Division	:	Worldwide Development
Information Type	:	Statistical Analysis Plan (SAP)

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 (NSCLC)

Study Number: 213400

Compound Number: Niraparib (GSK3985771)

Abbreviated 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

Acronym: TESARO/ZEAL-1L

Sponsor Name: GlaxoSmithKline Research & Development Limited

Regulatory Agency Identifier Number(s)

Registry	**ID**
Clintrials.gov	NCT04475939
IND	134,426
EU CT	2023-508443-40

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VERSION HISTORY

This Statistical Analysis Plan (SAP) for study 213400 is based on the protocol Amendment 5 dated 06 November 2024.

Table 1 SAP Version History Summary

SAP Version	Document Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
1	06-Aug-2020	13-May-2020	Not Applicable	Original version
2	12-May-2022	08-Dec-2021	Add CNS-PFS as secondary endpoint.	
3	14-Apr-2023	12-Jan-2023	Protocol amendment 04 is a global amendment to update the statistical testing strategy of the dual primary endpoints of PFS and OS in the overall population and addition of subgroups due to emerging evidence from an external trial. The multiplicity	The multiplicity strategy has been adjusted based on external information to GSK. Other analyses clarifications were made.

SAP Version	Document Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
			strategy has been adjusted for the PFS and OS endpoints with inclusion of key secondary endpoints for PFS and OS in subgroups of interest. Minor editorial and typographical changes were also made as part of this amendment.	
4	03-Jul-2024	12- Jan-2023	Set target thresholds for eCOA compliance.	Adjustments based on internal recommendations.
5	30 Dec 2024	06-Nov-2024	Changes based on Protocol Amendment 05. Target number of PFS/OS events were revised, interim analysis removed, primary/key secondary	Slower than expected PFS/OS event accumulation has been observed and the target number of PFS/OS events were revised accordingly. OS interim analysis was removed to

SAP Version	Document Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
			endpoints updated, multiplicity testing strategy revised, and minor changes to safety, PRO, and tertiary endpoints were included. Additional sensitivity analyses added.	preserve all OS alpha for a single final analysis. Recent emerging evidence from multiple external trials with IMPs in the same class and in the same indication along with consultations with key opinion leaders have informed the end point and statistical changes. Other changes were for clarification purposes or uphold best practices in study and safety analyses. Sensitivity analyses added per external feedback.

1. INTRODUCTION

The purpose of this SAP is to describe the planned analyses to be included in the Clinical Study Report for Study 213400 (ZEAL-1L). Details of the planned analyses are provided.

Descriptive study population analyses such as summary of demography and baseline characteristics and additional detail with regards to data handling conventions and the specification of data displays will be provided in the Output and Programming Specification (OPS) document.

Analyses of population pharmacokinetics will be described in a separate modeling and simulation analysis plan. Supplementary analysis plans may also be created for additional analyses of patient reported outcomes and biomarkers.

1.1. Objectives, Estimands and Endpoints

1.1.1. Objectives and Endpoints

The objectives and endpoints of this study are provided in Table 2.

Table 2 Objectives and Endpoints

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 is 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 is 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

Objectives	Endpoints
	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).
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 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]	
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] CCI [redacted]; EORTC QLQ-C30=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire 30-item Core module; EORTC QLQ-LC13=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire 13-item lung cancer-specific module; CCI [redacted] CCI [redacted] CCI [redacted] CCI [redacted] CCI [redacted]; OS=overall survival; CCI [redacted]; PD-L1=programmed cell death-ligand 1; PFS=progression-free survival; CCI [redacted] CCI [redacted] 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] CCI [redacted].

1.1.2. Estimands

Primary and key secondary study objectives with additional information, including prespecified estimands with related attributes are presented in Table 3 with additional information, including prespecificed estimands with related attributes. The intercurrent

events identified are those events that occur after randomization and either preclude observation of the variable of interest or affect its interpretation.

The population of interest is defined by the inclusion and exclusion criteria as part of the protocol consisting of 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 platinum-based first-line induction chemotherapy with pembrolizumab.

The following intercurrent event strategies are provided according to International Conference on Harmonization (ICH) E9 guideline 'Statistical Principles for Clinical Trials' (ICH E9) Addendum:

- Treatment Policy - the data collected for the variable of interest are used regardless of whether or not the intercurrent event occurs.
- Composite – the occurrence of the intercurrent event is taken as a component of the variable (i.e. treated as an event).
- Hypothetical – a hypothetical scenario is envisaged in which the intercurrent event would not occur.
- While on Treatment - response to treatment prior to the occurrence of the intercurrent event is of interest.

