologous recombination deficiency positive (HRDpos) subgroup without germline *BRCA* mutation (non-g*BRCA*mut) (median PFS: 12.9 months versus 3.8 months; HR: 0.38; 95% CI: 0.243 to 0.586; p <0.001) and in the overall non-g*BRCA*mut patient population (median PFS: 9.3 months versus 3.9 months; HR: 0.45; 95% CI: 0.338 to 0.607; p <0.001). Thus, PFS was significantly longer for patients who received niraparib than for those who received placebo regardless of *BRCA* mutation or HRD status.

The secondary endpoints of chemotherapy-free interval (CFI), time to first subsequent therapy (TFST), and progression-free survival 2 (PFS2) confirmed the results of the primary endpoint in both cohorts. Niraparib did not reduce responsiveness to subsequent therapy. There was a persistent treatment effect in favor of the niraparib arm. There was no evidence for a detrimental impact of niraparib treatment on OS. The robustness of the results was supported by sensitivity analyses, which were consistent with the primary efficacy analyses. Importantly, niraparib dose reduction had no impact on PFS outcomes.

The primary efficacy and safety data of niraparib as treatment in patients with advanced epithelial ovarian cancer (EOC) treated with 3 or more prior chemotherapy regimens and whose cancer is associated with HRDpos status are derived from the Phase 2 study QUADRA. The highest response rates observed were among patients with tumors that were HRDpos and platinum-sensitive or *BRCA*mut regardless of platinum sensitivity status. Within the biomarker-defined population of 98 patients with 3 or more prior lines of treatment, the objective response rate (ORR) was 25.5%, and median duration of response (DOR) was 8.3 months. The observed ORR was meaningful and higher than would be expected with approved chemotherapy in this late-line disease setting, including patients with *BRCA*mut disease regardless of platinum sensitivity (ORR: 28.6%; median DOR: 9.2 months) and patients with non-*BRCA*mut/HRDpos platinum-sensitive disease (ORR: 20%; median DOR: 6.6 months).

The primary efficacy and safety data of niraparib as maintenance treatment in patients with advanced EOC who are in CR or PR to 1L platinum-based chemotherapy are derived from the Phase 3 study PRIMA (PRIMA/ENGOT-OV26/GOG-3012: Niraparib in Patients with Newly Diagnosed Advanced Ovarian Cancer). In the PRIMA study, a significantly reduced risk of disease progression or death was demonstrated in patients who received niraparib compared to those who received placebo. The primary endpoint was met in patients with HRD tumors; median PFS based on Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) 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). In the overall population, median PFS for patients randomized to niraparib was 13.8 months versus 8.2 months on placebo (HR 0.62 [95% CI: 0.502 to 0.755]; p<0.0001). Patients benefited from niraparib therapy regardless of tumor HRD status. Median PFS for patients with homologous recombination proficient tumors randomized to the niraparib arm was 8.1 months versus 5.4 months in the placebo arm (HR 0.68 [95% CI: 0.492 to 0.944]; p=0.0203).

Additional information regarding the safety and efficacy data that supported the approval of niraparib for these indications can be found in the current version of the Investigator's Brochure and the locally approved product label.

2.5.3. Overall Benefit/Risk Conclusion

Niraparib, as a once daily oral treatment, prolonged the effect of platinum-based chemotherapy, substantially improved PFS and significantly reduced the risk of recurrence or death in a broad ovarian cancer population of patients thereby enabling a delay in disease recurrence and the need for additional platinum-based or other

chemotherapy with its associated cumulative toxicities as demonstrated in multiple pivotal clinical trials (see current version of the Investigator's Brochure).

The AE profile of niraparib consists of AEs that are commonly managed in the patient population of advanced cancer. The key safety concerns include hematological toxicities, hypertension, MDS/AML, and a potential risk of second primary malignancies. Common AEs including Grade 3 and higher AEs were generally manageable with dose modification and clinical treatment and most of which resolved without discontinuation of study drug.

The benefit-risk profile of niraparib is anticipated to be favorable in the populations in this study with utilization of the risk mitigation strategies as outlined in the study protocol (Section 4.4).

3. STUDY OBJECTIVES AND ENDPOINTS

Table 5: Objectives and Endpoints for Study 213400

Objectives	Endpoints
Primary	
To compare PFS as assessed by BICR using Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) of niraparib plus pembrolizumab versus placebo plus pembrolizumab as maintenance therapy in best response to SoC induction chemotherapy with complete and partial response (CR/PR) Population	PFS in the CR/PR Population is defined as the time from the date of randomization to the date of first radiographic progression as determined by BICR or death from any cause in the absence of progression, whichever occurs first.
Key Secondary	
To compare PFS as assessed by BICR using RECIST v1.1 of niraparib plus pembrolizumab versus placebo plus pembrolizumab as maintenance therapy in the overall population	PFS in the ITT Population is defined as the time from the date of randomization to the date of first radiographic progression as determined by BICR or death from any cause in the absence of progression, whichever occurs first.
To compare OS of niraparib plus pembrolizumab versus placebo plus pembrolizumab as maintenance therapy in the best response to SoC induction chemotherapy with CR/PR Population	OS in CR/PR population defined as the time from randomization to the date of death due to any cause.
To compare OS of niraparib plus pembrolizumab versus placebo plus pembrolizumab as maintenance therapy in the overall population	OS, defined as the time from randomization to the date of death due to any cause.
CCI [redacted]	
Secondary	
To evaluate PFS as assessed by the Investigator using RECIST v1.1	PFS for this objective is defined as the time from the date of randomization to the date of first radiographic progression as determined by the Investigator or death from any cause in the absence of progression, whichever occurs first.
To evaluate CNS-PFS as assessed by BICR using RANO-BM	PFS is defined as the time from the date of randomization to the date of first radiographic progression in the CNS as determined by BICR using RANO-BM criteria or until death due to any cause (whichever occurs first).

Objectives	**Endpoints**
To evaluate PFS as assessed by BICR using RECIST v1.1 and OS by PD-L1 status (PD-L1 TCs <1% and NE versus ≥1%)	PFS is defined as the time from the date of randomization to the date of first radiographic progression as determined by BICR or death from any cause in the absence of progression, whichever occurs first. OS is defined as the time from randomization to the date of death due to any cause.
To evaluate and compare TTD, defined as time from randomization to meaningful deterioration on single and composite endpoints of dyspnea, chest pain, and cough, from the EORTC QLQ-LC13	TTD is defined as the time from randomization to meaningful deterioration on single and composite endpoints of dyspnea, chest pain, and cough on the EORTC QLQ-LC13.
To evaluate changes from baseline in HRQoL, functioning, and symptoms as assessed by the EORTC QLQ-C30 and the EORTC QLQ-LC13 total and domain scores	The EORTC QLQ-C30 and EORTC QLQ-LC13 will be analyzed descriptively by changes from baseline in domain scores, and individual items when applicable.
To evaluate safety and tolerability in participants treated with niraparib plus pembrolizumab compared to placebo plus pembrolizumab	Assess the incidence of AEs, SAEs, and AESIs.
To describe the exposure of niraparib when given in combination with pembrolizumab	Plasma concentrations of niraparib at the time points specified in the Schedule of Activities.
Exploratory	
CCI [redacted]	

Objectives	Endpoints
CCI [redacted]	

Abbreviations: AE=adverse event; AESI=adverse event of special interest; BICR=blinded independent central review; CCI [redacted]; CR=complete response; CCI [redacted]; EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire 30-item Core module; EORTC QLQ-LC13=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire 13-item lung cancer-specific module; CCI [redacted] OS=overall survival; CCI [redacted]; PD-L1=programmed cell death-ligand 1; PFS=progression-free survival; CCI [redacted] PK=pharmacokinetics; PR=partial response; CCI [redacted]

CCI [redacted]; RANO-BM=Response Assessment in Neuro-Oncology Brain Metastases; RECIST v1.1=Response Evaluation Criteria in Solid Tumors version 1.1; SAE=serious adverse event; SAP=Statistical Analysis Plan; TC=tumor cell; SoC=standard of care; CCI [redacted]; TTD=time to deterioration in lung symptoms; CCI [redacted]

Estimands

Estimands are defined in the Statistical Analysis Plan.

4. STUDY DESIGN

4.1. Overall Design

This is a multicenter, randomized, double-blind, placebo-controlled study of niraparib plus pembrolizumab versus placebo plus pembrolizumab as maintenance therapy in participants with advanced or metastatic NSCLC who have SD, PR, or CR following completion of SoC 1L platinum-based induction chemotherapy with pembrolizumab. A study schema is presented in Section 1.2.

In order to be a candidate for this study, participants must have SD, PR, or CR, as assessed by the Investigator per RECIST v1.1 criteria, following 4 to 6 cycles of SoC induction treatment. To support the transition from 1L induction to 1L maintenance therapy, a transition period that is 6 weeks, in duration, starting from the last dose of 1L induction therapy should occur (up to 7 weeks may be permitted with Sponsor approval). This transition period allows for recovery from chemotherapy-related hematological toxicity before initiating treatment with niraparib/placebo.

In addition, a tumor specimen must be submitted for central PD-L1 testing and stratification. Tumor specimen collected prior to initiating cytotoxic or radiation therapy (ie, tumor specimen collected at the time of diagnosis) is preferred. If available, a FFPE tissue block should be provided; if not available, freshly cut, unstained slides (<30 days from the date of sectioning) are acceptable. Participants whose submitted tissue is not evaluable for PD-L1 status may be eligible to participate in the study and will be stratified to the PD-L1 staining in TCs (TC <1% and NE) group. Information on oncologic surgery, SoC induction therapy and regimen, any changes to treatment and regimen, and histology at diagnosis/staging will be collected CCI [redacted]

Participants who have achieved SD, PR, or CR following SoC induction treatment and who meet all eligibility criteria will be randomized in a 1:1 ratio to receive niraparib plus pembrolizumab or placebo plus pembrolizumab as maintenance therapy. The proportion of participants with SD will be carefully monitored at the time of randomization, and a cap will be applied at SD enrollment threshold of 50% of total sample size to prevent the proportion of participants entering the study to differ significantly from the proportions observed in the KEYNOTE-189 and KEYNOTE-407 studies (approximately 35% to 40%) [Gadgeel, 2020; Paz-Ares, 2018].

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

Treatment with pembrolizumab will continue for up to a total maximum of 35 cycles from the beginning of SoC induction therapy (ie, approximately 92 weeks from randomization). Treatment with pembrolizumab may extend beyond 2 years (>35 cycles) in countries where continued pembrolizumab use is approved in accordance with SoC per label and upon Sponsor approval. As of November 16, 2023, the Sponsor may no longer approve new requests for pembrolizumab treatment beyond 35 cycles. After completing

35 cycles of pembrolizumab, or if the participant has discontinued pembrolizumab for another reason, participants may receive a 6-week supply of niraparib/placebo and return for clinic visits on an every other cycle basis to collect assessments. In such instances where a 6-week supply of niraparib/placebo is provided, these dispensing visits should be planned to coincide with visits in which PROs are administered at the site (Table 3); laboratory samples required for the skipped visits should be done and can be performed at a local laboratory.

Treatment with niraparib/placebo will continue until radiographic PD is documented per RECIST v1.1 and verified by BICR or other treatment discontinuation criterion is met. Participants with evidence of disease at 3 years who, in the opinion of the treating physician may derive further benefit from continuous treatment, may be treated beyond 3 years. Participants continuing niraparib treatment at the time of final analysis may be offered the option to continue niraparib (see Section 6.7). Dose interruptions of either agent may be implemented according to the interruption guidelines in this protocol. Dose reductions of niraparib/placebo should be implemented according to the guidelines in this protocol (see Section 4.4.1).

Randomization may occur up to 3 days prior to Cycle 1/Day 1 if all eligibility criteria are met. Administration of pembrolizumab will continue every 21 (±3) days.

Clinic visits will occur as indicated in Table 3. CBC will be monitored weekly for the first 4 weeks of the treatment period, and BP and heart rate will be monitored weekly for the first 8 weeks of the treatment period. If participants are unable to attend the clinic visits on Cycle 1/Day 8, Cycle 2/Day 15, and Cycle 3/Day 8 for medical reasons or due to circumstances outside their control, alternative means of performing study assessments may be implemented by the Sponsor that may include deploying trained staff to the participant's home to perform protocol-required assessments.

Approximately 650 participants are expected to be randomized in the study.

Participants will be stratified by:

- histology (squamous versus non-squamous),
- PD-L1 status (TC <1% and NE versus ≥1%), and
- best response to SoC induction chemotherapy (PR/CR versus SD).

The proportion of participants with PR/CR versus SD will be monitored and the total amount of participants with SD will be capped at approximately 50%.

Imaging will be collected/conducted as follows. Baseline imaging for all participants will include the chest, abdomen, CNS, and other sites as clinically indicated. Additional details are provided in Section 8.1.1.1.

- Baseline: Eligibility scan(s) conducted within 28 days prior to randomization
- On Study: Every 6 weeks (every 42 days [±7] days) from the date of randomization for a total of 48 weeks or until radiographic PD is documented

per RECIST v1.1 and verified by BICR. From Week 49 on, subsequent imaging for participants who remain on treatment will be performed every 12 weeks (every 84 days [±7] days), or more frequently if clinically indicated, until radiographic PD is documented per RECIST v1.1 and verified by BICR.

- In Follow-up: For participants who reach the 35 cycle limit and choose to stop all study treatment but continue pembrolizumab alone (through means outside the study), imaging should continue to be sent as per the study schedule until radiographic PD is documented per RECIST v1.1 and verified by BICR, death, withdrawal of consent, or becoming lost-to-follow-up, whichever comes first.

Assessment of CNS lesions will be made per RECIST v1.1 as part of the overall baseline assessment by the Investigator. In order to be identified as a target lesion, CNS lesions must be at least 10 mm in diameter. Up to 2 brain lesions may be identified and followed as target lesions; additional measurable and non-measurable brain lesions should be followed as non-target lesions.

Each participant will have an EOT Visit at the time it is decided to discontinue study treatment. Safety Follow-up Visits are conducted at 30 (±3) days and 90 (±3) days after the EOT Visit, and Survival Follow-up Visits every 90 (±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). Information regarding subsequent anticancer treatments (including regimen and number of cycles), as well as the date of any subsequent PD (ie, for PFS2 determination), will be collected during these Safety and Survival Follow-up visits.

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 EOT Visit, and the EORTC QLQ-C30, EORTC QLQ-LC13, and CCI [redacted] should be collected at the 30- and 90-day Safety Follow-up Visits, as described in Table 3.

An IDMC will be established to provide independent review and assessment of the efficacy and safety data in a systematic manner and to safeguard the interest and safety of the participants in the study. An interim safety analysis will be assessed by the IDMC when approximately 120 participants total across both treatment arms have completed at least 2 cycles of maintenance therapy. IDMC periodic safety data reviews will be performed as specified in the IDMC charter.

All AEs and SAEs will be collected and recorded for each participant from the day of signing the main study 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 all AESIs will be collected and reported until study closeout, or as otherwise indicated in Section 8.3.7. Any pregnancies that occur within 180 days post-treatment will be reported.

CCI

The exposure of niraparib in combination with pembrolizumab will also be evaluated.

CCI

4.2. Number of Participants

Approximately 650 participants are expected to be randomized in the study.

4.3. Treatment Assignment

Participants who have achieved SD, PR, or CR following SoC induction with platinum-based chemotherapy and pembrolizumab and who meet all eligibility criteria will be randomized in a 1:1 ratio to receive niraparib plus pembrolizumab or placebo plus pembrolizumab as maintenance therapy. Participants will be stratified by:

- histology (squamous versus non-squamous),
- PD-L1 status (TC<1% and NE versus ≥1%), and
- best response to SoC induction chemotherapy (PR/CR versus SD).

The proportion of participants with SD will be carefully monitored at the time of randomization, and a cap will be applied at SD enrollment threshold of 50% of total sample size to prevent the proportion of participants entering the study to differ significantly from the proportions observed in the KEYNOTE-189 and KEYNOTE-407 studies (approximately 35% to 40%) [Gadgeel, 2020; Paz-Ares, 2018].

4.4. Risk Minimization Measures: Criteria for Dose Adjustment and IMP Discontinuation

4.4.1. Niraparib/Placebo

To manage adverse reactions, Investigators may consider interruption of treatment, dose reduction, or discontinuation, consistent with the following guidance. Participants who discontinue treatment with niraparib/placebo may continue treatment with pembrolizumab.

CCI

Table 7: Risk Minimization Measures for Non-Hematologic Adverse Reactions

Adverse Reaction	Risk Minimization Measure
Nonhematologic NCI-CTCAE Grade ≥3 adverse reaction where prophylaxis is not considered feasible or adverse reaction event persists despite treatment	Withhold niraparib/placebo until resolution of adverse reaction and/or for a maximum of 28 days. Resume niraparib/placebo at a reduced dose per Table 6. For recurrence of Grade 3 (with no resolution to a baseline or Grade 1) and Grade 4 adverse reactions, IMPs should be discontinued (see Section 7.1).
NCI-CTCAE Grade ≥3 treatment-related adverse reaction event lasting more than 28 days while the participant is administered niraparib/placebo 100 mg/day	Discontinue medication.
Posterior Reversible Encephalopathy Syndrome (PRES)[a]: There have been reports of PRES in patients receiving niraparib.	Discontinue niraparib and treat specific symptoms including hypertension.

Abbreviation: NCI-CTCAE=National Cancer Institute-Common Terminology Criteria for Adverse Events; PRES=Posterior Reversible Encephalopathy Syndrome.

[a] PRES is a rare, reversible, neurological disorder which can present with rapidly evolving symptoms including seizures, headache, altered mental status, visual disturbance, or cortical blindness, with or without associated hypertension. A diagnosis of PRES requires confirmation by brain imaging, preferably MRI.

Table 8: Risk Minimization Measures for Hematologic Adverse Reactions

Laboratory follow-up: Weekly blood draws for CBC will be monitored until the adverse reaction resolves, and to ensure safety of the new dose, weekly blood draws for CBC will also be required for an additional 4 weeks after the adverse reaction has been resolved to the specified levels, after which monitoring every 4 weeks may resume. **IMP discontinuation:** For recurrence of NCI-CTCAE Grade 3 (with no resolution to a baseline or Grade 1) and NCI-CTCAE Grade 4 toxicity/adverse reaction, IMPs should be discontinued (see Section 7).	
Adverse Reaction	**Risk Minimization Measure**
Platelet count <100,000/µL	First occurrence: Withhold niraparib/placebo for a maximum of 28 days and monitor blood counts weekly until platelet counts return to ≥100,000 /µL. Resume niraparib/placebo at the same or reduced dose per Table 6. If nadir platelet count was <75,000/µL, resume at a reduced dose after recovery.
	Second occurrence: Withhold niraparib/placebo for a maximum of 28 days and monitor blood counts weekly until platelet counts return to ≥100,000/µL. Resume niraparib/placebo at a reduced dose per Table 6. Discontinue niraparib/placebo if the platelet count has not returned to acceptable levels within 28 days of the dose interruption period or if the participant has already undergone dose reduction to 100 mg once daily.[a]
Neutrophil <1,000/µL or Hemoglobin <8 g/dL	Withhold niraparib/placebo for a maximum of 28 days and monitor blood counts weekly until neutrophil counts return to ≥1,500/µL or hemoglobin returns to ≥9 g/dL. Resume niraparib/placebo at a reduced dose per Table 6. Discontinue niraparib/placebo if neutrophil or hemoglobin level has not returned to acceptable levels within 28 days of the dose interruption period, or if the participant has already undergone dose reduction to 100 mg once daily.[a]
Hematologic adverse reaction requiring red blood cell and/or platelet transfusion	For participants with platelet count ≤10,000/µL, 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. RBC transfusion is at the discretion of the Investigator. Resume niraparib/placebo at a reduced dose.

Adverse Reaction	Risk Minimization Measure
MDS/AML	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 standards of practice. The study site must receive a copy of the hematologist's report of aspirate/biopsy findings, which must include a classification according to the WHO, and other sample testing reports related to MDS/AML. If a diagnosis of MDS/AML is confirmed by a hematologist, the participant must permanently discontinue study treatment.

Abbreviations: AML=acute myeloid leukemia; CBC=complete blood count; MDS=myelodysplastic syndrome; NCI-CTCAE=National Cancer Institute - Common Terminology Criteria for Adverse Events; RBC=red blood cell; WHO=World Health Organization.
[a] If MDS/AML is confirmed, discontinue niraparib/placebo.

4.4.2. Pembrolizumab

Dose reductions of pembrolizumab are not permitted in this study. Pembrolizumab treatment may be interrupted or discontinued due to toxicity. AEs (both non-serious and serious) associated with pembrolizumab exposure may represent an immunological etiology. These AEs may occur shortly after the first dose or several months after the last dose of treatment. Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs. Adverse reactions to pembrolizumab should be managed consistent with local practice guidelines and/or local prescribing information. See Section 6.6.3 for a description of rescue medications and supportive care guidelines.

Pembrolizumab dose interruptions will also be permitted for reasons not related to study therapy (eg, vacation or surgical event). Interruptions exceeding 3 weeks duration must be discussed with the Sponsor. Reasons for interruptions must be documented in the eCRF.

Participants who discontinue treatment with pembrolizumab may continue treatment with niraparib/placebo.

4.5. End of Study

The end of the study is defined as the date of the last scheduled procedure shown in Table 3 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 shown in Table 3.

Survival follow-up will continue until approximately 60% of the total number of randomized participants have died. Participants deriving benefit who are still receiving niraparib at the time of study completion may continue to receive niraparib under this protocol or under an extension study, managed access, or other program, as applicable. Refer also to Section 6.7 for further details.

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. If a site is using the pre-screening period, the participant must also sign the pre-screening ICF. Baseline and on-study imaging for all participants will include the chest, abdomen, CNS, 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 days prior to randomization. Note that source documents must clearly identify the SoC 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).

Assessment of CNS lesions will be made per RECIST v1.1 as part of the overall baseline assessment by the Investigator. In order to be identified as a target lesion, CNS lesions must be at least 10 mm in diameter. Up to 2 brain lesions may be identified and followed as target lesions; additional measurable and non-measurable brain lesions should be followed as non-target lesions.

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.

   Note: Participants in Korea are eligible if they are ≥19 years of age at the time informed consent is obtained.

2. Participants must have a histologically or cytologically confirmed diagnosis of NSCLC without known targetable driver alteration (either non-squamous or squamous histology; mixed histology is allowed) for which an approved targeted therapy is available in the 1L induction/maintenance therapy setting.

3. Participants must have advanced (Stage IIIB or Stage IIIC, not amenable to definitive chemoradiotherapy [CRT]) or metastatic (Stage IV) NSCLC as defined by the AJCC 8th Edition Staging Manual.

4. Participants must have completed at least 4 but no more than 6 cycles of SoC 1L platinum-based induction chemotherapy with pembrolizumab (according to SoC defined by NCCN and/or ESMO Clinical Practice Guidelines for NSCLC).

   Note: To support the transition from 1L induction to 1L maintenance therapy, a transition period that is 6 weeks, in duration, starting from the last dose of 1L induction therapy should occur (up to 7 weeks may be permitted with Sponsor approval). This transition period allows for recovery from chemotherapy-related hematological toxicity before initiating treatment with niraparib/placebo. During this transition period, pembrolizumab administration in the absence of chemotherapy should occur in the cycle immediately following the last cycle of 1L induction therapy (ie, 21 [±3] days after the last cycle of induction). If a transition period with administration of pembrolizumab only is not in accordance with standard prescribing directions and/or a pembrolizumab dose delay is needed that is greater than 3 weeks then the delay must be discussed with the Sponsor and reasons for the delay should be documented in the eCRF.

5. Participants must have SD, PR, or CR of their NSCLC per Investigator's assessment after completion of 4 to 6 cycles of SoC 1L platinum-based induction chemotherapy with pembrolizumab.

   Note: Baseline imaging may be done as part of SoC 1L induction period so long as imaging is within 28 days of randomization. If baseline imaging falls outside of this 28-day window, then new imaging will be needed (CT [preferred] or MRI scan [if clinically indicated] of the chest and abdomen, and MRI [preferred; CT if MRI not possible] of the brain).

   Note: For participants with only non-measurable/non-target disease at the onset of platinum-based induction therapy with pembrolizumab, a RECIST v1.1 response of non-complete response (CR)/non-progressive disease (PD) is consistent with SD as an overall response.

6. Participants must have an ECOG performance status of 0 or 1.

7. Participants must have a life expectancy of at least 12 weeks.
8. Participants must have adequate organ and bone marrow function defined as:

Absolute neutrophil count:	≥1,500/µL
Platelets:	≥100,000/µL
Hemoglobin:	≥9 g/dL or 5.6 mmol/L
CL_{Cr}:	>30 mL/min as estimated by the Cockcroft-Gault equation (Appendix 11)
Total bilirubin:	≤1.5×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%)
AST and 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 current active liver or biliary disease are excluded (with the exception of Gilbert's syndrome or asymptomatic gallstones, liver metastases, or otherwise stable chronic liver disease per Investigator assessment).

9. Participants must submit FFPE tumor specimens preferably collected after being diagnosed with metastatic disease and prior to initiating SoC induction therapy (chemotherapy or radiation) (ie, collected at time of diagnosis of advanced [Stage IIIB/IIIC] or metastatic [Stage 4] NSCLC), from location(s) not irradiated prior to biopsy. If available, a FFPE tissue block should be provided; if not available, freshly cut, unstained slides (<30 days from the date of sectioning) are acceptable.
10. Participants with toxicity from SoC 1L induction therapy must have recovered to a level of organ and bone marrow function as defined by Inclusion Criterion #8 and there is no ongoing toxicity of CTCAE Grade ≥3.
11. Participants must be able to swallow and retain orally administered study treatment.
12. 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 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, as described in Appendix 3, 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 relationship 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.
- Additional requirements for pregnancy testing during and after study treatment are described in Section 6.6.2.
- 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.

See Appendix 3 for a list of acceptable birth control methods. Information must be captured appropriately within the site's source documents.

13. 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 sexual activity as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent

      or
    - Must 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; See Appendix 3)
14. 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 mixed small cell lung cancer or sarcomatoid variant NSCLC.
2. Participants have received prior PARP inhibitor(s) in prior lines of treatment.
3. Participants have systolic BP >140 mmHg or diastolic BP >90 mmHg.
4. Participants have any clinically significant gastrointestinal abnormalities that may alter absorption such as malabsorption syndrome or major resection of the stomach and/or bowels.
5. Participants have leptomeningeal disease, carcinomatous meningitis, symptomatic BM, or radiographic signs of CNS hemorrhage.

Note: Participants with asymptomatic BM (ie, off corticosteroids and anticonvulsants for at least 7 days) are permitted.

6. Participants have received colony-stimulating factors (eg, granulocyte macrophage colony-stimulating factor or recombinant erythropoietin) within 4 weeks prior to the first dose of study treatment.
7. Participants have active or previously documented autoimmune or inflammatory disorder, including:
    a. Active infection
    b. Known diagnosis of immunodeficiency (including known history of human immunodeficiency, HIV, or infection) or is receiving chronic systemic steroid therapy (eg, >30 days) or any other form of immunosuppressive therapy within 7 days prior to the first dose of study treatment
    c. Active autoimmune disease that has required systemic treatment in the past 2 years (ie, with use of disease-modifying agents, corticosteroids, or immunosuppressive drugs). Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment.
    d. History of organ transplant
8. Participants are receiving chronic systemic steroids (prednisone >20 mg per day). Participants with asthma who require intermittent use of bronchodilators, inhaled steroids, or local steroid injections would not be excluded from the study.
9. Participants have previously or are currently participating in a treatment study of an investigational agent within 4 weeks of the first dose of SoC 1L induction therapy preceding the study.
10. Participants have received prior systemic cytotoxic chemotherapy (IV or intraperitoneal), biological therapy (including checkpoint inhibitor), or hormonal therapy for cancer, or received thoracic radiation therapy of >30 Gy within 6 months of the first dose of the start of standard of care 1L induction therapy.
11. Participants have received live vaccine within 30 days of planned start of study randomization.
12. Participants have known hypersensitivity to the components of niraparib, placebo, or pembrolizumab or their formulation excipients.
13. 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.
14. Participants have other active concomitant malignancy that warrants systemic, biologic, or hormonal therapy.
15. Participants 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.

16. Participants 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.
17. Participants have high medical risk due to a serious, uncontrolled medical disorder; non-malignant systemic disease; or active, uncontrolled infection. 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.
18. Participant is 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.
19. 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. For potent immunosuppressive agents, participants with presence of hepatitis B core antibody should also be excluded.
20. Participants have a known history of MDS or AML.
21. Participants have a known history of active tuberculosis [Lewinsohn, 2017].
22. Participants have current active pneumonitis within 90 days of planned start of the study or a known history of interstitial lung disease, drug-related pneumonitis, or radiation pneumonitis requiring steroid treatment.

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.

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened.

6. STUDY TREATMENT(S) AND CONCOMITANT THERAPY

6.1. Study Treatment(s) Administered

Details about the investigational products are provided in Table 9.

Table 9: Investigational Products

	Investigational Product		
Intervention name	CCI [redacted]		Pembrolizumab (25 mg/mL)
Intervention description			Solution for infusion See Section 6.1.2
Type	Drug	Drug	Biologic
Dosage formulation	CCI [redacted]	Tablet	Single-dose vial
Unit dose strength		100 mg	100 mg/4 mL (25 mg/mL)
Dosage levels	CCI [redacted]		200 mg every 3 weeks (See Section 6.1.2 and Section 6.2.3.2)
Route of administration	CCI [redacted]	Oral	Intravenous
Use	CCI [redacted]		
Authorized AxMP/Unauthorized AxMP	Not applicable	Not applicable	Not applicable
Sourcing	Provided centrally by the Sponsor.	Provided centrally by the Sponsor.	Provided centrally by the Sponsor or locally by the study site, subsidiary, or designee.
Physical description (Packaging and labeling; also see Section 6.2.1)	CCI [redacted] Each CCI [redacted] will be labeled as required per country requirement.	CCI [redacted] Each CCI [redacted] will be labeled as required per country requirement.	Solution for intravenous infusion. Where supplied centrally by the sponsor, CCI [redacted] will be labeled as required per country requirement. Where supplied locally by the study site, subsidiary, or designee, CCI [redacted] will be provided as commercially available.

	Investigational Product		
Intervention name	CCI		Pembrolizumab (25 mg/mL)
Current/former name(s) or alias(es)	CCI	NA	CCI
Manufacturer	GSK		CCI

6.1.1. CCI

CCI

6.1.2. Pembrolizumab

Pembrolizumab is a potent and highly selective humanized mAb of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Pembrolizumab for injection may be supplied as 50-mg lyophilized powder single-use vials or 100 mg/4 mL (25 mg/mL) solution in a single-dose vial.

Pembrolizumab will be administered by IV infusion at a dose of 200 mg over an approximate 30-minute time period.

Details on the dose calculation, preparation, and administration are provided in the local prescribing information.

6.2. Preparation/Handling/Storage/Accountability

6.2.1. Study Drug Packaging and Labeling

Niraparib tablets and matching placebo will be packaged in high-density polyethylene bottles with child-resistant closures. Participants will be provided enough tablets to accommodate 21 days of dosing with up to +5 days for visit flexibility.

Pembrolizumab may be provided centrally by the Sponsor or may be provided locally by the study site, and it is provided as a commercially available dosage formulation; CCI will be labeled as required per country requirement. Where supplied locally by the study site, subsidiary, or designee, CCI will be provided as commercially available. Pembrolizumab is an approved treatment for participants with NSCLC; it is expected that pembrolizumab will be supplied as SoC for this cohort. Refer

to pembrolizumab prescribing information for instructions and precautions regarding preparation.

The label text of the study treatments will comply with Good Manufacturing Practice and national legislation to meet the requirements of the participating countries. The niraparib study treatment will be labeled in a blinded fashion.

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 Reference 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. Administration

CCI

Niraparib/placebo will be dispensed to participants on Day 1 of every cycle (every 21 days) thereafter until radiographic PD is documented per RECIST v1.1 and verified by BICR or other treatment discontinuation criterion is met. Participants with evidence of disease at 3 years, who in the opinion of the treating physician can derive further benefit from continuous treatment, can be treated beyond 3 years. The Study Reference Manual contains descriptions of the packaging of niraparib/placebo and instructions for administration of niraparib/placebo. After completing 35 cycles of pembrolizumab, or if the participant has discontinued pembrolizumab for another reason, participants may receive a 6-week supply of niraparib/placebo and return for clinic visits on an every other week cycle basis to collect assessments. In such instances where a 6-week supply of

niraparib/placebo is provided, these dispensing visits should be planned to coincide with visits in which PROs are administered at the site (see Table 3).

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

Dose adjustments are described in Section 4.4.1.

CCI

[redacted]

6.2.3.2. Pembrolizumab

On Cycle 1/Day 1, the first dose of niraparib/placebo and the first dose of on-study pembrolizumab will be administered. Administration of pembrolizumab will continue every 21 (±3) days. Pembrolizumab will be administered before the niraparib dose at the study site after all procedures and assessments have been completed as detailed in Table 3. Treatment with pembrolizumab may continue for up to a maximum total of 35 cycles from the beginning of SoC induction therapy (ie, approximately 92 weeks from randomization), after which the participant may continue to receive niraparib or placebo monotherapy. Treatment with pembrolizumab may extend beyond 2 years (>35 cycles) in countries where continued pembrolizumab use is approved in accordance with SoC per label and upon Sponsor approval. As of November 16, 2023, the Sponsor may no longer approve new requests for pembrolizumab treatment beyond 35 cycles. Any participant who is still receiving pembrolizumab through the study will need to acquire the drug through means outside of the study.

Pembrolizumab will be administered in accordance with the product's standard prescribing instructions at a dose of 200 mg as an IV infusion over approximately 30 minutes. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. Given the variability of infusion pumps from site to site, however, a window between -5 minutes and +10 minutes is permitted (ie, infusion time is 30-minutes [-5 minutes / +10 minutes]).

Participants may receive premedication for mild to moderate infusion reactions in accordance with the CCI [redacted] label including antipyretic and antihistamines.

Refer to the prescribing information for specific instructions for the preparation of the pembrolizumab infusion and administration of the infusion solution.

Descriptions of the packaging of pembrolizumab and instructions for administration of pembrolizumab will be provided in the local prescribing information.

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 Reference Manual.

The Pharmacist will dispense study treatment for each participant according to the protocol and Study Reference 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 Study Reference Manual 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 on-site 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. Measures to Minimize Bias: Randomization and Blinding

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

6.3.1. Randomization Scheme

Randomization will occur centrally in a double-blind manner using an integrated web response system. Participants will be assigned randomly in a 1:1 ratio to either the

niraparib/pembrolizumab or the placebo/pembrolizumab arms of the study. Participants will be randomized according to the following stratification factors:

- histology (squamous versus non-squamous),
- PD-L1 status (TC <1% and NE versus ≥1%), and
- best response to SoC induction chemotherapy (PR/CR versus SD).

Participants with a not evaluable PD-L1 status will be included in the PD-L1 TC <1% and NE group. The proportion of participants with PR/CR versus SD will be monitored and the total amount of participants with SD will be capped at approximately 50%.

6.3.2. Blinding and Breaking the Blind

The identity of the treatments will be concealed by the use of study treatments that are all identical in appearance, packaging, labeling, and schedule of administration.

The participant, Investigator, blinded study staff, and the blinded Sponsor study team and its representatives will be blinded to the participant's assigned treatment from the time of randomization until database lock. At the time of database freeze for the primary PFS/OS analysis, select members of the Sponsor study team will be unblinded to conduct the final analysis and review the results in accordance with the study unblinding plan.

If an individual's role on the study requires information about treatment assignment (eg, an individual is involved in emergency unblinding), procedures will be used to ensure all other personnel remain blinded.

In the event unblinding has occurred, the circumstances necessitating unblinding (ie, date and details about the situation leading to unblinding) must be documented promptly, and the Sponsor Medical Monitor notified as soon as possible. Only the Principal Investigator or delegate should be unblinded to the respective participant's code. Study site personnel and Sponsor personnel directly associated with the conduct of the study should not be unblinded.

In case of an emergency, the Investigator or appropriate delegate has the sole responsibility for determining if unblinding of a participants' intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. Full instructions for emergency unblinding procedures are provided in the electronic randomization system and user guide.

If the Investigator decides that unblinding is warranted, the Investigator should make every effort to contact GSK prior to unblinding a participant's intervention assignment unless this could delay emergency intervention of the participant. If a participant's intervention assignment is unblinded GSK must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and case report form, as applicable.

A participant will be discontinued from study intervention if the participant's intervention code is unblinded by the investigator or treating physician. The primary reason for

discontinuation (the event or condition that led to the unblinding) will be recorded in the eCRF; refer to Section 7.1 for additional details.

GSK's Global Clinical Safety and Pharmacovigilance (GCSP) staff may unblind the intervention assignment for any participant with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the participant's intervention assignment, may be sent to the Investigators in accordance with local regulations and/or GSK policy.

Designated independent representatives may be unblinded for population PK and PK/PD analyses as outlined in Section 9.4.6.

6.4. Study Treatment Compliance

Compliance with inclusion and exclusion criteria will be assessed as outlined in Section 5.1 and Section 5.2, respectively.

Study treatment (niraparib/placebo and pembrolizumab) 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(s) at home, compliance with niraparib/placebo will be assessed by direct questioning or counting returned tablets 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 as detailed in Section 6.2.4.

6.5. Treatment of Overdose

For this study, a dose of niraparib/placebo or pembrolizumab 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.

6.6. 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.

6.6.1. Prohibited Medications

Known prior medications that exclude a participant from participating in the study are described in the exclusion criteria (Section 5.2).

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
- Prolonged systemic glucocorticoid therapy (>7 days) for any purpose other than to modulate symptoms from an immune-related AE(s)

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, clozapine, theophylline, and ropinirole). Caution is then recommended when niraparib is combined with substrates of breast cancer resistance protein (eg, irinotecan, 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 co-administered 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 and local practice guidelines, and package insert for pembrolizumab for information on the general management of the participants receiving these therapies.

6.6.2. Contraception

Niraparib and pembrolizumab are known to have properties that require participants to use contraception. For details on niraparib, refer to the current niraparib Investigator's Brochure and the pembrolizumab package insert.

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 (see Appendix 3), or be of non-childbearing potential, as defined in Section 5.1.

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 (Table 11). See Appendix 3 for a list of acceptable contraceptive methods. Abstinence is acceptable if this is the established and preferred contraception for the participant.

Table 11: 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

6.6.3. Rescue Medications and Supportive Care Guidelines During Treatment with Pembrolizumab

Refer to the pembrolizumab prescribing information for specific instructions on rescue medication and supportive care guidelines.

6.6.4. Other Study Restrictions

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

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

6.7. Continued Access to Study Intervention After the End of the Study

Following database freeze (see Section 6.3.2), participants deriving benefit who were receiving niraparib may be provided an option to continue receiving niraparib under an extension study, managed access, or other program, as applicable. Participants will not be offered continued access to pembrolizumab.

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 may discontinue either treatment with pembrolizumab or niraparib/placebo and continue in the study. Participants who discontinue from all study treatment or from the study will not be replaced. Participants who discontinue from all study treatment will undergo an EOT Visit within 7 days of the decision to discontinue all study treatment for any reason. Safety Follow-up Visits at 30 (±3) days and 90 (±3) days after the EOT Visit, and Survival Follow-up Visits every 90 (±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). Information regarding subsequent anticancer treatments (including regimen and number of cycles), CCI [redacted], will be collected during these visits.

Specific reasons for discontinuing either treatment include the following, in addition to those indicated in Section 4.4. Pembrolizumab treatment discontinuation guidance in local prescribing information should also be followed.

- AE
  - If a participant has any treatment-related NCI-CTCAE v5.0 Grade 3 or 4 AEs (see Table 8 on separate guidelines for platelet count) 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.
  - MDS or AML
  - New primary malignancy other than MDS or AML
  - PRES
  - Thrombocytopenia, if the platelet count has not returned to ≥100,000/µL within 28 days of dose interruption
- Radiographic PD that is documented per RECIST v1.1 and/or verified by BICR
- Risk to the participant as judged by the Investigator, Sponsor, or both
- Clinical progression as defined by the Investigator
- Severe noncompliance with protocol as judged by the Investigator, Sponsor, or both
- Pregnancy
- Patient decision to end treatment

- Inadvertent participant unblinding
- Lost to follow-up
- Death

Treatment with niraparib/placebo will continue until radiographic PD is documented per RECIST v1.1 and/or verified by BICR or another treatment discontinuation criterion is met. Participants with evidence of disease at 3 years who, in the opinion of the treating physician may derive further benefit from continuous treatment, may be treated beyond 3 years. In the instance of recurrence, participants may be permitted to resume treatment after discussion with the Sponsor's Medical Monitor if the Investigator believes the participant may derive benefit from ongoing treatment.

If a participant discontinues treatment for any reason other than Investigator assessed PD per RECIST v1.1, which has been verified by BICR, then tumor assessment scans should continue at the specified intervals until radiographic PD is documented per RECIST v1.1 and verified by BICR or until the start of subsequent anticancer treatment. For those continuing pembrolizumab alone beyond 35 cycles, see Section 4.1 and Section 8.1.1.1 regarding continued imaging.

Participants who discontinue from all study treatments will continue to receive follow-up assessments as part of the study unless they withdraw their consent from the study. If participants are unable or unwilling to attend clinic visits during follow-up, contact to assess survival may be made via another form of communication (eg, telephone, email).

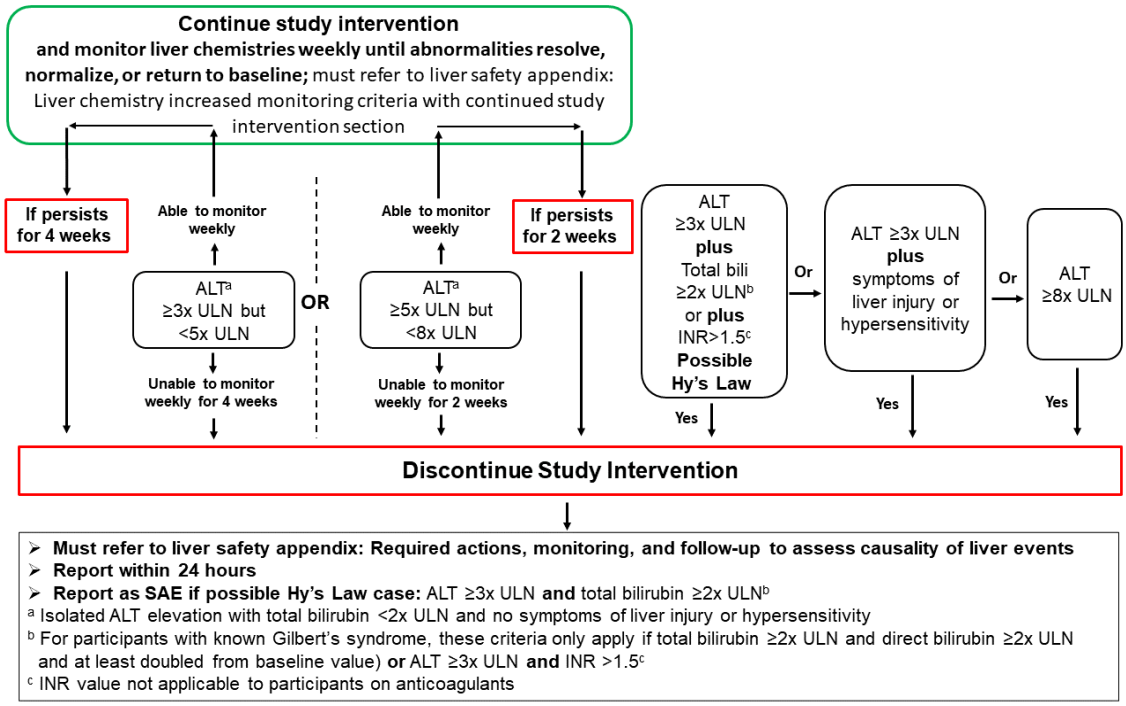
If a participant does not agree to continue in-person visits during the Follow-up Period but is willing to continue participation in the study, a modified follow-up must be arranged to ensure the collection of endpoints and safety information. This follow-up must be done in accordance with the local regulations and could include telephone contact with the participant, contact with a relative or treating physician, or collection of information from medical records. The approach taken should be recorded in the medical records. A participant who agrees to a modified follow-up is not considered to have withdrawn consent or to have withdrawn from the study.