Table 3 Estimands

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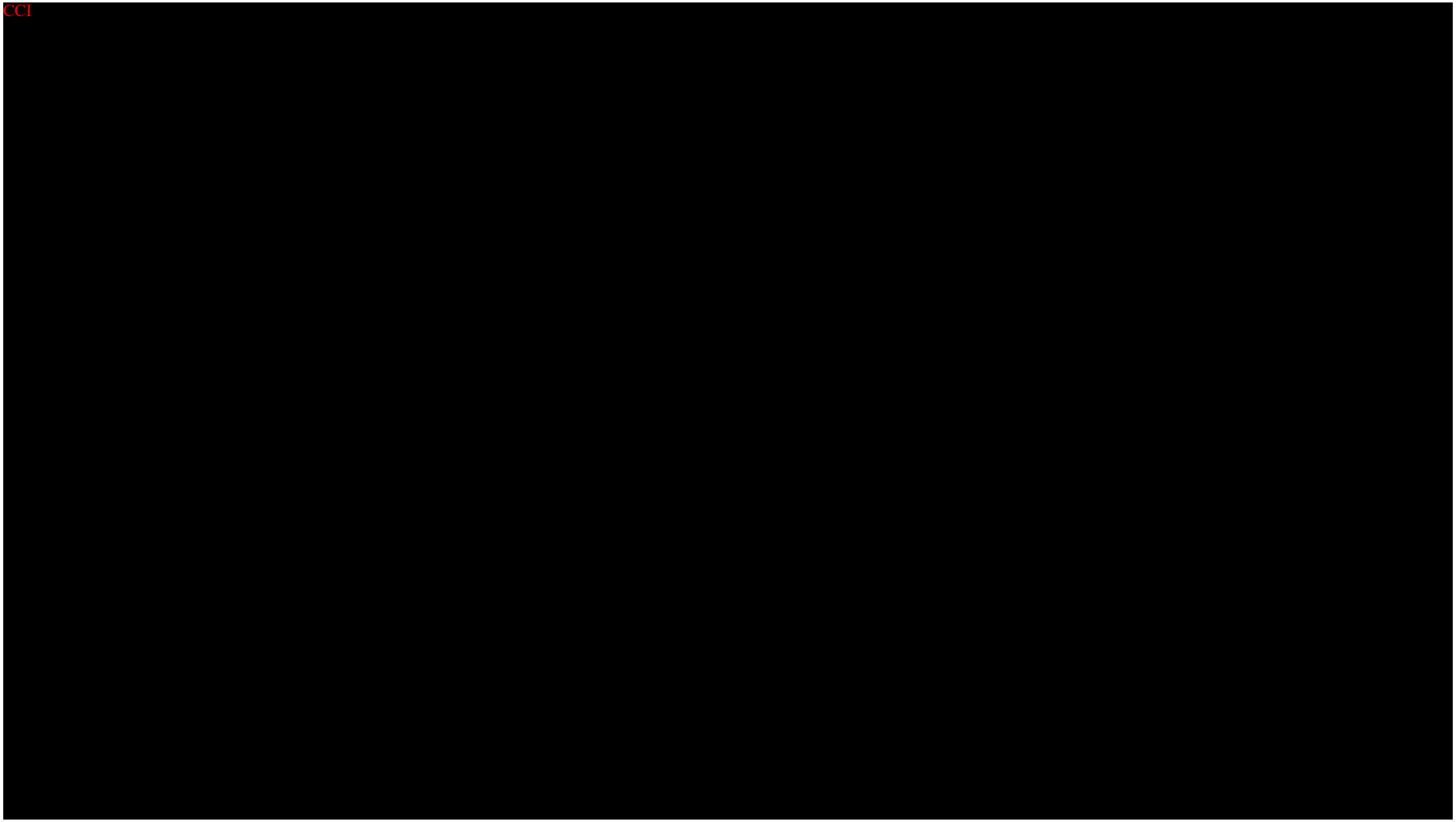

CCI

[redacted]

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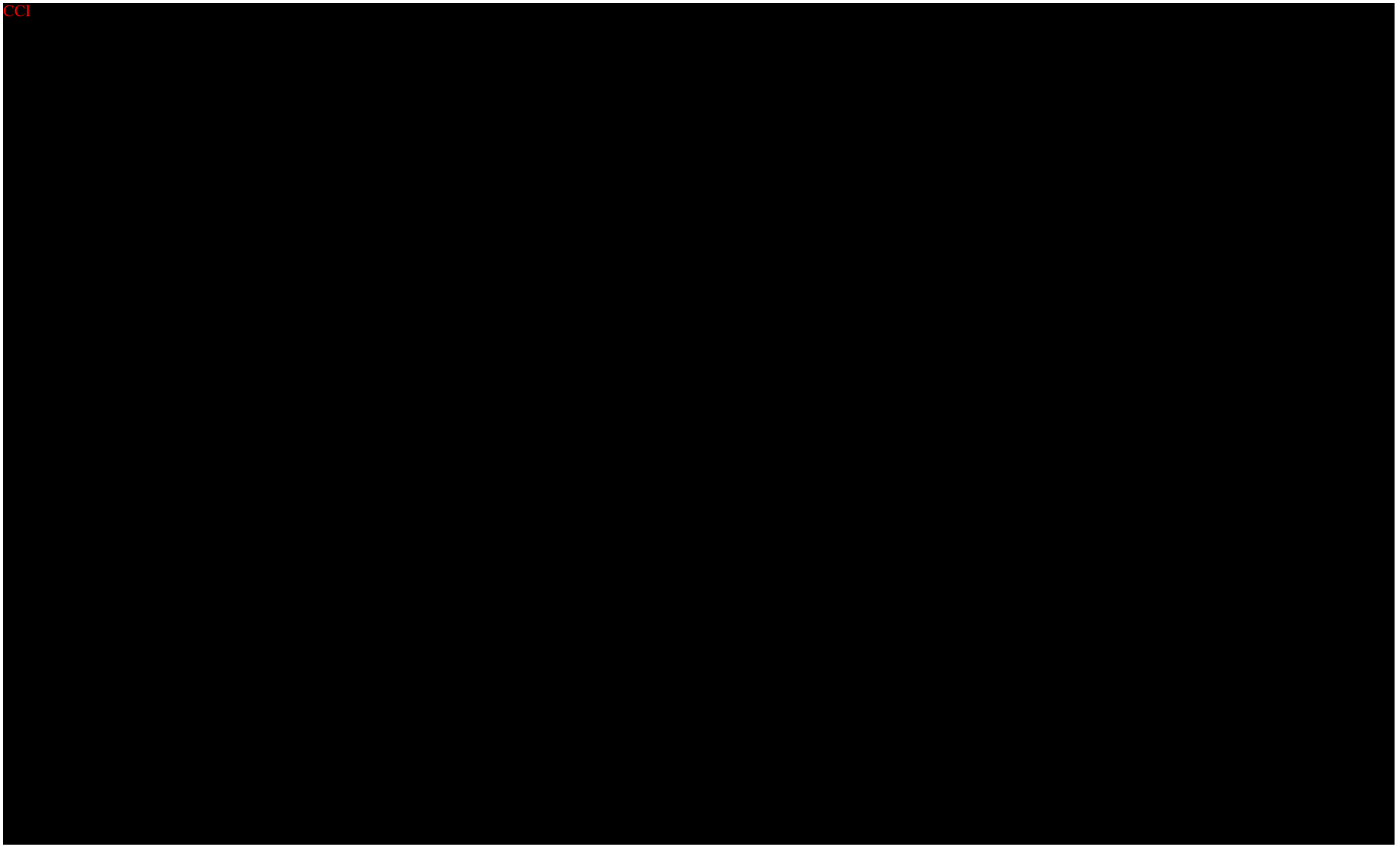


CCI

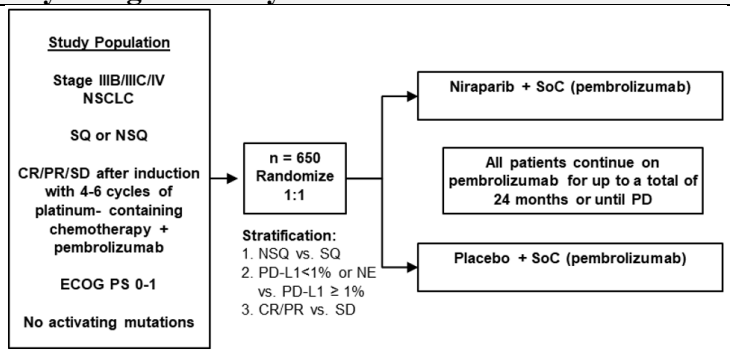
Objective (Hypothesis[1])	Estimand Category	Estimand			
		Variable/ Endpoint[2]	Population of interest (Analysis Set)	Intercurrent Event Strategy[3]	Population Level Summary Measure
	CCI [redacted]				

CCI [redacted]