7.1.1. Liver Chemistry Stopping Criteria

Liver chemistry stopping and increased monitoring criteria have been designed to assure participant safety and evaluate liver event etiology.

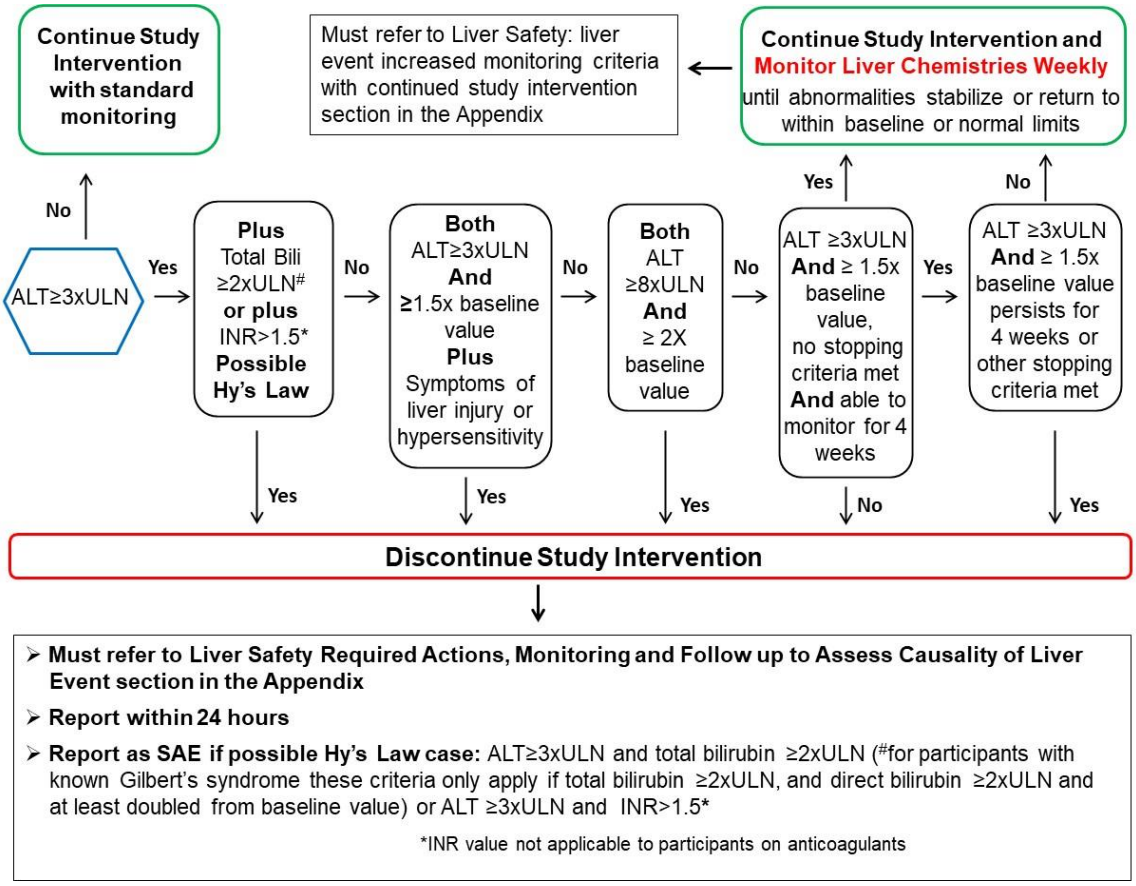
Discontinuation of study treatment for abnormal liver tests is required when a participant meets one of the conditions outlined in the algorithm below or in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules, if the Investigator believes that it is in the best interest of the participant.

Figure 2: Liver Chemistry Stopping and Increased Monitoring Algorithm for Participants With Entry Criteria ALT ≤2.5×ULN



Abbreviations: ALT=alanine transaminase; INR=international normalized ratio; SAE=serious adverse event; Total bili = total bilirubin; ULN=upper limit of normal.

Figure 3: Liver Chemistry Stopping and Increased Monitoring Criteria – Liver Stopping and Monitoring Event Algorithm Including Participants With Documented Liver Metastases/Tumor Infiltration at Baseline and Entry Criteria ALT>2.5×ULN but ≤5×ULN



Abbreviations: ALT=alanine transaminase; INR=international normalized ratio; SAE=serious adverse event; Total bili = total bilirubin; ULN=upper limit of normal.

Liver Safety Required Actions and Follow-up Assessments Section can be found in Appendix 4.

7.1.2. Rechallenge

7.1.2.1. Study Intervention Restart or Rechallenge After Liver Event Stopping Criteria Are Met

Study intervention restart or rechallenge after liver event stopping criteria are met by any participant in this study are not allowed.

7.2. Withdrawal of Consent

If a participant withdraws consent from study treatment, the Investigator is to determine whether the participant is willing to be followed up for subsequent procedures in the long-term follow-up period 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
- Investigator's decision

All participants must be followed for survival, up to the end of the study as defined in the protocol. Discontinuation of study intervention does not affect a study subject's participation in the study. The participant should comply with the protocol SoA (Section 1.3) and data collection should continue.

If the study participant does not agree to continue in-person visits, a modified follow-up must be arranged to ensure the collection of endpoints and safety information. The local regulations must be followed. This could be a telephone contact with the participant, a contact with a relative or treating physician, or collecting information from medical records. The approach taken should be recorded in the medical records. A participant who agrees to modified follow-up is not considered to have withdrawn consent or to have withdrawn from the study.

All participants who permanently discontinue study treatment will be followed for survival and subsequent anticancer therapy including radiotherapy and date of subsequent disease progression. If a participant is unable or unwilling to attend clinic visits during follow-up, contact to assess survival may be made via another form of communication (e.g., telephone, email, etc.).

At the time of planned database locks (e.g., external IDMC reviews, and/or Final Analysis), the Sponsor may request updated survival status to ensure survival data is current and complete. All participants who do not/will not have a scheduled study visit during the defined time period may be contacted for their health status upon Sponsor notification.

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 (Table 3). See SoA (Table 3) for data to be collected at the time of study treatment discontinuation and follow-up and for any further evaluations, including survival status, that need to be completed.

Following study discontinuation, site personnel or an independent third party will attempt to collect publicly available survival status information of the participant, within legal and ethical boundaries, for all participants randomized/enrolled, including those who did not receive study intervention. Public sources may be searched for survival status information. If the survival status of the participant is determined to be deceased or known alive, this will be documented along with other relevant study information. Sponsor personnel will not be involved in any attempts to collect survival status information. The inclusion and analysis of survival status information obtained from an independent third party or study staff review of public records (or other permitted sources) for those participants withdrawn or lost to follow-up is permitted, dependent upon local regulations**.**

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 (every 90 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 or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 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.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

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

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” [ICH E15, 2007].

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. Assessment of Efficacy

8.1.1. Primary Efficacy Endpoints

The primary efficacy endpoint is PFS in the CR/PR Population. PFS is defined as the time from the date of randomization to the date of first radiographic progression as determined by BICR or death from any cause in the absence of progression, whichever occurs first. Progression will be assessed by BICR using the RECIST v1.1 criteria.

8.1.1.1. Radiographic Evaluation of Tumor Response

Images of the chest, abdomen, CNS, 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 and abdomen 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.

Imaging of the CNS (brain only, unless otherwise clinically indicated) will be performed for all participants by IV contrast-enhanced MRI at baseline and all CNS assessments throughout the study. However, IV contrast-enhanced 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, X-ray) as clinically indicated, in the judgment of the Investigator.

All study participants are required to have CNS images at baseline and at each scheduled image assessment throughout the study to address the key secondary endpoint of CCI [redacted] If the participant has CNS lesions on brain MRI at the required baseline imaging assessment of CNS lesions will be made per RECIST v1.1 as part of the overall baseline assessment by the Investigator. In order to be identified as a target lesion, CNS lesions must be at least 10 mm in diameter. Up to 2 brain lesions may be identified and followed as target lesions; additional measurable and non-measurable brain lesions should be followed as non-target lesions.

Overall progression will be assessed by the Investigator per RECIST v1.1 and/or verified by BICR.

Progressive Disease (PD) should be recorded as the Overall Response per RECIST 1.1 and Verification of Progression (VOP) should only be requested when the Investigator is confident radiologic progression is unequivocal.

If radiologic progression is suspected but not certain, imaging should be re-evaluated at the next scheduled or unscheduled imaging visit and VOP should **not** be requested until PD based on Investigator assessment per RECIST 1.1 has been documented. (As a reminder, equivocal new lesions should be assessed following a “wait and see” approach. An equivocal new lesion has no impact on overall response unless at a later visit it is determined to be unequivocal and evidence of PD.)

Details on RECIST v1.1, including evaluation of target and non-target lesions and definitions of response, are provided in Appendix 6. Imaging will be collected/conducted as follows in Table 12:

Table 12: Overview of Imaging Requirements for Study 213400 by Visit

Imaging Visit	Description
Baseline	• Performed within 28 days prior to randomization • Performed by CT of chest, abdomen, and other sites as clinically indicated. MRI of the brain is preferred for CNS scan requirement • Assessed by Investigator per RECIST v1.1 ○ Eligible participants must have achieved a SD, PR or CR in response to SoC induction chemotherapy • Imaging assessment conducted as part of routine care after the SoC induction chemotherapy period may be used if it is performed within the 28-day window

Treatment Period	• On-study imaging should be scheduled based on the date of randomization (not based on the date of the previous scan(s)).
	  ○ Performed every 6 weeks (every 42 [±7] days) from the date of randomization for 48 weeks (Weeks 6, 12, 18, 24, 30, 36, 42, 48).
	  ○ After Week 48, performed every 12 weeks (every 84 [±7] days) from the date of randomization. (Weeks 60, 72, 84, 96, etc).
	• Performed more frequently if clinically indicated
	• CNS brain scan required at all scheduled timepoints to assess CCI
	• Assessed by Investigator per RECIST v1.1 with radiographic PD verified by BICR

EOT	• For participants who discontinue study treatment due to BICR-verified progression, additional imaging assessment is not required at EOT • For participants who begin a subsequent anticancer treatment prior to BICR-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 Investigator-assessed PD per RECIST v1.1, which has been verified by BICR, should continue monitoring disease status by tumor imaging every 6 weeks (every 42 [±7] days) through week 48 and every 12 weeks (every 84 [±7] days) thereafter until Investigator assessment of radiographic PD is documented per RECIST v1.1 and verified by BICR or until the start of subsequent anticancer treatment. For participants who reach the 35 cycle limit and choose to stop all study treatment but continue pembrolizumab alone (through means outside the study), imaging should continue to be sent as per the study schedule until radiographic PD is documented per RECIST v1.1 and verified by BICR, death, withdrawal of consent, or becoming lost-to-follow-up, whichever comes first.

Abbreviations: BICR=blinded 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; SoC=standard of care; CCI .

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 of combination treatment cycle intervals.

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

8.1.2. Key Secondary Efficacy Endpoints

8.1.2.1. PFS in the ITT Population

PFS in the ITT Population will be evaluated as outlined for the CR/PR Population.

8.1.2.2. OS in the CR/PR Population and in the ITT Population

OS is defined as the time from randomization to the date of death due to any cause. Participants who are alive will be censored at the last date they were known to be alive.

OS will be evaluated in the ITT Population and in CR/PR Population.

8.1.3. Secondary Efficacy Endpoints

8.1.3.1. PFS and CNS-PFS

PFS will be assessed per RECIST v1.1 based on Investigator assessment as a secondary endpoint to serve as a sensitivity analysis for the primary PFS endpoint.

CNS-PFS will be assessed by BICR using RANO-BM.

8.1.3.2. BICR-Assessed PFS per RECIST v1.1 and OS by PD-L1 Status

PFS will be assessed per RECIST v1.1 based on BICR per RECIST v1.1 by PD-L1 status (PD-L1 TC <1% and NE versus ≥1%).

OS will be assessed by PD-L1 status (PD-L1 TC <1% and NE versus ≥1%).

8.1.3.3. Time to Deterioration in Lung Symptoms

TTD is defined as the time from randomization to meaningful deterioration on single and composite endpoints of dyspnea, chest pain, and cough on the EORTC QLQ-LC13.

8.1.3.4. Patient-Reported Outcomes

TTD will be evaluated as a secondary endpoint in this study and is defined as the time from randomization to meaningful deterioration on single and composite endpoints of dyspnea, chest pain, and cough, from the EORTC QLQ-LC13.

In addition, change from baseline in the EORTC QLQ-C30 and EORTC QLQ-LC13 domains will be evaluated as secondary endpoints.

CCI

8.1.5. Patient-Reported Outcome Measures

Summaries of each PRO instrument are provided in Appendix 8.

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 in different regions 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. Free text captured on some PROs such as the PRO CTCAE are not to be used to report AEs.

8.1.6. Pharmacokinetic Sample Collection

Blood samples for niraparib PK will be collected at the time points specified in Table 3 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.

A blood sample for measuring niraparib concentration may be collected for a liver event (Appendix 4).

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

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

CCI

[redacted]

8.2. Assessment of Safety

8.2.1. 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, thyroid function, and urinalysis), vital sign measurements, observations during physical examination, and use of concomitant medications.

All safety parameters will be performed in accordance with Table 3.

8.2.2. 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 SoC induction chemotherapy and cancer history will also be collected.

8.2.3. Physical Examination

Physical examinations and symptom-directed physical examinations will be performed in accordance with the SoC for oncology patients, including those treated with immunotherapy, 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 (see Section 8.3.7), the finding should be recorded and reported according to the SAE reporting process (see Section 8.3.4).

8.2.4. Vital Signs, Height, and Weight

Vital signs, including BP, temperature, pulse rate, respiratory rate, weight, and height and will be measured in accordance with Table 3. 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 (see Section 8.3.7), the event should be recorded and reported according to the SAE reporting process (see Appendix 2).

Height will be measured at Screening only. Weight will be measured at Screening and at every visit.

8.2.5. Pregnancy Testing

Niraparib and pembrolizumab are known to have properties that require the participant to use contraception and may have adverse effects on a fetus in utero. Contraception guidelines are provided in Appendix 3. A negative serum or highly sensitive urine pregnancy test is required within 72 hours prior to Cycle 1/Day 1 and as indicated in Table 3 for females of childbearing potential. The results from these tests must be available and negative before study treatment is administered. Additional pregnancy testing may be necessary if required by local practices or regulations, or if potential pregnancy is suspected.

Female participants of childbearing potential should start using birth control from Screening throughout the study period up to 180 days after the last dose of study treatment. Male participants should use birth control from Screening up to 90 days after the last dose of study treatment. If there is any question that a participant will not reliably

comply with the contraception requirements, they should not be enrolled in the study, and any participant who becomes pregnant should be withdrawn from the study. Any pregnancies that occur within 180 days post-treatment discontinuation are to be reported as described in Section 8.3.5.

8.2.6. Laboratory Assessments

The laboratory variables listed in Table 13 will be determined in accordance with Table 3. During the Screening period; CBC must be measured within 10 days prior to the first dose of study treatment.

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 (see Section 8.3.7), the event should be recorded and reported according to the SAE reporting process (see Section 8.3.4).

Hematologic, blood chemistry and coagulation factor testing may occur more frequently than is specified in Table 3, if medically indicated per Investigator judgment or if the event meets the criteria for study treatment dose modification (see Section 4.4). 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 standards of 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 second primary 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 SoC is sufficient as long as the methods are deemed acceptable after consultation with the Sponsor's Medical Monitor.

Table 13: 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	TSH
Hematocrit		Chloride	Phosphorus	Glucose	T3[c]
Platelet count[d]		CO_2 or bicarbonate[e]	Albumin	Ketones	FT4
Absolute neutrophil count		BUN or urea[f]	Total Protein	Protein	Blood for correlative studies
Absolute lymphocyte Count		Uric acid	Alkaline phosphatase	Nitrite	Lipid panel[g]
		Creatinine	ALT	Leukocyte esterase	
		Glucose	AST	Urobilinogen	
			Lipase or amylase[h]	Bilirubin	
			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; T3=total triiodothyronine; TSH=thyroid-stimulating hormone; 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. PT/INR is not required for those on oral non-VKA oral anticoagulants (NOAC).

[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] Total T3 is preferred; if not available, then free T3 may be tested.

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

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

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

[g] Lipid panel (fasted or non-fasted) should be tested as part of the screening procedures for all participants. Any participant with abnormal levels should be referred to their general practitioner for statin consultation.

[h] Lipase testing may be used in place of amylase testing, as needed. Where both lipase and amylase are available, lipase testing is preferred.

8.2.7. 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.

8.2.8. ECOG Performance Status

Performance status will be assessed using the ECOG scale (see Appendix 9) in accordance with Table 3. The same observer should assess ECOG performance status each time.

8.2.9. General Guidance for Treatment Continuity when Participants are Unable to Come into the Clinic

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

Prior to utilization of any of the measures outlined in this section, discussion and approval must be obtained from Sponsor/Contract Research Organization (CRO).

It is expected that sites participating in niraparib clinical studies will make every effort to ensure proper monitoring and wellbeing of enrolled participants by adhering to safety monitoring as outlined in the protocol SoA. The use of local labs and local radiology centers or of home nursing to reduce the need for the participant to come into the hospital are supported, if deemed necessary for the wellbeing of the participant. These local facilities should be added to regulatory documents, as required. Utilization of home nursing should be as follows:

The Sponsor has retained an in-home nursing vendor to provide aspects of a traditional site visit in the participant's own home, allowing for consistency, continuity, and quality of care throughout the study when a participant may be unable to travel. This service can be utilized for participants who do not wish to travel to the study site or if it was determined not to be in the best interest of the participant to report to the study site.

If sites opt to utilize this service, they must inform the participant that the service will be provided their name, address, and telephone number. Participants must also be told that this information will not be shared with the Sponsor. This conversation must be documented in the source documents. Language describing this process is available for use in the ICF, dependent on local regulations.

The home nursing service may perform the following functions:

- Participant training and education for self-administration of IMP
- Measurement of vital signs
- Limited physical examination including symptom-directed physical examinations
- Local safety and central laboratory assessment sample collection, including blood and urine

- Submission to the participant's site for processing and analysis of safety laboratory assessments
- Processing and submission of the central laboratory assessments to appropriate vendors
- Review/documentation of AEs, SAEs, concomitant medications, and questionnaires to supplement the Investigator
- Completion of visit documentation

Additionally, regulatory guidance issued in response to the COVID-19 pandemic supports the use of central and remote monitoring programs to maintain oversight of clinical sites. Any restrictions in place at the site that will impact monitoring and/or participant access to the site and care providers should be communicated to the Sponsor and CRO.

General rules for participant with limited possibility to travel:

- If possible, replace in-person visits with telephone contact, or alternative location for assessment such as home nursing and local labs and imaging centers.
- In instances where it is desired to reduce participant exposure in clinic, in-person visits every other cycle are acceptable if no ongoing AEs or new AEs. At this time, these missed visits will be considered protocol deviations.
- Delay in oral niraparib/placebo treatment for up to 28 days is acceptable if the participants do not have access to local labs and whereby the site's pharmacy would not dispense the study drug unless participant is cleared with lab tests by Principal Investigator per institution standard operating procedure (SOP).
    - If longer than 28 days interruption is required, contact the Medical Monitor around Day 28 of interruption. This will be reviewed, and recommendations will be made on a case-by-case basis.
- Drug dispensation for niraparib/placebo is possible for multiple cycles, with a maximum of 2 bottles dispensed at once to participants who have not experienced an SAE related to the study medication within the last 3 months (=no ongoing "related" SAE)

Table 14: Critical Data Collection and Safety Precautions

Assessment	Recommendation
CBC	Local laboratory, if possible, or utilize home nursing. Arrangements for the use of a local laboratory should be made by the site including the reporting of results to the Principal Investigator (PI) for review.
Chemistry	Local laboratory, if possible, or utilize home nursing. Arrangements for the use of a local laboratory should be made by the site including the reporting of results to the PI for review.
Pregnancy test	Local laboratory, if possible, or utilize home nursing. Arrangements for the use of a local laboratory should be made by the site including the reporting of results to the PI for review. Per ICF, participant must take measures to avoid pregnancy (Appendix 3)
Niraparib/placebo study medication/dose modifications	CCI [redacted] Niraparib/placebo shipments directly to participants are possible but **must be prospectively discussed and approved by Sponsor**. All required country level, EC/IRB, and/or institutional approvals must be in place prior to any shipment. Shipments made by sites to the participant must comply with protocol requirements. See Section 8.2.9.1. If there have been dose modifications due to AE(s) within the last cycle and monitoring is required, recommended a weekly CBC, done locally; non-hematologic AEs may be monitored by telephone Assess participant missed doses by telephone or home nursing.
AEs	Review ongoing AEs and SAEs by telephone or home nursing. If hematologic AEs are ongoing, a local CBC is desirable. New AEs/SAEs may be assessed by telephone or home nursing; (SAE documentation should be submitted within 24 hours of learning of the event).
Concomitant medications	Reviewed by telephone or home nursing and via medical record review.
PROs on study treatment and follow-up	PRO questionnaires may be conducted via telephone.
Evaluation of response (RECIST v1.1)	CT/MRI if possible.