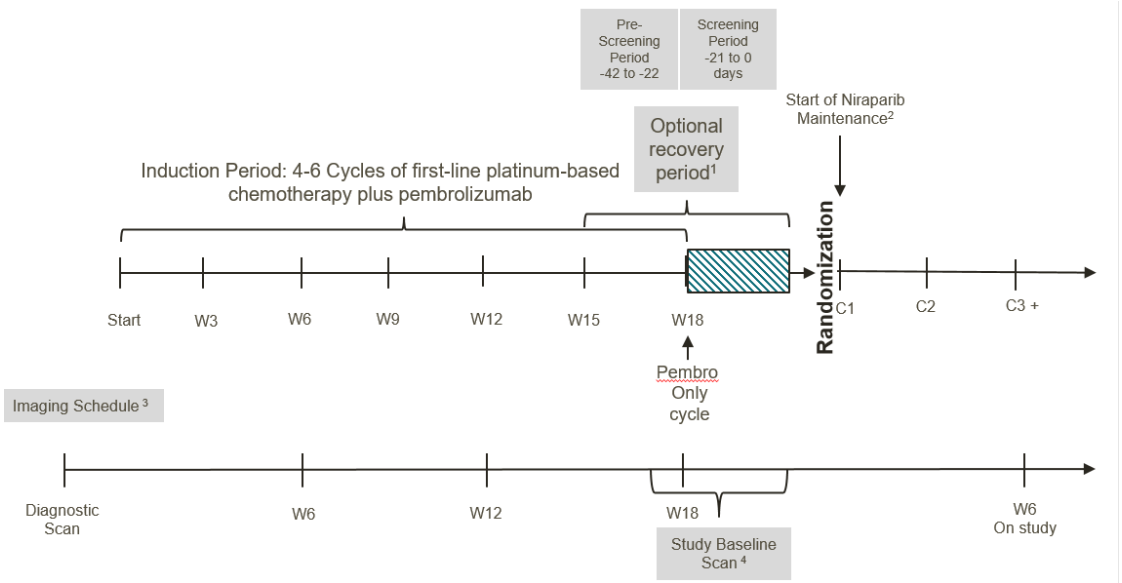
1.2. Study Design

Figure 1 Overall Study Schemas

Overview of Study Design and Key Features



Enrollment cap: Stable disease ~50%



Abbreviations: BICR = Blinded Independent Central Review; CNS = central nervous system; CR = complete response; CTCAE = Common Terminology Criteria for Adverse Events; ECOG = Eastern Cooperative Oncology Group; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire 30-item Core module; EORTC QLQ-LC13 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire 13-item lung cancer-specific module; EQ-5D-3L = European Quality of Life 5-Dimensions 3Level Scale; HRQoL = health-related quality of life; NSCLC = non-small cell lung cancer; NSQ = non-squamous; OS = overall survival; PD = progression of disease; PD-L1 = programmed cell death-ligand 1; Pembro = pembrolizumab; PFS = progression free survival; PR = partial response; QoL = quality of life; SD = stable disease; SOC = standard of care; SQ = squamous.

1. Transition period is 6 weeks, or up to 7 weeks with Sponsor approval.
2. Niraparib/placebo must start and pembrolizumab must continue on C1D1.
3. Imaging during the 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 will be performed Q6W (±7 days) for 48 weeks; from Week 49 on scans are performed Q12W (±7 days).
4. 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.

Overview of Study Design and Key Features	

Design Features	• This is a Phase 3, 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 platinum-based first-line induction chemotherapy with pembrolizumab.
	
	• 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 standard of care induction chemotherapy (PR/CR versus SD).
	
	• The proportion of participants with PR/CR versus SD will be monitored and the total number of participants with SD will be capped at approximately 50%. The study is comprised of pre-screening/screening, treatment, and safety/survival follow-up periods. The total duration of study participation begins with the signing of the informed consent form (ICF) through the final protocol-defined follow-up assessment for survival.
	
	  ○ For participants who meet all eligibility criteria and are randomized within the study, the maximum duration of treatment with pembrolizumab is expected to be approximately 2 years, or up to a maximum total of 35 cycles from the beginning of standard of care first-line induction therapy. Treatment with pembrolizumab may extend beyond 2 years (>35 cycles) in countries where continued pembrolizumab use is approved in accordance with standard of care 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, [redacted]. 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, or for up to 3 years. 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.

Overview of Study Design and Key Features	
	○ The follow-up period begins when study treatment is permanently discontinued; participants will undergo follow-up assessments for safety, CCI [redacted] and survival as indicated in the Schedule of Activities (SoA) in the protocol. CCI [redacted]
Study intervention	CCI [redacted] • Pembrolizumab will be administered 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.
Study intervention Assignment	• Participants 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.
Interim Analysis	• The study will use an Independent Data Monitoring Committee (IDMC) 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. • IDMC periodic safety data reviews will be performed as specified in the IDMC Charter. • No formal efficacy/futility interim analysis is planned. • The final OS analysis is planned when approximately 60% OS maturity is observed in the overall population.
Multiplicity	CCI [redacted]

2. STATISTICAL HYPOTHESES/ SUCCESS CRITERIA

CCI

[redacted]

CCI

[redacted]

CCI

CCI

CCI

3. ANALYSIS SETS

The analysis sets are defined in Table 4.

Table 4 Analysis Sets

Analysis Sets	Definition/Criteria	Analyses Evaluated
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.	Disposition/ Screen Failure

Analysis Sets	Definition/Criteria	Analyses Evaluated
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.	Study Population Efficacy
Response Evaluable – RECIST	The Response Evaluable Population – RECIST will consist of all randomized participants with evidence of disease at baseline by BICR per RECIST v1.1.	Efficacy (CCI per RECIST)
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.	Efficacy (CCI per RANO-BM)
Safety	The Safety Population will consist of all randomized participants who take at least 1 dose of study treatment (post-randomization). Participants will be analyzed according to the intervention they actually received.	Safety
PK	The PK Population will consist of those participants in the Safety Population (niraparib + pembrolizumab arm) from whom at least 1 PK sample has been obtained and analyzed. This population will be the primary population for PK analyses.	PK

3.1. Protocol Deviations

Protocol deviations will be tracked by the study team throughout the conduct of the study. These protocol deviations will be reviewed to identify those considered as important (management or participant assessment). Important deviations will be summarized.

A separate summary of all inclusion/exclusion criteria deviations will also be provided. This summary will be based on data as recorded on the eligibility page of the eCRF.

4. STATISTICAL ANALYSES

4.1. General Considerations

4.1.1. General Methodology

The Intent-to-Treat (ITT) analysis set will be used for all study population analyses, efficacy analyses and PRO analyses, unless otherwise specified.

Stratified statistical analyses (the stratified log-rank test and the stratified Cox model) will be based on the following stratification factors, histology (squamous versus non-squamous), PD-L1 status (TC <1%/NE versus ≥1%), and best response to induction chemotherapy (CR/PR versus SD). 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%/NE) group.

The primary analyses will be performed based on the strata data collected in Interactive Response Technology (IRT) at randomization, even if it is subsequently discovered that these values were incorrect.

Confidence intervals (CIs) will use 95% confidence levels unless otherwise specified.

Unless otherwise specified, continuous data will be summarized using descriptive statistics: n, mean, standard deviation, median, quantiles, minimum and maximum. Categorical data will be summarized as the number and percentage of participants in each category.

Unless otherwise specified, time-to-event endpoints will be calculated in months as: (event or censoring date – randomization date + 1)/30.4375.

4.1.2. Baseline Definition

For all endpoints, unless otherwise specified, the baseline value will be the latest pre-dose (of study treatment) assessment with a non-missing value, including those from unscheduled visits. If time is not collected, Day 1 assessments are assumed to be taken prior to first dose and used as baseline. For participants who did not receive study treatment during the study, baseline will be defined as the latest, non-missing collected value.

4.1.3. Multicenter Studies

In this multicenter global study, enrolment will be presented by country and site.

Data from all participating centers will be integrated and no controlling for center-effect will be considered in the statistical analyses. It is anticipated that participant accrual will be spread thinly across centers and summaries of data by center would unlikely be informative and will not be provided.

4.1.4. Visit Windows

It is expected that all visits should occur according to the protocol schedule. Unless specified otherwise, by-visit summaries and analyses will be by nominal visit (all data will be tabulated per the evaluation visit as recorded on the eCRF even if the assessment is outside of the visit window for analysis).

4.1.5. Study Population Summaries

The OPS document will provide additional details regarding the study population summaries, including, but not limited to, summaries describing disposition, baseline characteristics, disease characteristics, prior cancer therapy, induction therapy, prior and concomitant radiotherapy, prior and concomitant surgery, biomarker status, medical history, prior and concomitant drug use.

4.2. Primary Efficacy Endpoint Analyses

This study has one primary efficacy endpoint: PFS in the CR/PR population. The study will have met its primary objective if niraparib plus pembrolizumab is superior to placebo plus pembrolizumab for PFS CR/PR at the final analysis. All analyses outlined in this section will be conducted within the CR/PR Population and in the ITT Population unless specified otherwise.

4.2.1. Definition of endpoint(s)

PFS (in the CR/PR Population) as assessed by BICR using RECIST v1.1 is defined as the time from the date of randomization to the date of the first objectively documented disease progression per RECIST v1.1 based on BICR assessment, or death due to any cause, whichever occurs first.

The treatment effect for the primary analysis of PFS will be assessed as if subsequent anticancer treatment was not available and extended time without disease assessment is not present.

- Data will be censored for patients receiving subsequent anticancer treatment, considering systemic treatment, radiotherapy or cancer-related surgery, including localized treatment for brain metastases. Note: concomitant palliative radiotherapy (excluding palliative radiotherapy encompassing >20% of the bone marrow within 1 week of the first dose of study treatment) is allowed per protocol 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. Data will not be censored for this situation. Additionally, patients who are discontinued from pembrolizumab due to reaching 35 cycles and have subsequent anticancer treatment of commercial pembrolizumab only will not be included in censoring due to initiation of subsequent anticancer treatment as it will be considered continuation of study treatment only in regards to efficacy endpoints Therefore, this exception to censoring applies to all other endpoints that also have initiation of subsequent anticancer therapy as censoring rule such as CCI [redacted], CCI [redacted], etc.

- Since PFS is interval censored, extended time without adequate follow-up prior to PD or death increases the uncertainty of when the event occurs. As such, PFS will be analyzed censoring for extended time without an adequate assessment to account for missed response assessments prior to disease progression or death.

A summary of the assignments for progression and censoring dates for the primary analysis of PFS per RECIST v1.1 is described in Table 5 .

CCI

CCI

CCI [redacted]

4.2.2. Main analytical approach

Statistical hypotheses and multiplicity strategy for PFS in the CR/PR Population are described in Section 2.

PFS analysis in the CR/PR population will be conducted at the time of the planned final analysis.

The distribution of PFS CR/PR for each treatment arm will be estimated using the Kaplan-Meier method. CCI [redacted].

CCI [redacted]

4.2.3. Sensitivity analyses

4.2.3.1. Evaluation Time Bias for PFS

Imaging will be performed every 6 weeks (42 days ±7 days) from the date of randomization for a total of 48 weeks or until PD per RECIST v1.1 assessed by BICR.

Subsequent imaging for participants who remain on treatment for 1 year (48 weeks) will be performed every 12 weeks (84 days ±7 days), or more frequently if clinically indicated, until PD per RECIST v1.1.