Table 14: Critical Data Collection and Safety Precautions (Continued)

Assessment	Recommendation
PD	CT/MRI if possible.
Follow-up assessments	Contact participant by telephone or home nursing. This discussion should include assessment of new therapies and OS. Utilize home nursing for other EOT and follow-up assessments if needed.

Abbreviations: AE=adverse event; CBC=complete blood count; CT=computed tomography; EC=Ethics Committee; EOT=End-of-Treatment; IMP=investigational medicinal product; IRB=Institutional Review Board; MRI=magnetic resonance imaging; OS=overall survival; PD=progressive disease; PI=Principal Investigator; PRO=patient-reported outcome; RECIST v1.1=Response Evaluation Criteria in Solid Tumors version 1.1; SAE=serious adverse event.

8.2.9.1. Direct to Participant IMP Shipments

IRB/EC approvals must be obtained as required by your local requirements prior to shipping IMP (i.e., niraparib/placebo) directly to participants. It should be noted that no pre-emptive measures for shipment of pembrolizumab as outlined in this study have been identified at the time of this protocol issuance. Thus, discussion with the Sponsor/CRO and written documentation is required before utilizing this measure.

For delivery of niraparib/placebo from the clinical site to the participant's home, if needed, a vendor has been identified. If sites opt to utilize this service, they must inform the participant that a courier will be provided their name, address, and telephone number to deliver the medication. They must also be told that this information will not be shared with the Sponsor. This conversation must be documented in source documents.

The courier has mitigations for sites that are not allowing external vendors into the clinics; the Sponsor/CRO must be informed of any site-specific barriers so that adequate arrangements can be made prior to shipment of any materials.

For sites that do not wish to utilize the GSK courier service, the following requirements must be met:

The site must provide either the SOP outlining the transportation process if available, or documentation of site transport policies for GSK/CRO review.

CCI

[redacted]

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

The definitions of an AE, SAE, and treatment-emergent AE (TEAE) can be found in Appendix 2. The AESIs are defined in Section 8.3.7.

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 and remain responsible for following up all events.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 2.

8.3.1. 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 3. 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 3.

- AESIs will be collected and reported from the signing of the main study ICF until study closeout at the time points specified in Table 3 and as described in Section 8.3.7.
- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded as Medical History/Current Medical Conditions, not as AEs.
- All SAEs will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 2. The Investigator will submit any updated SAE data to the Sponsor 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.

8.3.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrence. Freely reported symptoms on questionnaires such as the PRO-CTCAE are not reviewed by the study staff as safety data and are not to be used to report an AE.

8.3.3. 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 (including AESIs) will be followed until the event is resolved, stabilized, or otherwise explained; until the participant is lost to follow-up (as defined in Section 7.4); or until the participant has died. Further information on follow-up procedures is given in Appendix 2.

8.3.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the Investigator to the Sponsor 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.

- Investigators have to report to the Sponsor pregnancies, medication errors, abuse, and misuse even in an absence of an AE/SAE, as these may be subjected to local regulatory reporting requirements for the Sponsor.
- 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 (For example, in the EU, the Sponsor will assess expectedness of all serious adverse reactions (SARs) and report SUSARs in an expedited manner to EudraVigilance in accordance with CTR 536/2014 in the EU). Sponsor policy and applicable provision to Investigators as necessary should also apply.

8.3.5. Pregnancy

- Details of all pregnancies in female participants and, if indicated, 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 as described in Section 8.3.4. 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.

8.3.6. 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.

8.3.7. Adverse Events of Special Interest (AESIs)

Selected non-serious AEs and SAEs are also known as AESIs. 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.
- Pneumonitis should be reported to the Sponsor through 90 days after the last dose of study treatment (or until the start of alternate anticancer treatment, whichever occurs first).

8.3.8. Participant Card

The Investigator (or designee) must provide the participant/LAR(s) with a “participant card” containing information about the clinical study. The participant/LAR(s) must be instructed to always keep the participant card in their possession for the duration of the study. In an emergency, this card serves to inform the responsible attending physician/LAR/caregiver/family member that the participant is in a clinical study and that relevant information may be obtained by contacting the Investigator(s) or their back up.

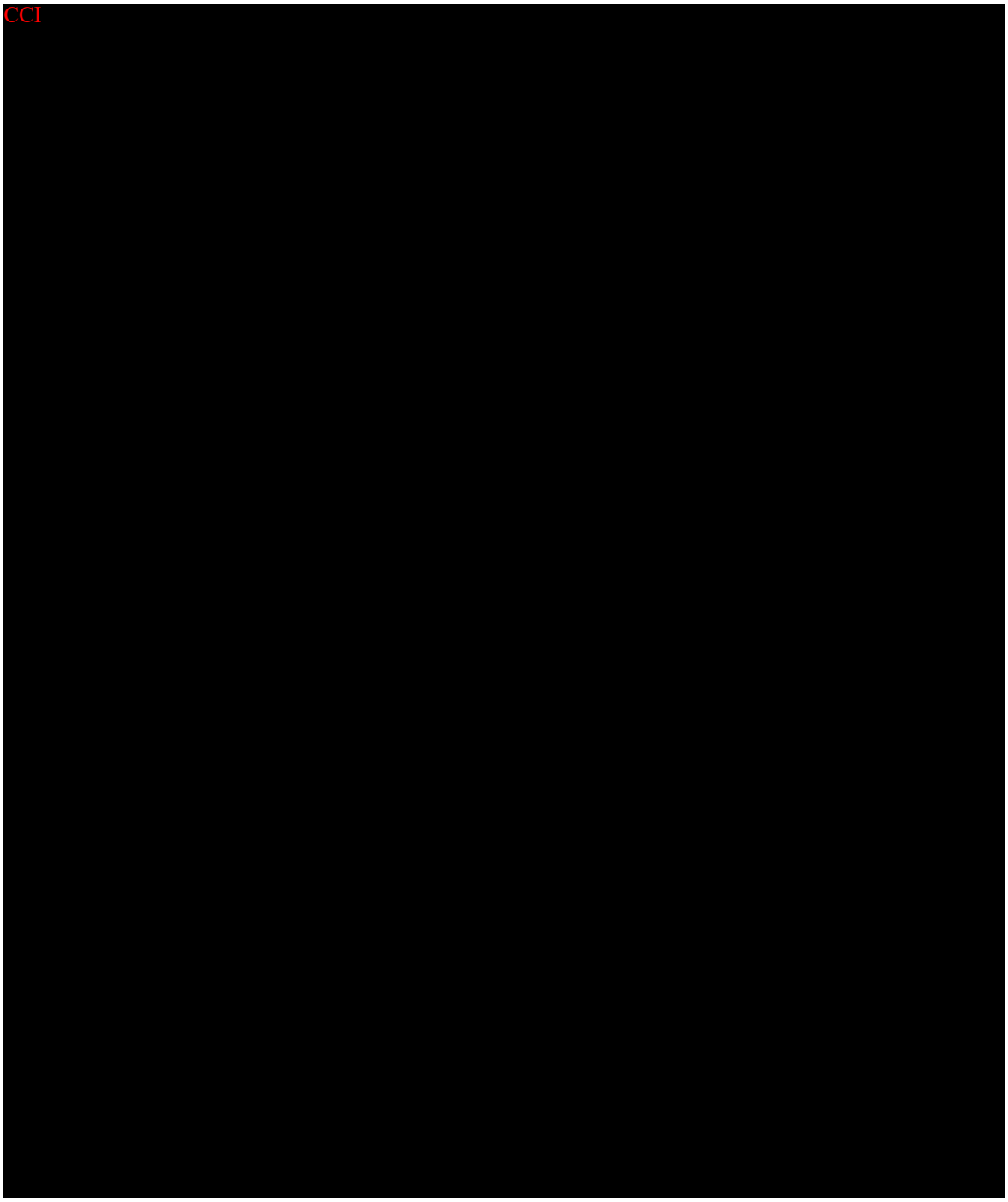
9. STATISTICAL CONSIDERATIONS

Details of the statistical analyses presented below will be provided in the study's SAP. A change to the data analysis methods described in the protocol will require a protocol amendment only if it alters a principal feature of the protocol. The SAP will be finalized prior to database lock. Any changes to the methods described in the plan will be described and justified in the final clinical study report (CSR).

9.1. Statistical Hypotheses

PFS in the CR/PR Population is the primary endpoint for the study.

CCI



CCI

[redacted]

9.2. Sample Size Determination

CCI

[redacted]

CCI

[redacted]

9.3. Analysis Populations

Four analysis populations will be defined as shown in Table 15.

Table 15: Analysis Populations

Population	Description
All Screened	The All Screened Population will consist of all participants who sign the main study ICF to participate in the clinical study. Participants in this population will be used for screen failure summary.
Intent-to-Treat	The ITT Population will consist of all randomized participants whether or not randomized treatment was administered. This population will be based on the treatment and strata to which the participant was randomized and will be the primary population for the analysis of efficacy data. Any participant who receives a treatment randomization number will be considered to have been randomized. Efficacy analyses in the CR/PR population will be conducted in patients with best response to SoC induction chemotherapy with CR/PR in the ITT Population.
Response Evaluable – RECIST	The Response Evaluable Population – RECIST will consist of all randomized participants with evidence of disease at baseline per RECIST v1.1.
Response Evaluable – RANO-BM	The Response Evaluable Population – RANO-BM will consist of all randomized participants with evidence of disease at baseline per RANO-BM BICR assessment.
Safety	The Safety Population will consist of all randomized participant who take at least 1 dose of study treatment. Participants will be analyzed according to the intervention they actually received.
PK	The PK Population will consist of those participants in the Safety Population from whom at least 1 PK sample has been obtained and analyzed. This population will be the primary population for PK analyses.

Abbreviations: ICF=Informed Consent Form; ITT=Intent-to-Treat; PK=pharmacokinetics.

9.4. Statistical Analyses

9.4.1. General Considerations

All participating sites will be pooled for analyses. Unless otherwise specified, all continuous endpoints will be summarized using descriptive statistics, which will include the number of participants (n), mean, standard deviation, median, minimum, and maximum. All categorical endpoints will be summarized using frequencies and percentages. The baseline measurement will be the last value on or before the date of first study treatment.

Demographics, baseline characteristics, and medical history information will be summarized by treatment (i.e., niraparib plus pembrolizumab or placebo plus pembrolizumab) for the ITT Population using descriptive statistics. No formal statistical comparisons will be performed.

Demographics, baseline characteristics, and medical history data for each participant will be provided in data listings.

For the analysis of OS, participants without documented death will be censored at the date the participant was last known to be alive. The PFS event and censoring rules for the primary and supplementary analyses are summarized in Appendix 10. Additional details on handling of missing and spurious data will be documented in the study SAP.

9.4.2. Primary Endpoint

PFS in the CR/PR Population is defined as the primary endpoint for the study. PFS is defined as the time from randomization until the earliest date of PD as assessed by BICR per RECIST v1.1 (Appendix 6), or death due to any cause. Determination of dates for PFS event and dates for censoring is described in Appendix 10.

PFS analysis will be conducted at the time of planned final analysis. The distribution of PFS for each treatment arm will be estimated using the Kaplan-Meier method. The median, 25th, and 75th percentiles and corresponding 95% confidence intervals (CIs) will be estimated using the Brookmeyer-Crowley method (1982). The proportional hazard assumption will be checked through the Kaplan-Meier plot, log(-log(survival) against log (survival time) plot, Schoenfeld residuals, and evaluation of time dependency of HR by adding an interaction term of time by treatment in the Cox proportional hazard model. The distribution of PFS will be compared between the 2 treatment arms using log-rank test stratified by the stratification factors used for randomization. HR and corresponding 95% CI will be estimated from Cox proportional hazard model stratified by randomization factors with treatment arm as the sole explanatory variable. If the proportional hazard assumption does not hold, Restricted Mean Survival Time (RMST) and/or piecewise HR test may be conducted in addition as appropriate.

9.4.3. Secondary Endpoints

9.4.3.1. Key Secondary Endpoints

PFS in the ITT Population, and OS in the CR/PR and ITT Populations are key secondary endpoints (OS is as defined in Section 3). PFS and OS analyses for all of these endpoints will be conducted following a similar approach as for PFS CR/PR.

CCI [redacted]

Cumulative incidence will be estimated by treatment group accounting for competing risk due to non-CNS progression and death. Gray's test will be used to compare the risk of CNS progression between treatment groups. Landmark cumulative incidence function rates at 6 and 12 months as well as corresponding 95% CIs will be calculated.

9.4.3.2. Other Secondary Endpoints

TTD will be analyzed following a similar approach for PFS and OS. TTD is defined as the time from randomization to meaningful deterioration on single and composite endpoints of dyspnea, chest pain, and cough, on the EORTC QLQ-LC13. The single and composite endpoints of dyspnea, chest pain and cough will be scored following the

QLQ-LC13 manual including items 31, 33 to 35, and 40 to assess cough, shortness of breath and chest pain, respectively. The SAP will include the definition of a clinically meaningful threshold of deterioration.

PFS based on Investigator assessment per RECIST v1.1 will be evaluated as a secondary endpoint, serving as a sensitivity analysis for the primary PFS endpoint.

PFS and OS analyses following a similar approach as for the primary analysis will be conducted by PD-L1 status (TC <1% and NE versus ≥1%).

The secondary HRQoL assessments of EORTC QLQ-C30 and EORTC QLQ-LC13 will be analyzed descriptively by changes from baseline in overall score, sub-scores, and individual items when applicable. A repeated measures model adjusting for covariates may be conducted.

Items selected from the CCI were patient-reported symptoms associated with treatment with niraparib or pembrolizumab. As both the CCI and the QLQ-LC13 report shortness of breath and cough, the symptoms of cough and shortness of breath will be measured by QLQ-LC13. This is intended to minimize the participant burden of reporting similar symptoms in different tools.

CCI

9.4.5. Safety Analyses

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

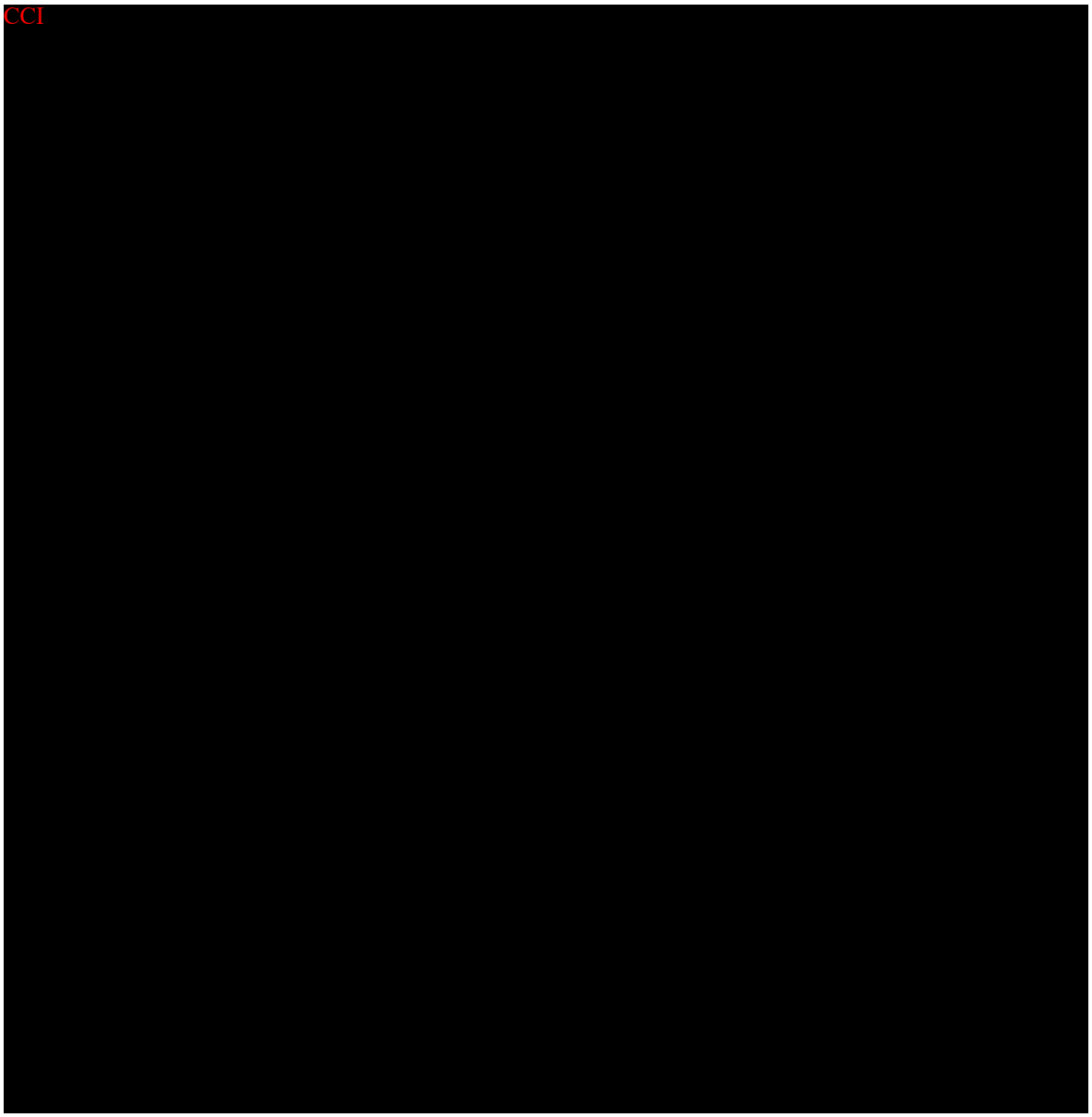
Table 16: Statistical Analytical Methods: Safety

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.
CCI [redacted]	

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.

CCI [redacted]

CCI



9.6. Independent Data Monitoring Committee

An IDMC will be established to provide independent review and assessment of the efficacy and safety data in a systematic manner and to safeguard the interest and safety of the participants in the study. The IDMC charter will describe the procedures related to IDMC operations in greater detail.

An IDMC consisting of at least 2 physicians and 1 statistician as defined in the IDMC charter will review data from the interim analyses and periodic safety reviews. The IDMC will be tasked with making a recommendation to the Sponsor to continue, modify, or stop the study based on their assessment of efficacy and safety information.

Ad hoc meetings may be convened at the discretion of the IDMC or if requested by the Sponsor. Additional details will be provided in the IDMC charter.

An interim safety analysis will be assessed by the IDMC when approximately 120 participants total across both treatment arms have completed at least 2 cycles of maintenance therapy. IDMC periodic safety data reviews will be performed as specified in the IDMC charter.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

11. REFERENCES

Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst. 1993;85(5):365-376.

Ahn MJ, Bondarenko I, Kalinka E, et al. Durvalumab in Combination With Olaparib Versus Durvalumab Alone as Maintenance Therapy in Metastatic NSCLC: The Phase 2 ORION Study. J Thorac Oncol. 2023 Nov;18(11):1594-1606. doi: 10.1016/j.jtho.2023.06.013. Epub 2023 Jun 29.

CCI [redacted]

Bergman B, Aaronson NK, Ahmedzai S, et al. The EORTC QLQ-LC13: a modular supplement to the EORTC Core Quality of Life Questionnaire (QLQ-C30) for use in lung cancer clinical trials. EORTC Study Group on Quality of Life. Eur J Cancer. 1994;30A(5):635-642.

Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: A Cancer Journal for Clinicians. 2018;68(6):394-424.

Camidge DR, Lee EQ, Lin NU, et al. Clinical trial design for systemic agents in patients with brain metastases from solid tumours: a guideline by the Response Assessment in Neuro-Oncology Brain Metastases working group. Lancet Oncol. 2018;19(1):e20-e32.

Cella DF, Tulsky DS, Gray G, et al. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. J Clin Oncol. 1993;11(3):570-579.

Cockcroft DW and Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16(1):31-41.

ESMO Guidelines. Clinical Practice Guidelines - Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2019.

Fennell DA, Porter C, Lester J, et al. Olaparib maintenance versus placebo monotherapy in patients with advanced non-small cell lung cancer (PIN): A multicentre, randomised, controlled, phase 2 trial. EClinicalMedicine. 2022 Aug 11;52:101595. doi: 10.1016/j.eclinm.2022.101595.

Ferlay J, Colombet M, Soerjomataram I, et al. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. Int J Cancer. 2019;144(8):1941-1953.

Gadgeel S, Rodriguez-Abreu D, Speranza G, et al. Updated Analysis From KEYNOTE-189: Pembrolizumab or Placebo Plus Pemetrexed and Platinum for Previously Untreated Metastatic Non-squamous Non-Small-Cell Lung Cancer. J Clin Oncol. 2020:Jco1903136.

Gandhi L, Rodriguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus Chemotherapy in Metastatic Non-Small-Cell Lung Cancer. N Engl J Med. 2018;378(22):2078-2092.

CCI [redacted]

Hanna NH, Schneider BJ, Temin S, et al. Therapy for Stage IV Non-Small-Cell Lung Cancer Without Driver Alterations: ASCO and OH (CCO) Joint Guideline Update. J Clin Oncol. 2020:Jco1903022.

Hochmair M, Schenker S, Dols M, et al. Results from Phase 3 KEYLYNK-008: Pembrolizumab (pembro) with and without maintenance olaparib (ola) after first-line (1L) pembro plus chemotherapy (chemo) for metastatic squamous non-small-cell lung cancer (sqNSCLC). Presented at AACR Annual Meeting. San Diego, California. 08 April 2024. https://www.abstractsonline.com/pp8/#!/20272/presentation/11410

ICH E15. ICH Guideline E15 Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. 2007: Available at: https://database.ich.org/sites/default/files/E15_Guideline.pdf.

Karlic H, Thaler R, Gerner C, et al. Inhibition of the mevalonate pathway affects epigenetic regulation in cancer cells. Cancer Genet. 2015;208(5):241-252.

Konstantinopoulos PA, Waggoner S, Vidal GA, et al. Single-Arm Phases 1 and 2 Trial of Niraparib in Combination With Pembrolizumab in Patients With Recurrent Platinum-Resistant Ovarian Carcinoma. JAMA Oncol. 2019.

Lewinsohn DM, Leonard MK, LoBue PA, et al. Official American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention Clinical Practice Guidelines: Diagnosis of Tuberculosis in Adults and Children. Clin Infect Dis. 2017;64(2):e1-e33.

Lin NU, Lee EQ, Aoyama H, et al. Response assessment criteria for brain metastases: proposal from the RANO group. Lancet Oncol. 2015;16(6):e270-278.

McCarron MM and Devine BJ. Clinical Pharmacy: Case Studies: Case Number 25 Gentamicin Therapy. 1974;8(11):650-655.

NCCN (2020). Non-Small Cell Lung Cancer (NCCN Guidelines), National Comprehensive Cancer Network.

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

Passiglia F, Reale ML, Cetoretta V, et al. Repositioning PARP inhibitors in the treatment of thoracic malignancies. Cancer Treat Rev. 2021 Sep;99:102256. doi: 10.1016/j.ctrv.2021.102256. Epub 2021 Jul 7.

Paz-Ares L, Luft A, Vicente D, Tafreshi A, Gumus M, Mazieres J, et al. Pembrolizumab plus Chemotherapy for Squamous Non-Small-Cell Lung Cancer. N Engl J Med. 2018;379(21):2040-2051.

Ramalingam SS, Blais N, Mazieres J, et al. Randomized, Placebo-Controlled, Phase II Study of Veliparib in Combination with Carboplatin and Paclitaxel for Advanced/Metastatic Non-Small Cell Lung Cancer. Clin Cancer Res. 2017;23(8):1937-1944.

Ramalingam SS, Thara E, Awad MM, et al. JASPER: Efficacy and Safety of First-Line (1L) Niraparib Plus a Programmed Death Receptor 1 Inhibitor (PD-1i) in Patients With Advanced Non–Small Cell Lung Cancer (NSCLC). Poster 1268P Presented at: European Society for Medical Oncology (ESMO) Virtual Congress 2020, 19–21 September, 2020. 2020.

Ramalingam SS, Thara E, Awad MM, et al. JASPER: Phase 2 trial of first-line niraparib plus pembrolizumab in patients with advanced non-small cell lung cancer. Cancer. 2022;128(1):65-74. doi: 10.1002/cncr.33885. Epub 2021 Sep 3.

Salmonson T, Dogné JM, Janssen H, et al. Non-vitamin-K oral anticoagulants and laboratory testing: now and in the future: Views from a workshop at the European Medicines Agency (EMA). Eur Heart J Cardiovasc Pharmacother. 2017 Jan;3(1):42-47. doi: 10.1093/ehjcvp/pvw032. Epub 2016 Dec 25.

Siegel RL, Miller KD, and Jemal A. Cancer statistics, 2020. CA: A Cancer Journal for Clinicians. 2020;70(1):7-30.

Torre LA, Siegel RL, and Jemal A. Lung Cancer Statistics. Adv Exp Med Biol. 2016;893:1-19.

US Food and Drug Administration Center for Drug Evaluation and Research. Guidance for Industry: Evaluating Cancer Drugs in Patients with Central Nervous System Metastases. 2021. Accessed 19 Oct 2021. Available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/evaluating-cancer-drugs-patients-central-nervous-system-metastases

Vinayak S, Tolaney SM, Schwartzberg L, et al. Open-Label Clinical Trial of Niraparib Combined With Pembrolizumab for Treatment of Advanced or Metastatic Triple-Negative Breast Cancer. JAMA Oncol. 2019.

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 require Health Authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- 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 (see Appendix 12 for additional information relating to the EU).
    - 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

CCI [redacted]

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 for the pre-screening period (if being utilized) as well as for the main study, both of which meet 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.
- Sample testing will be done in accordance with the recorded consent of the individual participant/LAR(s).
- By default, collected samples for the study will be stored for a maximum of 15 years. This storage period begins when the last participant performs the last study visit. This timeline can be adapted based on local laws, regulations or guidelines requiring different timeframes or procedures. In all cases, the storage period should be aligned with participant's consent. These additional requirements must be formally communicated to, discussed and agreed with GSK.
- 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.

GSK (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 separate section that addresses the use of participant data and remaining samples for optional further research. The Investigator or authorized designee will inform each participant of the possibility of further research not related to the study/disease. Participants will 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 by ticking the corresponding "Yes" or "No" box on the ICF.

Recruitment Strategy

Feedback from patients with lung cancer on the proposed study design was solicited and the study design amended accordingly. Prior to selecting a site for inclusion in the study,

data will be gathered to understand the numbers of participants that they may be able to enroll from their own patients and networks.

A third party vendor, and the Sponsor developed posters and flyers that may be used in local outreach efforts. These items will provide basic information and site contact information and are designed to assist with recruitment. In addition, a third-party vendor, and the Sponsor will develop several items designed to help the potential participant understand the study including for example, an SoA table to represent the visit tests and procedures, an informed consent flow chart to help site staff walk patients through the ICF, PK story flyer, a participant clinical trial booklet and awareness brochure.

Recruitment will be monitored throughout the study and mitigation plans put in place if needed.

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 only; participant names or any information that would make the participant identifiable will not be transferred.
- GSK will ensure protection of the personal data of the Investigator and site staff, which is collected within the framework of and for the purpose of the study.
- The participant 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.
- The contract between Sponsor and study sites specifies responsibilities of the parties related data protection, including handling of data security breaches and respective communication and cooperation of the parties.
- Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access. GSK and/or trusted third parties working on behalf of GSK and/or institutions working with GSK for the purposes of this study are contractually bound to protect participant coded data. GSK will protect participant coded data and will only share it as described in the ICF.
- GSK has a global, internal policy that requires all GSK staff and complementary workers to report data incidents or breaches immediately, using dedicated tools. Clear procedures are defined for assessing and investigating data breaches to identify and to take appropriate remediation steps, to contain and to mitigate any

risks for individuals resulting from a breach, in compliance with applicable laws.

Committees Structure

A Safety Review Team (SRT) is in place for each GSK product. It comprises a global cross-functional team responsible for the ongoing assessment of benefit-risk for a product. The SRT contribute to the continual assessment of incoming new efficacy and safety information.

Early Safety Data Review AND/OR Committee

An Independent Data Monitoring Committee (IDMC) will be established to ensure participants' safety during this study. The IDMC will convene periodically and will monitor the safety information of the participants. Meeting frequency and details regarding the data to be reviewed will be described in an IDMC charter.

Dissemination of Clinical Study Data

- The key design elements of this protocol and results summaries will be posted on www.ClinicalTrials.gov and/or GSK Study Register in compliance with applicable regulations/GSK policy. GSK will aim to register protocols summaries prior to study start and target results summaries submission within 6 months of primary/study completion date (pediatric population) and within 12 months of primary/ study completion date (adult population). Where external regulations require earlier disclosure, GSK will follow those timelines.
- Where required by regulation, summaries will also be posted on applicable national or regional clinical study registers.
- Where required by applicable regulatory requirements, an Investigator signatory will be identified for the approval of the CSR. The Investigator will be provided reasonable access to statistical tables, figures, and relevant reports. The full study report will be made available upon request, after decision on marketing authorization by regulatory authorities.
- GSK will also provide all Investigators who were involved in the study with the full summary of the study results, including a summary of trial results understandable to laypersons. The Investigator(s) is/are encouraged to share the layperson summary of results with the study participants, as appropriate.
- Where required by regulation, the names of the Sponsor signatory and Investigator signatory will be made public.
- GSK will provide the Investigator with the randomization codes and participant-level line listings for their site only after completion of the full statistical analysis.
- GSK intends to make anonymized participant-level data from this study available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve participant care. This helps ensure the data provided by study participants are used to maximum effect

in the creation of knowledge and understanding. Requests for access may be made through www.clinicalstudydatarequest.com.

- The procedures and timing for public disclosure of the protocol and results summary and for development of a manuscript for publication for this study will be in accordance with GSK Policy.

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.
- Guidance on completion of eCRFs will be provided in eCRF completion guidelines.
- Quality tolerance limits (QTLs) will be pre-defined in the quality plan 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 different 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.

- When copies of source documents are shared externally for review by a central reader mechanism (e.g., expert reader), documents are stored by the external body according to the contract executed between the Sponsor and vendor.

Source Documents

- For this study there will not be source data recorded directly into the eCRF (i.e., no prior written or electronic record of data is available).
- 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.
- Definition of what constitutes source data and its origin can be found in (e.g., source data acknowledgment or monitoring guidelines).
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The Sponsor or designee will perform monitoring to confirm that data entered into the eCRF 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.
- Copies of source data are shared with external third parties contracted by GSK for review by a central reader mechanism (e.g., expert reader). The non-exhaustive list of documents shared to inform the central reader may include, discharge summaries, imaging reports, ECG reports etc. Participant names or any information that would make the participant identifiable or is not essential for the central reader mechanism will be redacted by the Investigator sites prior to transfer. Details of the participant information redaction strategy are provided in the relevant third party manuals and/or study plans. These source data will be used by the third party solely for the purpose indicated within this protocol.

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

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

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

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

For study termination:

- Discontinuation of further study 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
- Total number of participants included earlier than expected
- 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

- 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 before submission. This 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.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

APPENDIX 2. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS: 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 pre-defined local and systemic events for which the participant is specifically questioned, and which are noted by the participant in their diary.
Events <u>Meeting</u> 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 that occur as a result of protocol-mandated procedures (i.e., invasive procedures, modification of participant's previous therapeutic regimen).
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

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: Possible Hy's Law case: ALT ≥ 3x ULN AND total bilirubin ≥ 2x ULN (for participants with known Gilbert's syndrome these criteria only apply if total bilirubin ≥2x ULN, and direct bilirubin ≥2x ULN and at least doubled from baseline value) or INR >1.5 must be reported as SAE 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.
g. Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy).
h. Is a suspected transmission of any infectious agent via an authorized medicinal product.

Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:
Investigators will be required to fill out the specific CV event page of the CRF 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 (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event. • The Investigator will then record all relevant AE/SAE information. • It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the GSK required form. • There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, except for the participant number, will be redacted on the copies of the medical records before submission to GSK.

- 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.

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.

In general, NCI-CTCAE severity grades are as follows:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated; easily tolerated.
- Grade 2: Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADLs) (instrumental ADLs refer to preparing meals, shopping for groceries or clothes, using the telephone, or managing money).
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL (self-care ADLs refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and being not bedridden).
- Grade 4: Life-threatening consequences; urgent intervention indicated.
- Grade 5: Death related to AE.

A distinction should be made between serious and severe AEs. Severity is a measure of intensity, whereas seriousness is defined by the criteria presented in the Definition of SAE section above. For example, a mild degree of gastrointestinal bleeding requiring an overnight hospitalization for monitoring purposes may be considered an SAE but is not necessarily severe. Similarly, an AE that is severe in intensity is not necessarily an SAE. For example, alopecia may be assessed as severe in intensity but may not be considered an SAE.

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 GSK. 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 GSK.**
- Where multiple interventions are administered in the same visit, the Investigator should specify, when possible, if the AE/SAE could be causally related to a specific study intervention. When a causal relationship to a specific study intervention cannot be determined, the Investigator should indicate the AE/SAE to be related to all interventions.
- 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.

Assessment of outcomes

The Investigator will assess the outcome of all serious and non-serious unsolicited AEs recorded during the study as:

- Recovered/resolved.
- Recovering/resolving.
- Not recovered/not resolved.
- Recovered with sequelae/resolved with sequelae.
- Fatal (SAEs only).

Follow-up of AEs, SAEs, and Pregnancies

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK 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 GSK within 24 hours of receipt of the information.

- If a participant dies during their participation in the study or during a recognized follow-up period, GSK will be provided with any available postmortem findings, including histopathology.

Follow-up of pregnancies

Pregnant participants/Pregnant partners of male participants will be followed to determine the outcome of the pregnancy. At the end of the pregnancy, whether full-term or premature, information on the status of the mother and child will be forwarded to GSK using the paper pregnancy follow-up report and the S/AE Report if applicable. Generally, the follow-up period does not need to be longer than 6 to 8 weeks after the estimated date of delivery.

Regardless of the reporting period for SAEs in this study, if the pregnancy outcome is an SAE, it should always be reported as such.

Furthermore, the Investigator must report any SAE occurring as a result of a post-study pregnancy that is considered by the Investigator to be reasonably related to the study intervention, to GSK as described in the section on SAE reporting below.

Reporting of SAE to GSK

SAE Reporting to GSK via Electronic Data Collection Tool

- The primary mechanism for reporting SAE to GSK will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the CRO by telephone.
- Contacts for SAE reporting can be found in the Investigator Site File (ISF).

SAE Reporting to GSK via Paper Data Collection Tool
• Facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the **Medical Monitor**. • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE data collection tool within the designated reporting time frames. • Contacts for SAE reporting can be found in the ISF.

APPENDIX 3. CONTRACEPTION GUIDELINES

Definitions

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

1. Adolescents of childbearing potential: Tanner stage ≥2 (post-thelarche) irrespective of the occurrence of menarche or following menarche
2. From the time of menarche until becoming postmenopausal unless permanently sterile (see below)

Note: Menarche is the first onset of menses in a young female. Menarche is normally preceded by several changes associated with puberty including breast development and pubic hair growth.

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 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 permanently sterile individuals 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 first dose of study treatment, additional evaluation should be considered.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

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 WOCBP and the absence of sperm has been confirmed. If not, then an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days. **Note:** Documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
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, sympto-thermal, and post-ovulation 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; WOBCP=woman of childbearing potential.

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

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

Table 18: Liver Chemistry Stopping Criteria and Required Follow-up Assessments

Liver Chemistry Stopping Criteria –Liver Stopping Event Participant <u>with</u> 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 Note: if values reduce to <3x ULN or return to within baseline or normal limits for 2 consecutive weekly assessments, weekly monitoring may return to regular per protocol schedule
Bilirubin[a,b]	ALT ≥3×ULN and total bilirubin ≥2×ULN (for participants with known Gilbert's syndrome, these criteria only apply if total bilirubin ≥2x ULN and direct bilirubin ≥2x ULN and at least double from baseline value)
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 <u>with documented</u> liver metastases/tumor infiltration at baseline <u>and</u> 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 Note: if values reduce to <3x ULN and <1.5x baseline or return to within baseline or normal limits for 2 consecutive weekly assessments, weekly monitoring may return to regular per protocol schedule
Bilirubin[a,b]	ALT ≥3×ULN and total bilirubin ≥2×ULN (for participants with known Gilbert's syndrome, these criteria only apply if total bilirubin ≥2x ULN and direct bilirubin ≥2x ULN and at least doubled from baseline value)
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 18: Liver Chemistry Stopping Criteria and Required Follow-up Assessments (Continued)

Required Actions, Monitoring, and Follow-up Assessments to Assess Causality of Liver Event	
Actions and Monitoring	**Follow-Up to Assess Causality of Liver Event**
• **Immediately** discontinue study intervention • Report the event to GSK **within 24 hours** • Complete the liver event form and complete SAE data collection tool if the event also meets the criteria for an SAE[b] • Perform liver event follow-up to assess causality of liver event • Monitor the participant liver chemistries (see **MONITORING** below) **MONITORING:** **If ALT ≥3x ULN AND total bilirubin ≥2x ULN or INR >1.5:** • Repeat liver chemistries (include ALT, AST, ALP, total bilirubin, and INR) and perform liver event follow-up to assess liver event causality within **24 hours** • Monitor participants twice weekly until liver chemistries reduce to <3x ULN for ALT, <2x ULN for total bilirubin or ≤1.5 for INR or return to or remain within baseline or normal limits • A specialist or hepatology consultation is recommended **For all other stopping criteria (bilirubin <2x ULN and INR ≤1.5):** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, total bilirubin, and INR) and perform liver event follow-up to assess liver event causality within **24 to 72 hours** • Monitor participants weekly until liver chemistries resolve, reduce to <3x ULN for ALT, or return to within baseline or normal limits **RESTART and/or RECHALLENGE** • **Do not restart and/or rechallenge** participant with study intervention since not **allowed per protocol**; continue participant in the study for any protocol-specified follow-up assessments	• Viral hepatitis serology[d] • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total IgG or gamma globulins • Blood sample for PK analysis, obtained within 96 hours after last dose of study intervention[e] • Serum CPK and LDH, GGT, GLDH, and serum albumin • 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 liver event form • Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, recreational drugs, other over the counter medications. • Record alcohol use on the liver event alcohol intake form **If ALT ≥3x ULN AND total bilirubin ≥2x ULN or INR >1.5 obtain the following in addition to the assessments listed above:** • Serum acetaminophen adduct should be conducted (where available) to assess potential acetaminophen contribution to livery injury • Liver imaging (ultrasound, MRI, or CT) to evaluate liver disease,; complete liver imaging forms • Liver biopsy may be considered and discussed with local specialist if available: o In participants when serology raises the possibility of AIH o In participants when suspected DILI progresses or fails to resolve on withdrawal of study intervention o In participants with acute or chronic atypical presentation • If liver biopsy conducted complete liver biopsy form

Abbreviations: AE=adverse event; ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; CPK=serum creatine phosphokinase; CRF=case report form; CT=computed tomography; 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; ULN=upper limit of normal.

[a] Serum bilirubin fractionation should be performed if testing is available. 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** total bilirubin ≥2×ULN (for participants with known Gilbert's syndrome, these criteria only apply if total bilirubin ≥2x ULN and direct bilirubin ≥2x ULN and ≥2x baseline value) or ALT ≥3×ULN **and** INR>1.5, which may indicate severe liver injury (possible "Hy's Law"), **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**; the INR 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), hepatitis E IgM antibody, and RNA PCR test. HBV DNA quantification, and HDV antibody should be measured if participant is known to be HBsAg and/or HBcAb positive prior to onset of the liver event or is subsequently found to be HBsAg positive on investigation following the liver event. If hepatitis delta antibody assay cannot be performed, it can be replaced with a PCR of HDV RNA virus (where needed and if this is feasible).

[e] Record in the eCRF the date/time of the PK blood sample collection and the date/time of the last dose of study intervention prior to blood sample collection. If the date or time of the last dose is unclear, provide the 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 Laboratory Manual.

Table 19: Liver Chemistry Increased Monitoring Criteria with Continued Therapy

Liver Event Increased Monitoring Criteria and Actions with Continued Study Intervention	
Criteria	**Actions**
ALT ≥5×ULN and <8×ULN and total bilirubin <2×ULN or INR ≤1.5 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 total bilirubin <2×ULN or INR ≤1.5 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 intervention • Participant must return weekly for repeat liver chemistries (ALT, AST, ALP, total bilirubin, and INR) until they stabilize (i.e., ALT or AST <3x ULN and no increases in total bilirubin and INR) or return to, or remain within baseline or normal limits • If at any time participant meets the liver chemistry stopping criteria, proceed as described above • 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, stopping criteria have not been met but any of the monitored liver chemistry (ALT, AST, alkaline phosphatase, total bilirubin, and INR) remains abnormal /above baseline, monitor participants twice monthly until they stabilize or return to within baseline or normal limits. Alternatively, the monitoring can return to standard per protocol when the investigator and medical monitor agree that values are stable or no longer significantly abnormal (this may require local investigation of potential causes for liver chemistry abnormality)

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

APPENDIX 5. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

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

Table 20: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
1L	First line
AE	adverse event
AESI	adverse event of special interest
AJCC	American Joint Committee on Cancer
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BICR	blinded independent central review
BM	brain metastases
BP	blood pressure
BRCA	breast cancer susceptibility gene
CBC	complete blood count
CI	confidence interval
CL_{Cr}	creatinine clearance
C_{max}	maximum concentration
CNS	central nervous system
CPMS	Clinical Pharmacology Modeling and Simulation
CR	complete response
CRO	Contract Research Organization
CRT	chemoradiotherapy
CSR	Clinical Study Report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CCI [redacted]	
CV	cardiovascular event
CYP	cytochrome P450

Abbreviation or Specialist Term	**Explanation**
DOR	duration of response
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EGFR	epidermal growth factor receptor
EOC	epithelial ovarian cancer
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire 30-item Core module
EORTC QLQ-LC13	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire 13-item lung cancer-specific module
EOT	End-of-Treatment
CCI [redacted]	
ESMO	European Society for Medical Oncology
EU	European Union
CCI [redacted]	
FDA	(United States) Food and Drug Administration
FFPE	formalin-fixed, paraffin-embedded
GCP	Good Clinical Practice
GHS	global health status
HR	hazard ratio
HRD(pos)	homologous recombination deficiency (positive)
HRQoL	health-related quality of life
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IDMC	Independent Data Monitoring Committee
IDMV	Independent Drug Monitoring Visit
IEC	Independent Ethics Committee
IgG4	immunoglobulin G4
IMP	investigational medicinal product
IRB	Institutional Review Board
ISF	Investigator site file
ITT	Intent-to-Treat

Abbreviation or Specialist Term	Explanation
IV	intravenous
mAb	monoclonal antibody
MATE	multidrug and toxin extrusion transporter
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
NE	not evaluable
NED	no evidence of disease
NSCLC	non-small cell lung cancer
NSQ	Non-squamous histology
NTL	non-target lesion
ORR	objective response rate
OS	overall survival
PACT	Post Analysis Complete Treatment
PARP	poly(adenosine diphosphate-ribose) polymerase
PD	progressive disease
PD-1	programmed cell death protein 1
PD-L1	programmed cell death-ligand 1
PFS	progression-free survival
PFS2	progression-free survival 2
CCI [redacted]	
PK	pharmacokinetic(s)
PK/PD	pharmacokinetic/pharmacodynamic
PR	partial response
PRES	Posterior Reversible Encephalopathy Syndrome
PRO	patient-reported outcome
CCI [redacted]	

Abbreviation or Specialist Term	Explanation
QoL	quality of life
RANO-BM	Response Assessment in Neuro-Oncology Brain Metastases
RECIST v1.1	Response Evaluation Criteria in Solid Tumors version 1.1
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	stable disease
SoA	Schedule of Activities
SOP	standard operating procedure
TC	tumor cell
TEAE	treatment-emergent adverse event
TL	target lesion
TPS	Tumor Proportion Score
TTD	time to deterioration in lung symptoms
CCI [redacted]	
ULN	upper limit of normal
US	United States
VOP	Verification of Progression
WHO	World Health Organization
WOCBP	woman of childbearing potential

Definition of Terms

Term	Definition
ADR	An AE where a causal relationship between a medicinal product and the AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out. In the context of a clinical trial, an adverse drug reaction (ADR) can be serious or non-serious. Serious ADRs may be subject to expedited reporting if they are considered unexpected (see SUSAR definition). For marketed products, ADRs are subject to expedited reporting within the country where they are authorized.