The potential evaluation-time bias for those participants whose disease progressions were determined by scans not performed at the protocol-scheduled timepoints (i.e., outside the protocol defined visit windows) will be assessed. The stratification factors and censoring rules used in the primary analysis will be applied in this sensitivity analysis, with one exception. If progression is documented between scheduled visits (i.e., outside the protocol defined visit windows), progression will be assessed by using the earlier of date of the next scheduled timepoint and death (instead of the date of observed progression). This sensitivity analysis will be performed for PFS endpoint in the CR/PR population as well as the overall population.

4.2.3.2. Misclassification of Randomization Stratification Factors

In the case of a substantial amount of wrong stratification assigned at the time of randomization, a sensitivity analysis for PFS/OS in the CR/PR and overall population may be performed based on the data collected in the eCRF (or vendor, if collected outside of the eCRF). The censoring rules used in the primary analysis will be applied.

In addition, discrepancies between randomization stratification factors and the corresponding values recorded on the eCRF (or vendor, if collected outside the eCRF) will be summarized and listed.

4.2.3.3. Analysis without Randomization Stratification Factors.

For PFS in the CR/PR and the overall population, and OS in the CR/PR and the overall population, a sensitivity analysis will be performed without considering randomization stratification factors in the analysis. The censoring rules used in the primary analysis will be applied.

4.2.3.4. Non-censoring of Initiation of Subsequent Anti-cancer Therapy

A sensitivity analysis will be performed for the PFS endpoint where the same analyses will be performed as delineated in Section 4.2.2; however, initiation of subsequent anticancer therapy will not lead to censoring of the participant. This sensitivity analysis will also be performed for the CR/PR population.

4.2.3.5. Effect of US/EU sourced pembrolizumab on efficacy of niraparib

Efficacy analyses for PFS/OS in the CR/PR population and the overall population, between treatment arms will be performed within patients treated with US-sourced pembrolizumab, EU-sourced pembrolizumab, or treated with both US- and EU-sourced pembrolizumab. Cox regression model with no other covariate except for treatment arm will be fitted. Estimated HR, 95% CI and P-values will be reported for each subgroup. Those HRs and 95% CIs will be compared to HR estimated from overall population.

When sample size in US-sourced pembrolizumab treated group is too small (less than 10% of total population), Cox regression model will be fitted in EU-sourced

pembrolizumab treated group and in both US- and EU-sourced pembrolizumab treated group and compared to result in overall population.

4.2.4. Supplementary analyses

4.2.4.1. PFS per RECIST v1.1 assessed by BICR

The following additional supplementary analyses of PFS in the CR/PR Population and the overall population per RECIST v1.1 based on BICR assessment will be carried out as specified for the primary estimand but with different handling of specific intercurrent events:

- Supplemental Analysis 1: The treatment effect for the first supplemental analysis of PFS in the CR/PR Population and the overall population will be assessed, regardless of extended time without adequate follow-up, as if subsequent anticancer treatment was not available. The analysis will be the same as the primary analysis for PFS, except that if PD or death is documented after extended time without adequate follow-up, the participant is recorded as having an event on the date of documented PD or death (rather than being censored at the date of the last adequate radiological disease assessment prior to the missed disease assessments).

- Supplemental Analysis 2: Although the primary analysis of PFS in the CR/PR Population and the overall population is based on disease progression by BICR, it is possible that participants with progression as determined by Investigator or via methods other than radiographic imaging (e.g., clinical progression or tumor biopsy) may not have verification of progression by BICR and may lack further follow-up disease assessments, which may lead to informative censoring. The analysis will be the same as the primary analysis except that the following will be included as events, using the date of whichever occurs first:

    - undocumented radiographic progression (i.e., for participants who discontinue treatment due to Investigator-assessed progression, clinical progression or progression established via methods other than radiographic imaging without verification of progression by BICR)
    - use of subsequent anticancer treatment

The supplementary PFS in the CR/PR population and the overall population will be analyzed in the same manner as for the primary estimand.

4.2.5. Duration of Follow-Up Time

In addition, to estimate the median PFS follow-up time in the CR/PR population and the overall population at the time of analysis, a time-to censoring analysis will be performed by reversing the censoring indicator used in the primary PFS analysis, i.e., censoring becomes event and the PFS event becomes censored. The KM estimate of the median

potential survival follow-up, using reverse censoring of survival data, will be presented. Duration of OS in the CR/PR Population and the overall population follow-up will be analyzed in a similar fashion.

4.2.6. Non-Proportional Hazards

CCI [redacted]

CCI [redacted]

CCI [redacted]

4.3. Secondary Endpoint Analyses

4.3.1. Key secondary efficacy endpoint – Progression Free Survival in the overall population

Analyses for PFS in the overall population will be conducted following a similar approach for PFS in the CR/PR Population (see Section 4.2.).

4.3.2. Key secondary efficacy endpoint – Overall Survival in the CR/PR Population

OS is defined as the interval of time from the date of randomization to the date of death due to any cause.