Term	Definition
AxMP	Medicinal products used in the context of a clinical trial but not as IMPs, such as medicinal products used for background treatment, challenge agents, rescue medication, or used to assess endpoints in a clinical trial. AxMPs should not include concomitant medications, i.e., medications unrelated to the clinical trial and not relevant for the design of the clinical trial. Authorized AxMP = Medicinal product authorized in accordance with Regulation (EC) No 726/2004, or in any member state concerned in accordance with Directive 2001/83/EC, irrespective of changes to the labelling of the medicinal product. Note: Safety reporting with regard to authorized AxMPs shall be made in accordance with Chapter 3 of Title IX of Directive 2001/83/EC. Unauthorized AxMP = Medicinal product not authorized in accordance with Regulation (EC) No 726/2004 Safety reporting for unauthorized AxMPs will follow the same processes and procedures as SUSAR safety reporting.
Background treatment	Type of medicinal product administered to each of the clinical trial participants, regardless of randomization group, to treat the indication that is the object of the study. Background treatment is generally considered to be the current standard of care for the particular indication. In these trials, the IMP is given in addition to the background treatment and safety/efficacy are assessed. The protocol may require that the IMP plus the background treatment is compared with an active comparator or with placebo plus background treatment.
Blinding:	A procedure in which 1 or more parties to the study are kept unaware of the intervention assignment in order to reduce the risk of biased study outcomes. The level of blinding is maintained throughout the conduct of the study, and only when the data are cleaned to an acceptable level of quality will appropriate personnel be unblinded or when required in case of a SAE. In a double-blind study, the participant, the Investigator and Sponsor staff who are involved in the treatment or clinical evaluation of the participants and the review or analysis of data are all unaware of the intervention assignment.
Caregiver	A 'caregiver' is someone who: lives in the close surroundings of a participant and has a continuous caring role or has substantial periods of contact with a participant and is engaged in their daily health care (e.g., a relative of the participant, a nurse who helps with daily activities in case of residence in a nursing home). In the context of a clinical study, a caregiver could include an individual appointed to oversee and support the participant's compliance with protocol-specified procedures.
Co-administered product	A product given to clinical trial participants as required by the protocol as part of their standard care for a condition that is not the indication for which the IMP is being tested and is therefore not part of the objective of the study.
Combination product	Combination product comprises any combination of: • drug • device • biological product. Each drug, device, and biological product included in a combination product is a constituent part.

Term	Definition
Comparator	Any product used as a reference (including placebo, marketed product, GSK or non-GSK) for an investigational product being tested in a clinical trial. This is any product that is being used to assess the safety, efficacy, or other measurable value against the test product (IMP).
Database Freeze	A period during which no changes are allowed to be made to the clinical database (or to specific pages/fields) to prevent data loss or corruption and ensure data integrity during critical periods, such as data analysis milestones, system upgrades, etc. Requests for unfreezing of data after data delivery are reviewed and approved by the study team.
Eligible	Qualified for enrollment into the study based upon strict adherence to inclusion/exclusion criteria.
Home healthcare services (HHS; i.e., home nursing)	Deployment of mobile health care professional(s) (nurses or phlebotomists) to perform study activities remotely.
IMP	A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorization but used or assembled (formulated or packaged) in a way different from the authorized form, or when used for an unauthorized indication, or when used to gain further information about the authorized form.
Investigator	A person responsible for the conduct of the clinical study at a study site. If a study is conducted by a team of individuals at a study site, the Investigator is the responsible leader of the team and may be called the Principal Investigator. The Investigator can delegate study-related duties and functions conducted at the study site to qualified individual(s) or party(ies) to perform those study-related duties and functions.
LAR	An individual, judicial, or other body authorized under applicable law to consent on behalf of a prospective participant to the participant's participation in the clinical study. The terms legal representative or legally authorized representative are used in some settings.
LSLV	The date on which the last participant in a clinical study was examined or received an intervention/treatment to collect final data for the primary outcome measures, secondary outcome measures, or AEs (that is, the last participant's last visit or LSLV).
Participant	Term used throughout the protocol to denote an individual who has been contacted to participate or who participates in the clinical study as a recipient of the study intervention (vaccine[s]/product[s]/control). Synonym: subject
Participant identifier (ID)	A unique identification number assigned to each participant who consents to participate in the study.
Placebo	An inactive substance or treatment that looks the same as, and is given in the same way as, an active drug or intervention/treatment being studied.

Term	Definition
Primary completion date	This is the date that the final participant in the study was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the pre-specified protocol or was terminated. In other words, Primary Completion Achieved is the date of the last contact with the participant when data have been collected/intervention done for the purpose of data collection for analysis of all primary endpoints. In the case of clinical studies with more than 1 primary outcome measure with different completion dates, this term refers to the date on which data collection is completed for all of the primary outcomes. This date may occur prior to the study end or be the same date as the study end milestone.
Randomization	Process of random attribution of intervention to participants to reduce selection bias.
Rescue medication	Medicine(s) identified in the protocol as those that may be administered to the participants when the efficacy of the IMP is not satisfactory, or the effect of the IMP is too great and is likely to cause a hazard to the participant, or to manage an emergency situation.
Source data	All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents (original records or certified copies).
Standard of care (SoC)	Medicine(s) for a specific indication, or a component of the standard care for a particular medical indication, based on national and/or international consensus; there is no regulatory significance to this term. Products/regimens considered SoC may differ country to country, depending on consensus in individual countries.
Study intervention	Term used throughout the clinical study to cover all types of investigational and non-investigational products, including medical devices and vaccines, intended to be administered to the study participants during the study conduct. Procedures conducted to manage participants or to collect data are excluded from the usage of this term.
Study monitor	An individual assigned by the Sponsor and responsible for ensuring proper conduct of clinical studies at 1 or more investigational sites.
SUSAR	In a clinical trial, a serious adverse reaction that is considered unexpected, i.e., the nature or severity of which is not consistent with the reference safety information (e.g., IB for an unapproved IMP). All ADRs that are both serious and unexpected are subject to expedited reporting.

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

Imaging Modality Specifications*

* Please see the **Site Imaging Manual** for additional information regarding imaging assessments

The same imaging method, including use of contrast when applicable, must be used throughout the study per participant to evaluate tumor lesions. Contrast agents must be used in accordance with the Image Acquisition Guidelines.

CT and MRI: For body imaging [chest/abdomen (/pelvis)], IV contrast-enhanced CT with ≤5 mm contiguous slices (no intervening gap) is recommended. Minimum size of a measurable baseline lesion should be twice the slice thickness, with a minimum lesion size of 10 mm when the slice thickness is 5 mm. MRI is acceptable, but when used, the technical specification of the scanning sequences should be optimized for the evaluation of the type and site of disease, and lesions must be measured in the same anatomic plane by use of the same imaging examinations. Whenever possible the same scanner should be used.

The hierarchy of anatomical body imaging with the most preferred imaging listed first followed by alternatives for participants with contrast sensitivities or renal compromise is as follows:

1. IV contrast-enhanced CT of Chest/Abdomen(/Pelvis) (preferred)
2. If sensitive to IV CT contrast: Non-contrast CT Chest + IV contrast-enhanced MRI of Abdomen(/Pelvis)
3. If sensitive to both IV CT and IV MRI contrast or if renal insufficiency: Non-contrast CT of Chest/Abdomen(/Pelvis)

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

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

Bone Scan (typically bone scintigraphy): If a bone scan is performed and a new lesion(s) is equivocal, then correlative imaging (ie, X-ray, CT, or MRI) is required to demonstrate malignant characteristics of the lesion(s).

[18F]-Fluorodeoxyglucose-Positron Emission Tomography/CT (FDG-PET/CT): FDG-PET/CT is generally not suitable for ongoing assessments of disease. However, FDG-PET can be useful in confirming new sites of disease where a positive FDG-PET scans correlates with the new site of disease present on CT/MRI or when a baseline or prior FDG-PET was previously negative for the site of the new lesion.

FDG-PET may be used in lieu of a standard bone scan providing coverage allows interrogation of all likely sites of bone disease and FDG-PET is performed at all assessments.

If PET/CT is performed then the CT component can only be used for standard response assessments if performed to diagnostic quality, which includes the required anatomical coverage and prescribed use of IV contrast. The method of assessment should be noted as CT on the CRF.

Ultrasound: Ultrasound is not a suitable modality of disease assessment. If lesions are identified by ultrasound, confirmation by CT or MRI is required.

Clinical Examination: Clinically detected lesions will only be considered measurable when they are visibly superficial (eg, skin lesions) and have clear margins. In the case of skin lesions, documentation by color photography, that includes a ruler to measure the size of the lesion, is required. Palpable lesions not detectable radiologically or not superficially visible are not followed by RECIST 1.1 assessments.

Measurable and Non-measurable Definitions

Measurable Lesions

All measurements should be recorded in the CRF as whole millimeters (mm).

A non-nodal lesion that can be accurately measured in at least one dimension (longest dimension) of:

- long-axis diameter ≥10 mm with MRI or CT when the scan slice thickness is no greater than 5 mm. If the slice thickness is greater than 5 mm, the minimum size of a measurable lesion must be at least double the slice thickness (eg, if the slice thickness is 10 mm, a measurable lesion must be ≥20 mm).
- long-axis diameter ≥10 mm caliper/ruler measurement by clinical examination or medical photography.
- long-axis diameter ≥20 mm by chest X-ray.

A lymph node can be considered pathologically enlarged and measurable as a baseline target lesion if:

- short-axis diameter* ≥15 mm when assessed by CT or MRI (slice thickness recommended to be no more than 5 mm). At baseline and follow-up, the short-axis diameter will be recorded for lymph nodes.

*The short-axis diameter is the longest in-plane diameter perpendicular to long-axis diameter.

Non-measurable Lesions

All other lesions including lesions too small to be considered measurable (long-axis diameter <10 mm or pathological lymph nodes with ≥10 mm and <15 mm short-axis diameter) as well as truly non-measurable lesions, which include: leptomeningeal disease, ascites, pleural or pericardial effusions, inflammatory breast disease, lymphangitic

involvement of the skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Baseline Definition of Target Lesions (TLs) and Non-Target Lesions (NTLs)

Measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as TLs, and recorded and measured at baseline. These lesions should be selected based on their size (measurable diameters) and their suitability for accurate repeated measurements (either by imaging techniques or clinically).

All other lesions or sites of disease should be recorded as NTLs at screening/baseline and should be followed qualitatively. NTLs will be grouped by organ. Measurements are not required, rather the status of NTLs should be determined as "present," "absent," or in rare cases "unequivocal progression" during follow-up.

Additional guidance for selection of target and NTLs at screening/baseline:

- For selection of TLs, paired organs such as the lungs and kidneys are considered together as a single organ, and no more than 2 lesions should be recorded as TLs within the pair. The skin and all lymph nodes are each considered a single organ for purposes of target lesion selection.
- Lesions identified by clinical assessment only should be followed as NTLs when other suitable TLs are available.
- Cystic lesions thought to represent cystic metastases should not be selected as TLs when other suitable TLs are available.
- Measurable lesions that have been previously irradiated and have not been shown to be progressing following irradiation should not be considered as TLs.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by CT or MRI can be considered measurable. Bone scans, FDG-PET scans or X-rays are not considered adequate imaging techniques to measure bone lesions.

Response Criteria by RECIST v1.1

<u>Evaluation of Target Lesions</u>

Complete Response (CR): Disappearance of all TLs. 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 TLs, taking as reference the baseline sum diameters

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of TLs, 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.

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 TLs 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 NTLs 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): Unequivocal progression of existing NTLs. A modest 'increase' in the size of one or more NTLs 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 NTLs at baseline.

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

Evaluation of New Lesions

New malignancies (i.e., new lesions) denoting disease progression must be unequivocal. Lesions identified post-baseline in an anatomical location not scanned at baseline are considered new lesions.

Any equivocal (suspected) new lesions should continue to be followed. Study intervention administration can continue at the discretion of the Investigator until the next scheduled assessment. If the new lesion is unequivocal at the next assessment, PD should be documented and BICR Verification of Progression (VOP) should be requested. Note: the date of progression will be the date the unequivocal lesion was first identified as equivocal.

Bone Lesions

As per RECIST guideline (v1.1), bone scans, PET scans, or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions. Since non-anatomical imaging (eg, bone/FDG-PET scans) is not required in this study at baseline, positive 'post-baseline' bone/FDG-PET scans, in the absence of baseline bone/FDG-PET scans to compare them to, are not considered a 'new lesion' unless the positive post-baseline bone/FDG-PET scan is confirmed by CT scan and there is a baseline CT scan that can be used for comparison. Importantly, solitary post-baseline bone or FDG-PET scans cannot trigger a 'new lesion'.

Table 21: 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 SoC 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 22: Evaluation of Response For Participants with only Non-Measurable Disease (ie, Non-Target Disease) at Baseline

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.

Table 23: Evaluation of Overall Response for Participants with No Evidence of Disease (NED) at Baseline

New Lesions	Overall Response
No	NED
NE	NE
Yes	PD

Abbreviations: NE=not evaluable; NED=no evidence of disease; PD=progressive disease

Evaluation of Best Overall Response

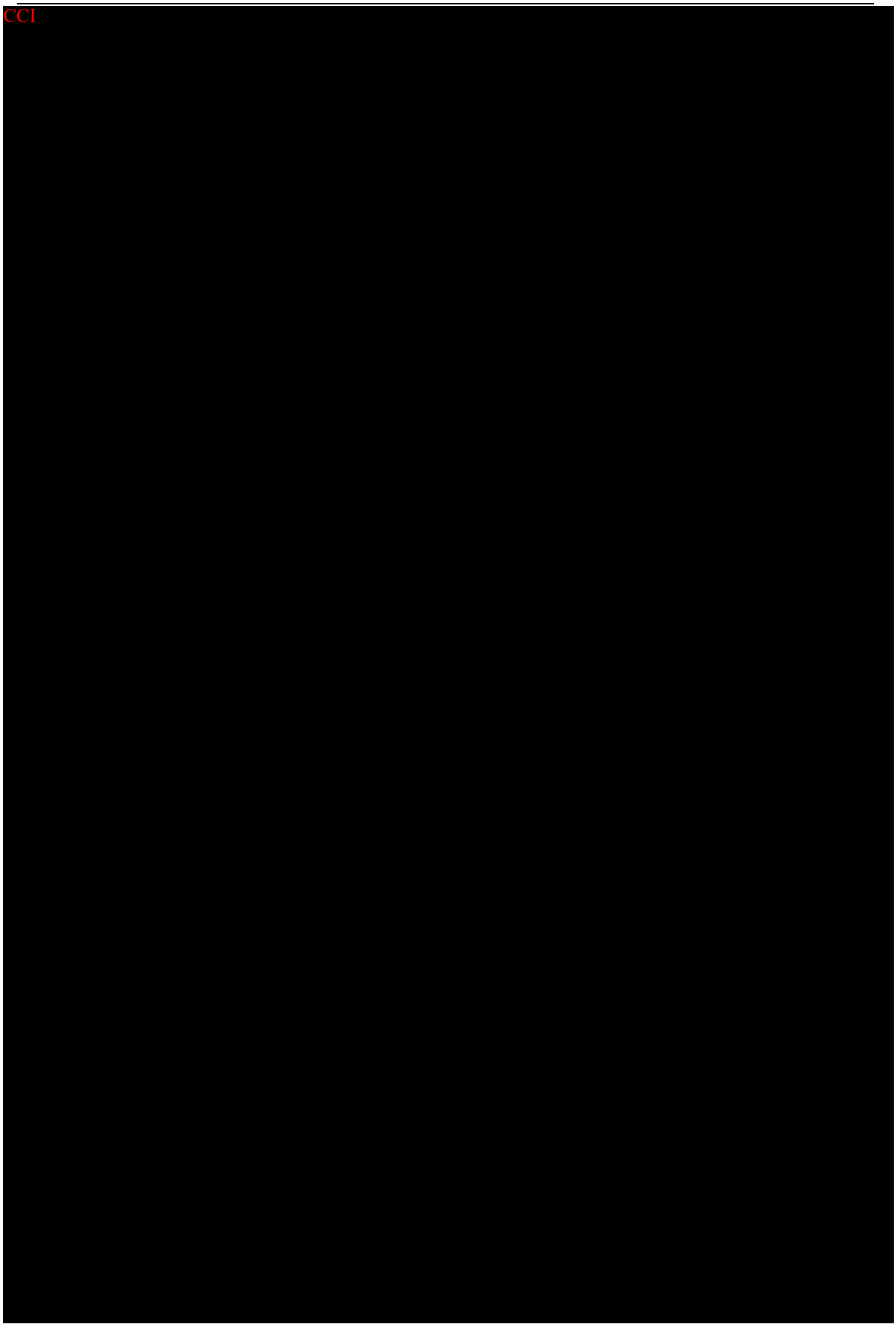
The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started) or death. The participant's best response assignment will depend on the achievement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

Duration of Response

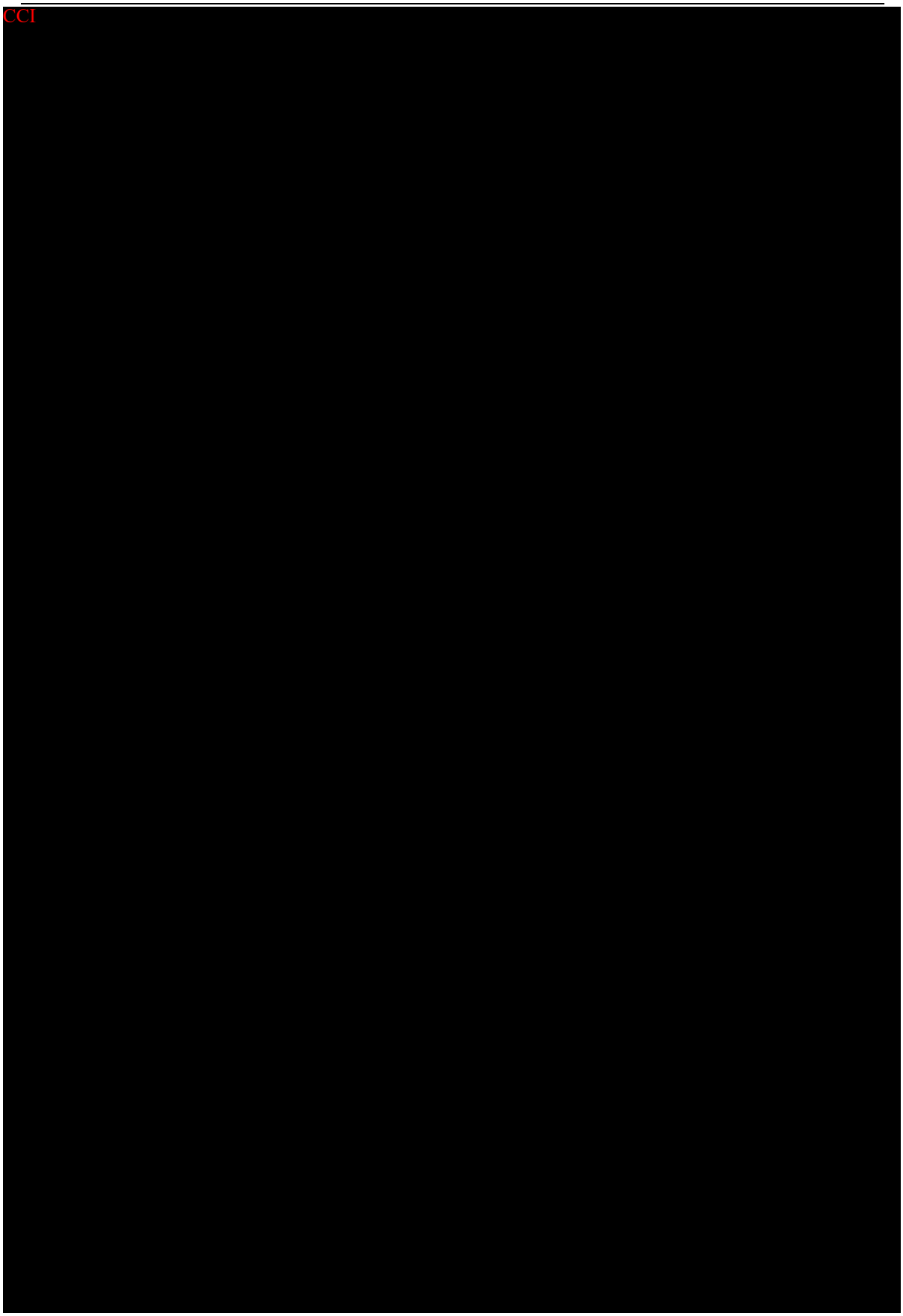
Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or PD is objectively documented (taking as reference for PD the smallest measurements recorded since the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

CCI



CCI



APPENDIX 8. 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].

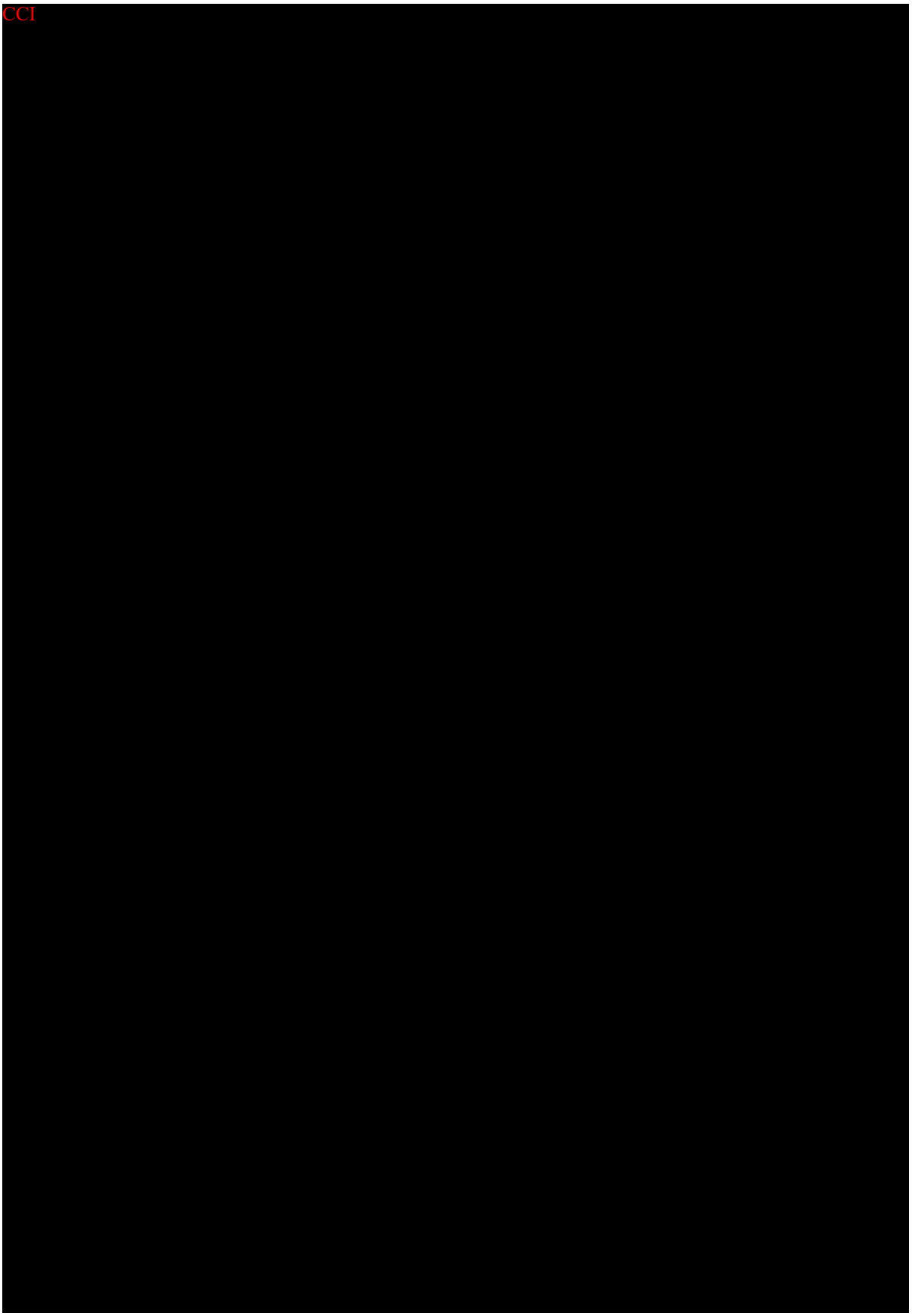
EORTC QLQ-LC13

The EORTC QLQ-LC13 is a lung cancer-specific questionnaire module designed to supplement the EORTC QLQ-C30 [Bergman, 1994]. The measures in the lung cancer questionnaire module assess both lung cancer-associated symptoms, such as coughing, shortness of breath (dyspnea), hemoptysis, and pain, as well as side effects from conventional chemo- and radiotherapy, such as hair loss, neuropathy, sore mouth, and dysphagia. The EORTC QLQ-LC13 is a clinically valid and useful tool for assessing disease- and treatment-specific symptoms in lung cancer participants of clinical studies when combined with the EORTC core quality of life questionnaire.

The EORTC QLQ-C30 and QLQ-LC13 are the most frequently utilized and reported patient- reported outcome measures in lung cancer clinical studies. The reliability, validity, and practicality of these instruments have been reported.

CCI

CCI



CCI

APPENDIX 9. EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS

Table 25: 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 housework, 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 10. PFS EVENT AND CENSORING RULES

Table 26: PFS Event and Censoring Rules

Scenario	Date of Event (Progression/Death) or Censored	Event (Progression/Death) Or Censored
No baseline assessments[a] and the participant has not died	Randomization	Censored
No adequate post-baseline assessments before start of new anticancer treatment[e] and the participant has not died	Randomization	Censored
Progression documented between scheduled visits	Date of assessment of progression[b] [(1) Earlier of date of (next scheduled visit, death)]	Event [(1) Event]
With adequate post-baseline assessment but no progression (or death)	Date of last 'adequate' assessment of response[c]	Censored
With adequate post-baseline assessment and new anticancer treatment started (prior to documented disease progression).[d]	Date of last 'adequate' assessment of response[c] (on or prior to starting anticancer treatment) [(2) Date of starting new anticancer treatment] [(5) Earlier of (date of assessment of progression, death)]	Censored [(2) Event] [(5) Event]
Death before first scheduled assessment	Date of death	Event
Death (regardless of having baseline assessment) before missing 2 scheduled assessments before Week 48 or 1 scheduled assessment after Week 48 and no progression	Date of death: a window of 91 days (12 weeks + 7-day window is per protocol day window) will be used to determine whether there is extended time before death.	Event
Death (regardless of having baseline assessment) or progression after missing two or more scheduled assessments before Week 48 or 1 or more scheduled assessment after Week 48	Randomization if there is no adequate post-baseline assessment or date of last 'adequate' assessment of response[c] (prior to missed assessments): a window of 91 days (12 weeks + 7-day window) will be used to determine whether there is extended time without adequate assessment. If the time difference between PD/death and last adequate disease assessment is more than 91 days, PFS will be censored at the last adequate disease assessment prior to PD/death. [(3) Date of death or progression]	Censored [(3) Event]

Table 26: PFS Event and Censoring Rules (Continued)

Scenario	Date of Event (Progression/Death) or Censored	Event (Progression/Death) Or Censored
[(4) Treatment discontinuation due to clinical relapse before PD or death]	[(4) Date of clinical progression]	[(4) Event]

Abbreviations: NE=not evaluable; PD=progressive disease; PFS=progression-free survival.
Note: (1), (2), (3), (4), and (5) rules are to be applied for PFS supplementary analysis.

[a] Participants are considered as not having baseline assessments if there is no disease assessment within 28 days of randomization.

[b] The earliest of (i) Date of radiographical assessment showing new lesion (if progression is based on new lesion); or (ii) Date of radiographical assessment showing unequivocal progression in NTLs, or (iii) Date of first radiographical assessment of measured lesions (if progression is based on increase in sum of measured lesions).

[c] An adequate assessment is defined as an assessment where the Investigator/Independent reviewer determined response is not: missing, NE, or PD.

[d] If PD and new anticancer treatment occur on the same day assume the progression was documented first, eg, outcome is progression and the date is the date of the assessment of progression. Clinical PD must be confirmed by radiographic assessment in order to qualify as appropriate for treatment discontinuation (see Section 7.1).

[e] CCI [redacted]

APPENDIX 11. 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 (see Table 27) [Cockcroft, 1976]. As estimated by the Cockcroft-Gault equation, mild renal impairment is considered CL_{Cr} of 60 to 89 mL/min and moderate renal impairment is considered CL_{Cr} of 30 to 59 mL/min.

Table 27: 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 12. COUNTRY-SPECIFIC REQUIREMENTS

EU

The sponsor will provide written summaries of the status of the study, information on SAEs or other significant safety findings to the agency in accordance with regulatory requirements.

France

This appendix includes all applicable requirements of French Public Health Code/ specific local GSK requirements and identifies, item per item, the mandatory modifications or additional information to the study protocol.

1. Concerning the « SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA»

   The following vulnerable subject populations will be excluded: minors, protected subjects, adult subjects not in condition to express their consent, subjects deprived of liberty, subjects receiving psychiatric cares, subjects hospitalized in a Health and Social Establishment for other purpose than the participation to the study.

   A subject will be eligible for inclusion in this study if he /she is either affiliated to or beneficiary of a social security category (French Public Health Code law L.1121-8-1). (exception for a participant to a non-interventional study or to a participant to an interventional study if authorised by the Ethics Committee).

   It is the investigator's responsibility to ensure and to document (in the source document - subject notes) that the subject:

   - is either affiliated to or beneficiary of a social security category;
   - has got an authorisation by the Ethics Committee.

2. Concerning the "STUDY GOVERNANCE CONSIDERATIONS"

- **In section "Regulatory and Ethical Considerations, including the Informed Consent Process" of study protocol**

  ⇒ Concerning **the process for informing the subject** and/or his/her legally authorized representative, the following text is added:

  French Patient Informed Consent is a document which summarizes the main features of the study and allows collection of the subject and/or his/her legally authorized representative written consent. It also contains a reference to the authorisation of ANSM and the approval from the French Ethics Committee.

  ⇒ **Concerning the management of the Patient Informed Consent Forms**, the following text is added:

  French Patient Informed Consent Form is in duplicate (triplicate for minor subject).

The first page of the Patient Informed Consent Form is given to the investigator. The copy is kept by the patient or legally authorized representative.

- **NOTIFICATION TO THE HOSPITAL DIRECTOR**

  In accordance with Article L1123-13 of the French Public Health Code, the Hospital Director is informed of the commitment to the trial in her/his establishment. The Hospital Director is supplied with the protocol and any information needed for the financial disposition, the name of the investigator(s), the number of sites involved in his establishment and the estimated time schedule of the trial (R.1123-69).

- **INFORMATION TO THE HOSPITAL PHARMACIST**

  In accordance with Article R.1123-70 of the French Public Health Code, the Hospital Pharmacist is informed of the commitment to the trial in her/his establishment. The Pharmacist is supplied with a copy of the protocol (which allows her/him to dispense the drug(s) of the trial according to the trial methodology), all information concerning the product(s) of the trial (e.g. included in the IB), the name of the investigator(s), the number of sites involved in her/his establishment and the estimated time schedule of the trial.

- **Ethnic Origin**

  In accordance with the data privacy regulation, the ethnic origin, as any personal data, can only be collected if the collection of this data is strictly necessary and relevant for the purpose of the study.

- **TESTING OF BIOLOGICAL SAMPLES**

  In accordance with the French Public Health Code law – article L1211-2, a biological sample without identified purpose at the time of the sample and subject's preliminary information is not authorized.

3. Concerning the " DATA MANAGEMENT " the following text is added:

Within the framework of this clinical trial, data regarding the identity of the investigators and/or co-investigators and/or the pharmacists if applicable, involved in this clinical trial, and data regarding the subjects recruited in this clinical trial (subject number, treatment number, subjects status with respect to the clinical trial, dates of visit, medical data) will be collected and computerized in GSK data bases by GSK or on its behalf, for reasons of follow up, clinical trial management and using the results of said clinical trial. According to the data privacy regulation, each of these people aforesaid has a right of access, correction and opposition on their own data through GSK (Clinical Operations Department).

4. Concerning Data Privacy

In accordance with the applicable data privacy regulation, personal data are processed in a manner that ensures appropriate security, including protection against unauthorized or unlawful processing and against accidental loss, destruction or damage, using appropriate technical or organizational measures.

The processing is whether deemed to be compliant with one of the methodology of reference (MR-001) or has been the subject of a request for authorization to the CNIL. The Investigator has, regarding the processing data related to her/him, a right of access, of rectification, erasure and of opposition with GSK in accordance with the legal provisions.

5. Investigational Product Accountability, Reconciliation, and Destruction

In specific situations where institutional practices dictate that the site disposes of and/or destroys IP prior to allowing the "monitor' to verify and document IP accountability, the following applies:

"During the conduct of the Study, Investigational Product (IP) will be destroyed by the Institution prior to a GSK "monitor" conducting final investigational product accountability. Institution agrees that such destruction will comply with Institution's investigational product accountability procedures and will provide GSK with investigational product accountability logs and supporting documentation to verify adherence to 'Bonnes Pratiques Cliniques' (decision dated on the 24th of November 2006).

APPENDIX 13. PROTOCOL AMENDMENT HISTORY

Amendment 04 EU-1 (05 Aug 2024)

Amendment 04 EU-1 is an administrative amendment to include elements required to address EU CTR requirements. Descriptions and brief rationales for all administrative changes are provided in Table 28.

Table 28: Summary of Changes for Amendment 04 EU-1

Section(s) Affected	Description of Change	Brief Rationale
Headers, Protocol Amendment Summary of Changes, Appendix 5 List of Abbreviations and Definition of Terms Appendix 12 Protocol Amendment History	Headers and title page were updated with new document number and amendment information; Protocol Amendment Summary of Changes section was updated to include rationale for this amendment (previous changes moved to Appendix). Definition of Terms added below List of Abbreviations to align with Sponsor template.	To align with the Sponsor's protocol template and ways of working.
Title Page	Medical Monitor EU CTR number added	To reflect change in personnel changes and to include the EU CTR number.
6.1 Study Treatment(s) Administered (Table 9) 6.2.1 Study Drug Packaging and Labeling 8.3.4 Regulatory Reporting Requirements for SAEs Appendix 1, Regulatory, Ethical, and Study Considerations	Changes to align with required Sponsor template updates and EU CTR elements, including study treatment table (and related information aligned in subsequent sections), suspected unexpected serious adverse reactions (SUSAR) statement, informed consent process, recruitment strategy, data protection, committees structure, dissemination of clinical study data, data quality assurance, source documents, and site termination.	Alignment with the global Sponsor template to include EU CTR elements.

Amendment 04 (12 January 2023)

This amendment is considered substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it significantly impacts the scientific value of the study.

Overall Rationale for the Amendment

Amendment 04 is a global amendment to update the CCI [redacted] Minor editorial and typographical changes were also made as part of this amendment. Descriptions and brief rationales for changes are provided in Table 29.

Table 29: Summary of Changes for Amendment 04

Section(s) Affected	Description of Change	Brief Rationale
Global Change	Company name updated where appropriate from GlaxoSmithKline plc to GSK plc.	To reflect the nomenclature of current global legal entity.
Global Change	Clarified throughout that the classification PD-L1 status <1% includes not evaluable samples.	To clarify the strata for PD-L1 status.
Section 1.1 Synopsis	CCI [redacted]	
Section 1.1 Synopsis Section 3 Study Objectives and Endpoints Section 8.1.2 Key Secondary Endpoints Section 9.4.3.1 Key Secondary Endpoints CCI [redacted]	Additional key secondary endpoints added to examine efficacy in the non-squamous (NSQ) population and the population of patients with a best response of complete or partial response (CR/PR) to standard of care induction chemotherapy.	CCI [redacted]

Section(s) Affected	Description of Change	Brief Rationale
Section 1.1. Synopsis Section 1.3. Schedule of Activities (SoA) Section 4.1. Overall Design Section 7.1. Discontinuation from Study Treatment	EOT visit timing description added: "at the time it is decided to discontinue study treatment." Safety follow up visit schedule description changed from "30 (±3) days and 90 (±3) days after last dose" to "30 (±3) days and 90 (±3) days after EOT Visit".	To clarify when the EOT visit should occur and the timeline that safety follow up visit should follow.
Section 2.5.3 Overall Benefit/Risk Conclusions	Minor update to the wording of identified key safety concerns.	Minor editorial updated to aligned with current DSUR.
Section 4.5 End of Study Section 7.3 Participant Discontinuation/Withdrawal from the Study	Survival follow-up information added.	To further clarify the process for survival follow-up, thus supporting the primary endpoint of Overall Survival.
Section 1.3. Schedule of Activities (SoA) Section 4.6.2 Screening under Molecular Disease Characterization Initiative Study 213299	References to screening in Study 213299 removed.	GSK has made the decision to close Study 213299. All references to the study have been removed from this trial. There were no participants from Study 213299 identified for this study (213400).
Section 7.1 Discontinuation from Study Treatment	Added clinical progression as defined by the Investigator to the list of reasons for treatment discontinuation.	Added for consistency with the eCRF.
Section 7.1 Discontinuation from Study Treatment	Additional guidance provided for follow-up of participants who elect not to continue in-person visits.	To further define and clarify that participants may choose to end all study procedures but be willing to be contacted for survival. Also clarifies that participants may be contacted for health status outside of the visit schedule during times of database locks.
Section 8.1.1.1 Radiographic Evaluation of Tumor Response	On-treatment imaging text rephrased in Table 12.	Updated proposed to clarify that on-study imaging should be planned based on a calendar schedule from the date of randomization.

Section(s) Affected	Description of Change	Brief Rationale
Section 1.3. Schedule of Activities (SoA) Section 8.1.1.1 Radiographic Evaluation of Tumor Response Appendix 6 Response Evaluation Criteria in Solid Tumors v1.1	Additional guidance added on the evaluation of new lesions and requesting BICR verification of progression.	To ensure diagnosis of new lesions are unequivocal prior to reporting radiographic progression.
Section 8.1.6 Pharmacokinetic Sample Collection	Added instruction for PK sampling following a liver event.	For additional clarity.
Section 1.1. Synopsis Section 9 Statistical Considerations	The multiplicity strategy for the dual primary endpoint has been adjusted such that alpha is split between the PFS and OS endpoints in the overall population and hierarchical reallocation of alpha to the key secondary endpoints of PFS and OS in the subgroups of interest and will be tested sequentially.	CCI [redacted]
Section 1.1. Synopsis Section 9.3 Analysis Populations	Updated phrasing to standard language of BICR assessment rather than verified BICR.	For additional clarity.
CCI [redacted]		
Appendix 1. Regulatory, Ethical, and Study Considerations	Additional detail on document retention policies added to the sections on Quality Assurance and Source Documents.	Added to align with current protocol template text.
Appendix 4 Liver Safety Required Actions and Follow Up Assessments	Window for collection of PK blood sample following a liver stopping event increased to 96 hours.	Adjusted to reduce burden on patients and site, given the long half life of niraparib.
Appendix 6 Response Evaluation Criteria in Solid Tumors V1.1	Table 24 added to define overall responses applicable for randomized participants assessed as CR following standard of care induction treatment.	For additional clarity.

Amendment 03 (08 DEC 2021)

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

Overall Rationale for the Amendment

Amendment 03 is a global amendment to address CCI [redacted] A description and brief rationale for each change is provided in Table 30.

Table 30: Summary of Changes for Amendment 03

Section(s) Affected	Description of Change	Brief Rationale
Headers and cover page	Headers and cover page were updated with a new document number and amendment information.	Editorial changes to align with the Sponsor's standard protocol template.
Protocol Amendment Summary of Changes	Protocol Amendment Summary of Changes section was updated to include a rationale for this amendment.	
Section 8.2.9.1. Direct to Participant IMP Shipments	In the 2nd paragraph, CCI [redacted] was replaced with 'vendor'.	
Appendix 12. Protocol Amendment History	Appendix 12 was added to include information for the previous Protocol Amendment 02.	
Section 1.1. Synopsis Section 5.1. Participant Inclusion Criteria	For Inclusion Criterion #1, a 'note' was added to indicate minimum eligibility age for participants in Korea (ie, ≥19 years).	To meet local regulatory requirements.
Section 1.1. Synopsis Section 5.1. Participant Inclusion Criteria	Inclusion Criterion #2 was expanded to include the statement 'for which an approved targeted therapy is available in the 1L induction/maintenance therapy setting'.	To reflect the line of therapy for the study population of interest.