All recorded deaths will be included in the analysis, regardless of the cause of death or if the death occurred after the initiation of subsequent anticancer treatment. Post End of Study (EOS) survival status data will also be utilized specifically for this endpoint. Participants without documented death will be censored at the date the participant was last known to be alive. The last known date to be alive will be determined by the maximum collection/assessment date among selected data domains within the clinical database; details will be provided in a separate OPS document. If any such date is beyond the data cut-off (DCO) date, then the last known alive date will be the DCO date.

If a participant is known to have died where only a partial death date is available, then the date of death will be imputed as the latest of the last complete known to be alive date + 1 from the database and the death date using the available information provided:

- For missing day only – use the 1st of the month
- For missing day and month- use the 1st of January

If there is evidence of death but the date is entirely missing, it will be treated as missing, i.e., censored at the last known alive date.

No imputation will be conducted for partial last contact dates if a participant did not die.

Analyses for OS in CR/PR will be conducted following a similar approach for PFS (see Section 4.2).

4.3.3. Key secondary efficacy endpoint – Overall Survival in the overall Population

Analyses for OS in the overall population will be conducted following a similar approach for PFS (see Section 4.2.).

4.3.4. Key secondary efficacy endpoint – CCI [redacted]

4.3.4.1. Definition of endpoint

The statistical hypothesis and multiplicity strategy for CCI [redacted] are described in Section 2CCI [redacted]
CCI [redacted]

Once a participant has documented systemic progression verified by BICR per RECIST v1.1, no further scans are required per protocol. In these cases, a systemic progression may hinder the observation of interest (CNS progression by BICR per RANO-BM criteria). To potentially account for this, competing events will be considered in the analysis.

The following three events will be defined:

- Radiologic documentation of progression in the CNS as assessed by BICR per RANO-BM criteria as the first site of progression (event of interest). This will include participants who had documented progression in the CNS at the same overall visit assessment as systemic progression.
- Radiologic documentation of systemic progression verified by BICR per RECIST v1.1 as the first site of progression in the absence of CNS progression (competing event)
- Death by any cause in the absence of the previous 2 events (competing event).

A summary of the censoring rules for the primary analysis of CCI [redacted] is described in Table 6 where systemic PD will be determined by RECIST v1.1 and CNS PD will be determined by RANO-BM. The RECIST v1.1 and RANO-BM assessments will be performed by different pools of radiologist and neuroradiologists as per the Blinded Independent Central Review Charter.

CCI [redacted]

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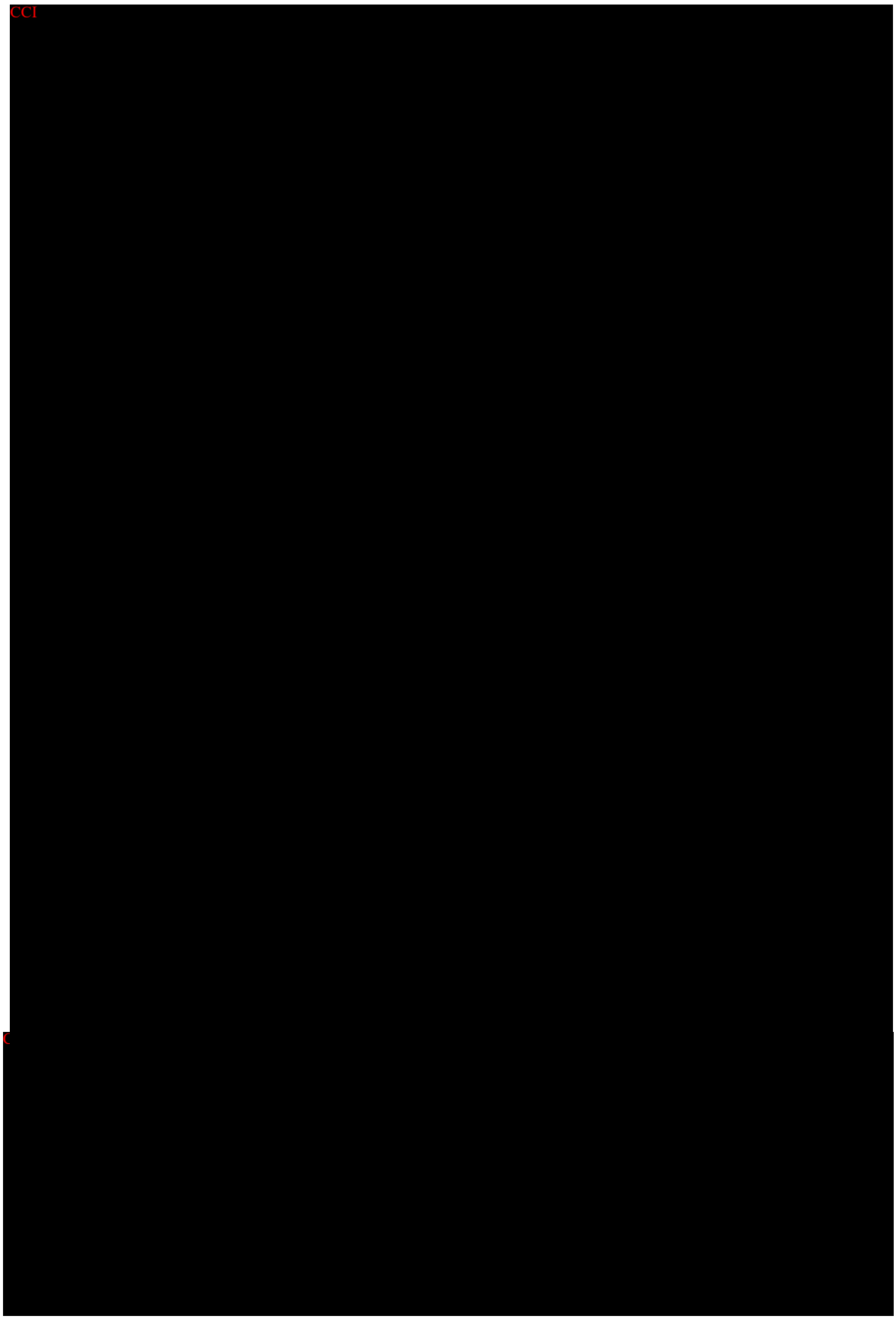