Section(s) Affected	Description of Change	Brief Rationale
Section 1.1. Synopsis Section 5.1. Participant Inclusion Criteria Section 2.2. Treatment Options for Patients with Stage III or Stage IV NSCLC	For Inclusion Criterion #3 and other relevant sections, 'Stage IIIC' was moved to appear before 'not amenable to definitive chemoradiotherapy'.	Since some patients with Stage IIIC NSCLC may be able to receive chemoradiotherapy, FDA requested this clarification.
Section 1.1. Synopsis Section 4.1 Overall Design Section 5.1. Participant Inclusion Criteria	In the Synopsis (Methodology), Overall Design, and the 'note' in Inclusion Criterion #4, the paragraph referring to an 'optional' recovery period was reworded to indicate that participants should undergo a 'transition period' with administration of pembrolizumab only.	A transition period will optimize participant comfort and safety.
Section 1.2. Schemas	Figure 1B was updated and 'optional recovery period' was renamed 'transition period'. Footer (a) wording was updated.	
Section 1.2. Schemas	Figure 1A was updated to indicate that participants in the niraparib and placebo arms will also be receiving standard of care (pembrolizumab).	To clarify the treatment arms in the schema as per the study design.
Section 1.1. Synopsis Section 5.1. Participant Inclusion Criteria	For Inclusion Criterion #5, a note was added regarding the acceptability of a RECIST v1.1 response of non-CR/non-PD, which is consistent with SD as an overall response, for participants with only non-measurable/non-target disease at the onset of induction therapy.	To clarify study eligibility criteria for participants with only non-measurable/non-target disease at the onset of induction therapy.
Section 1.1. Synopsis Section 5.1. Participant Inclusion Criteria	For Inclusion Criterion #10, the wording was updated so that recovery from toxicity is (i) defined by Inclusion Criterion #8 and (ii) defined by the absence of ongoing toxicity of CTCAE Grade ≥3.	To correct a previous inconsistency between Inclusion Criteria #8 and #10 with respect to study eligibility.

Section(s) Affected	Description of Change	Brief Rationale
Section 1.1. Synopsis Section 5.1. Participant Inclusion Criteria Section 6.6.2. Contraception Section 8.2.5. Pregnancy Testing	For Inclusion Criterion #13 and other relevant sections, for male participants, the length of time for abstinence or contraception, and for sperm to not be donated was changed from '180 days' to '90 days' following the last dose of study treatment.	To align with the recommendation in the current version of the Investigator's Brochure.
Section 1.1. Synopsis Section 5.1. Participant Inclusion Criteria	For Inclusion Criterion #13, the bullet regarding abstinence was updated and 'heterosexual intercourse' was replaced with 'sexual activity'.	To broaden the applicability of abstinence (to not be limited to heterosexual intercourse).
Section 1.3. Schedule of Activities (SoA)	Footer 's' to the SoA was updated to indicate that on-study imaging must be performed based on a schedule from the date of randomization and should not be adjusted for delays in cycle starts.	To clarify that on-study imaging should follow calendar days.
CCI [redacted]		

Section(s) Affected	Description of Change	Brief Rationale
Section 8.1.3.1. Investigator-Assessed PFS per RECIST v1.1	CCI [redacted]	
CCI [redacted]		
Section 2.3. Niraparib	A reference was added (Ramalingam et al., 2021).	To update the protocol with a recent and relevant publication.
CCI [redacted]		
Section 4.4 Dose Adjustment Criteria	The section was renamed 'Risk Minimization Measures: Criteria for Dose Adjustment and IMP Discontinuation'.	

Section(s) Affected	Description of Change	Brief Rationale
Section 4.4.1. Niraparib/Placebo	The second paragraph was updated and Table 7 and Table 8 were renamed to include the phrase 'risk minimization measures'. For Table 7 and Table 8, column titles were added ('Adverse Reaction' and 'Risk Minimization Measure', respectively) as were statements related to IMP discontinuation for recurrence of Grade 3 (with no resolution to a baseline or Grade 1) and Grade 4 adverse reactions. For Table 8, the phrase 'Laboratory follow-up' was included in the first row.	
Section 4.4.1. Niraparib/Placebo	In Table 7 (Risk Minimization Measures for Non-Hematological Adverse Reactions), PRES was added as an adverse reaction and an associated table footer was included regarding PRES symptoms and its diagnosis.	To reiterate a risk of clinical significance stated in Table 4 (Summary of Risks and Mitigations for the Product).
	In Table 8 (Risk Minimization Measures for Hematologic Adverse Reactions), MDS/AML was added as an adverse reaction.	To reiterate a risk of clinical significance stated in Table 4 (Summary of Risks and Mitigations for the Product) and the risk minimization measure discussed in Section 8.2.6. (Laboratory Assessments).
Section 2.5.3. Overall Benefit/Risk Conclusion	'Potential' risks of MDS/AML were changed to 'identified' risks.	To reflect safety updates made to the Investigator's Brochure.
Section 4.3. Treatment Assignment	For the 2nd bullet, 'and NE' was added: PD-L1 status (TC<1% and NE versus ≥1%).	For clarification purposes.

Section(s) Affected	Description of Change	Brief Rationale
Section 7.1. Discontinuation from Study Treatment	The bullets 'MDS or AML', 'New primary malignancy other than MDS or AML', and 'thrombocytopenia' were moved to occur as sub-bullets under 'AE'. PRES was added as an AE.	To highlight AEs of clinical significance which may warrant discontinuation of study treatment.
	'Withdrawn consent' was changed to 'Patient decision to end treatment'.	To clarify the option for patients to end treatment but continue in the study for follow-up on survival.
Section 8.3.7. Adverse Events of Special Interest (AESIs)	The last bullet pertaining to 'embryo-fetal toxicity' was removed.	Embryo-fetal toxicity events are captured with the reporting of pregnancy outcomes in Section 8.3.5 (Pregnancy).
Section 8.2.6. Laboratory Assessments	For Table 13 (Laboratory Assessments), 'Lipase' added where Amylase appears so the assessment reads 'Lipase or Amylase'; associated table footer 'h' was also added.	To indicate that lipase testing may be used in place of amylase testing, as needed. Where both lipase and amylase are available, lipase testing is preferred because it is considered a more sensitive test for the detection of pancreatitis.
Section 8.2.9. General Guidance for Treatment Continuity when Participants are Unable to Come into the Clinic	The paragraph pertaining to the availability of a 'global telemedicine platform' was removed. In Table 14 (Critical Data Collection and Safety Precautions), all occurrences of 'telemedicine' were removed.	The telemedicine platform is not being utilized.
Section 1.1. Synopsis Section 9.5. Interim Analyses	For two paragraphs that refer to 'If OS is positive' at 'IA2' and at the 'final analysis', respectively, IA1 was replaced with 'IA2' and 'final analysis', respectively.	To correct a typographical error and align with the Statistical Analysis Plan.
Appendix 2. Adverse Events and Serious Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow Up, and Reporting	For the section 'SAE Reporting to GSK via Electronic Data Collection Tool', the bullet pertaining to the review and verification of causality within 72 hours of SAE entry into the eCRF was removed.	CCI [redacted]

Section(s) Affected	Description of Change	Brief Rationale
Appendix 6. Response Evaluation Criteria in Solid Tumors v1.1	Additions were made to include content on imaging modality specifications, measurable and non-measurable lesion definitions, guidance on target and non-target lesions at screening/baseline, and bone lesions.	To provide clarification regarding standard current practices.
Whole document	Grammatical and typographical corrections made.	Grammar correction.

Amendment 02 (16 March 2021)

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

Overall Rationale for the Amendment

Amendment 02 is a global amendment CCI [redacted]

A description and brief rationale for each change is provided in Table 31.

Summary of Changes for the Amendment

Table 31: Summary of Changes for Amendment 02

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; Appendix 12 was added to include information for previous protocol amendment; editorial revisions for consistency with Sponsor's ways of working and to add clarification and/or remove discrepancies	Editorial changes to align with the Sponsor's standard protocol template and ways of working and for accuracy, clarity, conformity, flow, and typographical error correction

Table 31: Summary of Changes for Amendment 02 (Continued)

Section(s) Affected	Description of Change	Brief Rationale
Section 1.1. Synopsis (Methodology) Section 3. Study Objectives and Endpoints/Table 5: Objectives and Endpoints for Study 213400 Section 4.1. Overall Design	CCI [redacted]	
Section 7.4.1. Further Research Maintaining Confidential Participant Information (changed from "Future Biomedical Research…) CCI [redacted] Appendix 1. Regulatory, Ethical, and Study Considerations (Informed Consent Process subsection)		
Section 1.1. Synopsis (Criteria for Inclusion, criterion 14) Section 5.1. Participant Inclusion Criteria (criterion 14) Appendix 1. Regulatory, Ethical, and Study Considerations (Informed Consent Process subsection)	Removed the option for a legally authorized representative to provide informed consent for a study participant	Removed to be in accordance with the World Medical Association's Declaration of Helsinki and the International Council on Harmonisation's Good Clinical Practice guideline E6 whereby only patients capable of personally providing informed consent will be enrolled into the study
CCI [redacted]		

Table 31: Summary of Changes for Amendment 02 (Continued)

Section(s) Affected	Description of Change	Brief Rationale
Section 1.3. Schedule of Activities (SoA)/Table 3: Schedule of Activities (footnotes o and s)	Provided further guidance regarding the criteria for the mandatory tumor specimen to be collected from all participants at the start of the study and for the additional clinically indicated scans to be performed at baseline	Clarifications to support conduct
Section 8.1.1.1. Radiographic Evaluation of Tumor Response	Clarified that participants with known bone metastasis may, not should, undergo additional imaging (eg, radionuclide bone scan, CT scan, MRI, PET scan); scans are to be performed as clinically indicated, in the judgment of the Investigator	Clarification to support conduct
CCI [redacted]		
Section 8.2.9. General Guidance for Treatment Continuity when Participants are Unable to Come into the Clinic	Corrected text that language for including in the Informed Consent Form, not a separate Informed Consent Form addendum, is available for home nursing measures, should sites opt to use this service	Correction

Abbreviations: CT=computed tomography; MRI=magnetic resonance imaging; PET=positron emission tomography; PK=pharmacokinetic.

Amendment 01 (01 December 2020)

Overall Rationale for the Amendment

Amendment 01 is a global amendment CCI [redacted]

A description and brief rationale for each change is provided in Table 32.

Summary of Changes for the Amendment

Table 32: Summary of Changes for Amendment 01

Section(s) Affected	Description of Change	Brief Rationale
Headers, cover page, and Protocol Amendment Summary of Changes	Headers and cover page were updated with new document number; Protocol Amendment Summary of Changes section was created and updated to include rationale for this amendment	Editorial changes to align with the Sponsor's standard protocol template and ways of working
Entire document	Editorial changes were made throughout the document and to align with the Sponsor's standards and processes, including the protocol template	Editorial changes were made for conformity, clarity, flow, and typographical error correction (eg, the qualifier "standard of care" was added for clarity and consistency when referring to the induction chemotherapy period/treatment)

Table 32: Summary of Changes for Amendment 01 (Continued)

Section(s) Affected	Description of Change	Brief Rationale
Protocol Title (Title Page and Synopsis) Section 1.1. Synopsis (Criteria for Inclusion, criteria 3 and 9) Section 1.2. Schemas (Figure 1: Overall Study Schemas, A: Study Population) Section 1.3. Schedule of Activities (Table 3: Schedule of Activities, footnote o) Section 2.2. Treatment Options for Patients with Stage III or Stage IV NSCLC Section 2.4. Rationale for Current Study Section 5.1. Participant Inclusion Criteria (criteria 3 and 9)	Added study name (ZEAL-1L) (applies only to protocol title) Added Stage IIIC NSCLC to study population description	Study name and study population descriptions as originally intended
Section 1.1. Synopsis (Secondary Objectives, Methodology, PK Analysis) Section 3. Study Objectives and Endpoints (Table 5: Objectives and Endpoints for Study 213400, secondary PK objective and endpoint) Section 4.1. Overall Design Section 8.1.6. Pharmacokinetic Sample Collection Section 9.4.6. Pharmacokinetic Analysis	Revised and clarified PK language in the protocol, including the secondary objective, such that exposure of niraparib when given in combination with pembrolizumab and not population PK will be analyzed and described. Population PK, exposure-response, and other PK analyses may be conducted, if warranted, and may be combined with data from other studies	Error correction to accurately reflect planned study conduct

Table 32: Summary of Changes for Amendment 01 (Continued)

Section(s) Affected	Description of Change	Brief Rationale
CCI		

Table 32: Summary of Changes for Amendment 01 (Continued)

Section(s) Affected	Description of Change	Brief Rationale
CCI [redacted]		
Section 1.1. Synopsis (Methodology) Section 1.3. Schedule of Activities (Table 3: Schedule of Activities, footnote s) Section 4.1. Overall Design Section 4.6.1. Procedures by Visit Section 8.1.1.1. Radiographic Evaluation of Tumor Response	Updated wording for clarity that imaging of the brain is required for all participants at baseline	Participants must have brain imaging at baseline

Table 32: Summary of Changes for Amendment 01 (Continued)

Section(s) Affected	Description of Change	Brief Rationale
Section 1.1. Synopsis (Methodology and Criteria for Inclusion, criterion 9) Section 1.3. Schedule of Activities (Table 3: Schedule of Activities, footnote o) Section 4.1. Overall Design Section 5.1. Participant Inclusion Criteria (criterion 9)	Clarified that tumor tissue blocks are preferred, if available, and, if not, slides are acceptable. Removed the minimum number of slides advised.	Tissue block is preferred if available. If not, freshly cut, unstained slides should be provided. Further specimen details are provided in the laboratory manual.
Section 1.1. Synopsis (Methodology) Section 4.1. Overall Design Section 6.3.1. Randomization Scheme	SD enrollment language ("capped at approximately 50%") clarified and made consistent throughout the protocol	For consistency and clarity to accurately reflect the capping strategy used in this study
CCI [redacted]		

Table 32: Summary of Changes for Amendment 01 (Continued)

Section(s) Affected	Description of Change	Brief Rationale
Section 1.1. Synopsis (Criteria for Evaluation) Section 3. Study Objectives and Endpoints (Table 5: Objectives and Endpoints for Study 213400) Section 8.2.1. Safety Parameters Section 9.4.5. Safety Analyses (Table 16: Statistical Analytical Methods: Safety)	Updated secondary safety endpoint to include only incidence of adverse events; moved incidence of treatment discontinuations, dose interruptions and dose reductions due to adverse events and changes in clinical laboratory results to exploratory safety endpoint	Updated to reflect current study design
Section 1.1. Synopsis (Duration of Treatment) Section 4.1. Overall Design	Removed statement that participants have the option to retreat with niraparib for up to 1 year if PD occurs after stopping study treatment	Retreatment removed from the protocol due to its potential impact on/interference with the assessment of the study's primary efficacy endpoints
Section 1.1. Synopsis (Methodology, Statistical Methods) Section 4.1. Overall Design Section 9.5. Interim Analyses Section 9.6. Independent Data Monitoring Committee	Removed description of timing of IDMC periodic safety reviews (every 6 to 8 months or per request) and referred reader to IDMC charter for timing details, instead	Timing of IDMC periodic safety reviews is captured in the IDMC charter
CCI [redacted]		

Table 32: Summary of Changes for Amendment 01 (Continued)

Section(s) Affected	Description of Change	Brief Rationale
Section 1.1. Synopsis (Criteria for Inclusion, criterion 14) Section 5.1. Participant Inclusion Criteria (criterion 14)	Added language for clarity that study participation is voluntary and participants or their legally authorized representative may sign the informed consent	Language added for completeness and accuracy and to align with wording in Appendix 1
Section 1.1. Synopsis (Statistical Methods) Section 9.5. Interim Analyses/Table 17: Summary of Planned Analyses	Removed approximated median improvement measures provided in the statistical assumptions for IA1, IA2, and final analysis Clarified that provided HRs are approximate	To align with the study's statistical analysis plan
Section 1.2. Schema (Figure 1: Overall Study Schemas (B)) Section 1.3. Schedule of Activities (Table 3: Schedule of Activities, Pre-Screening and Screening column headers) Section 4.6.1. Procedures by Visit Appendix 1. Regulatory, Ethical, and Study Considerations (Informed Consent Process subheading)	Added parenthetical clarification that the Pre-screening period is optional/if needed and the Screening period is required. Also added a footnote to the Pre-screening column header of Table 3 to explain this	As originally intended/revision for clarity
Section 1.3. Schedule of Activities (Table 3: Schedule of Activities, randomization row)	Changed Randomization marker to be under Cycle 1/Day 1 instead of during Screening	As originally intended

Table 32: Summary of Changes for Amendment 01 (Continued)

Section(s) Affected	Description of Change	Brief Rationale
Section 1.3. Schedule of Activities (Table 3: Schedule of Activities, Screening column header and footnote w) Section 4.6.2. Screening under Molecular Disease Characterization Initiative Study 213299 (new section)	Added a new section (4.6.2.) to provide details pertaining to participants who may already be enrolled in GSK Study 213299 (molecular disease characterization study) that may not need to undergo repeated screening procedures for this study (213400) Added a footnote in the Schedule of Activities Screening header pointing to this new section as it could impact screening procedures for this study	Molecular disease characterization study 213299 is a nontherapeutic GSK study that may refer participants to this study (213400)
Section 1.3. Schedule of Activities (Table 3: Schedule of Activities, footnote s) Section 8.1.1.1. Radiographic Evaluation of Tumor Response (Table 12: Overview of Imaging Requirements for Study 213400 by Visit)	Imaging guidance for participants who begin subsequent anticancer treatment added EOT imaging guidance for participants who discontinue study treatment due to BICR-verified progression clarified (additional EOT imaging assessment not required)	Participants who begin subsequent anticancer treatment should undergo imaging assessment within 4 weeks of the date of treatment discontinuation Participants who discontinue study treatment due to BICR-verified progression do not require additional imaging assessments at EOT
Section 1.3. Schedule of Activities (Table 3: Schedule of Activities, new row added: Physical Examinations) Section 8.2.3 Physical Examination	Row added to Schedule of Activities to capture physical examination assessments that are required per protocol Inclusion of required physical examination assessments	Physical examinations are required assessments as indicated in Section 8.2.3 and should thus be reflected in the Schedule of Activities Request for additional guidance to be provided to Investigators and study staff
Section 2.5 Benefit/Risk Assessment	New section added summarizing the overall benefit/risk of the study	Consolidation of information provided separately into protocol

Table 32: Summary of Changes for Amendment 01 (Continued)

Section(s) Affected	Description of Change	Brief Rationale
Section 5.3. Lifestyle Considerations	Added that participants must be informed to avoid exposure to ultraviolet light and take precautions when exposed to direct sunlight	Added because photosensitivity has been reported for patients receiving niraparib
CCI [redacted]		
Section 6.2.5. Study Drug Handling and Disposal	Added a reference to the Study Reference Manual for niraparib	The study reference manual contains important information and guidance regarding warnings and precautions when handling niraparib
Section 6.3.2 Blinding and Breaking the Blind	Brief statement to provide reference to location of instructions for emergency unblinding	Request for inclusion of additional information as guidance on procedure for Investigators and study staff
Section 6.4 Study Treatment Compliance	Inclusion of details on monitoring of compliance with medication administration and accountability	Request for inclusion of additional detail within protocol
Section 6.6.1. Prohibited Medications	Added qualifier “bone” to metastases that may be managed with palliative radiotherapy while a participant is on study	Only bone metastases may be managed with palliative radiotherapy during the study
Section 7.1. Discontinuation from Study Treatment	Clarified criterion to discontinue treatment due to radiographic PD	A reason for discontinuation from treatment is radiographic PD that is documented per RECIST v1.1 and is verified by BICR
Section 8.1.1.1. Radiographic Evaluation of Tumor Response Table 12: Overview of Imaging Requirements for Study 2134000 by Visit (new table)	Section was reworded for clarity and flow, including the addition of a tabular presentation of imaging requirements per visit	Updated for clarity and consistency
8.2.6. Laboratory Assessments (Table 13: Laboratory Assessments)	Added bilirubin to the chemistry column	As originally intended; bilirubin will be tested by blood chemistry and urinalysis

Table 32: Summary of Changes for Amendment 01 (Continued)

Section(s) Affected	Description of Change	Brief Rationale
Section 8.2.9. General Guidance for Treatment Continuity when Participants are Unable to Come into the Clinic Table 14: Critical Data Collection and Safety Precautions	Added further details regarding the utilization of home nursing and telemedicine via the Sponsor's vendors including eligible assessments and expectations for use	Added for study conduct clarity and accuracy
Section 8.3.4. Regulatory Reporting Requirements for SAEs	Clarification of applicable regional reporting requirements to be adhered to for safety reporting	Request for additional guidance to be provided to Investigators and study staff
Section 8.3.5. Pregnancy	Removed text indicating that participants may request to continue on study treatment if they become pregnant	Text was errantly included in the original version of the protocol and does not apply to this study as participants who become pregnant while on study must discontinue treatment
Section 9.4.1 General Considerations	Brief statement to provide reference to location of information on censoring rules and missing data	Reference included to ensure that information present in the protocol is able to be located by all readers
Appendix 9. Eastern Cooperative Oncology Group Performance Status (Table 25: ECOG Performance Status Grading)	Added Grade 5 (Dead)	As originally intended
Appendix 10. PFS Event and Censoring Rules (Table 26: PFS Event and Censoring Rules)	Modified footnote to define an adequate assessment of response by what is not considered adequate (missing, NE, PD)	Per IRC charter, there will be several additional response categories to account for (aside from previously listed CR, PR, and SD) for an assessment; and to align with the study's statistical analysis plan

Abbreviations: BICR=blinded independent central review; CL_{Cr}=creatinine clearance; CR=complete response; ECOG=Eastern Cooperative Oncology Group; EOT=End-of-Treatment; HR=hazard ratio; IA=interim analysis; IDMC=Independent Data Monitoring Committee; IRC=Independent Review Committee; NE=not evaluable; NSCLC-non-small cell lung cancer; OS=overall survival; PD=progressive disease; PFS=progression-free survival; PK=pharmacokinetics; PR=partial response; RANOBM=Response Assessment in Neuro-Oncology Brain Metastases; RECIST v1.1=Response Evaluation Criteria in Solid Tumors version 1.1; SD=stable disease; ULN=upper limit of normal.

Signature Page for 213400 TMF-19100280 v2.0

Reason for signing: Approved	Name: PPD Role: Approver Date of signature: 06-Nov-2024 15:50:02 GMT+0000

Signature Page for TMF-19100280 v2.0