4.3.4.2. Main analytical approach

Cumulative incidence will be estimated by treatment group accounting for competing risk due to systemic progression per RECIST v1.1 and death. All participants in the ITT Population will be included in the analysis regardless of their baseline status of CNS metastases. Gray's test, stratified by the stratification factors used for randomization, will be used to compare the risk of CNS progression between treatment groups. Landmark cumulative incidence function rates at 6, 12 months and so on, as data allow, as well as corresponding 95% CIs will be calculated. Cumulative incidence rates will be visualized in a plot by treatment arm. Fine and Gray's competing risk model will be fitted with first documented progression in CNS as event (coded as 1) and first documented progression in other region (non-CNS) including death by any cause as competing event (coded as 2). Participants with no documented progression at any region will be censored (coded as 0). The subdistribution hazard ratio (SHR) and accompanying 95% CI will be presented.

4.3.4.3. Sensitivity analyses

4.3.4.3.1. Misclassification of Randomization Stratification Factors

In the case of a substantial amount of wrong stratification assigned at the time of randomization, a sensitivity analysis may be performed based on the data collected in the eCRF (or vendor, if collected outside of the eCRF). The censoring rules used in the primary analysis will be applied.

4.3.4.3.2. Analysis without Randomization Stratification Factors

A sensitivity analysis will be performed without considering randomization stratification factors in the analysis. The censoring rules used in the primary analysis will be applied.

4.3.4.3.3. Non-censoring of Initiation of Subsequent Anti-cancer Therapy

A sensitivity analysis will be performed for the CCI [redacted] endpoint similar to the sensitivity analysis in Section 4.2.3.4, where censoring of a participant will not occur upon the initiation of subsequent anticancer therapy.

4.3.4.4. Supplementary analyses

The following additional supplementary analysis of CCI [redacted] based on BICR assessment will be carried out as specified for the primary estimand but with different handling of specific intercurrent events:

- The supplementary analysis will be the same as the primary analysis except that if CNS PD, non-CNS PD or death is documented after extended time without an adequate assessment, the date of documented event and corresponding event status will be utilized (rather than being censored at the date of the last adequate radiological disease assessment prior to the missed disease assessment).

The supplementary CCI [redacted] analysis will be analyzed in the same manner as for the primary estimand.

4.3.5. Subgroup analyses

Table 7 describes the subgroup analyses that will be performed for OS and PFS per BICR RECIST v1.1 in the overall population.

Table 7 Subgroup Analyses for OS and PFS per RECIST v1.1

Subgroup	Categories[1]
Age at randomization	<65, ≥65 years of age
Sex	Male, Female
Race	White, Black/African-American, Asian, Other [Native Hawaiian/Pacific Islander or American Indian/Alaska Native or Others (including "Multiple"," Unknown", "Not reported")]
Ethnicity	Hispanic or Latino, Not Hispanic or Latino (including "Not Reported" and "unknown")
ECOG Performance Status at Baseline	0, 1
Region of Enrollment	North America, Europe, Asia, Rest of the World
BMI	Body mass index categorized as: Underweight (BMI < 18.5 kg/m2), Normal Weight (BMI: 18.5 to < 25 kg/m2), Overweight (BMI: 25 to < 30 kg/m2), Obese (BMI ≥ 30 kg/m2).
Smoking status	Former smoker/Current smoker, Nonsmoker CCI [redacted]
Histology	Squamous, Non-Squamous
Best Response after Induction Chemotherapy	CR/PR or SD
PD-L1 Status	TC≥1%, TC<1%/Not Evaluable CCI [redacted]
PD-L1 Status within Histology subgroups	TC ≥50%, TC < 50%/Not Evaluable within Squamous; TC ≥50%, TC < 50%/Not Evaluable within Non-Squamous
Presence of Baseline Brain Metastases	Yes, No

1. If the percentage of participants is small within a particular subgroup, then the subgroup categories may be refined prior to unblinding the trial.

Additional subgroups may be assessed if there is clinical justification, or an imbalance is observed between the study interventions. The purpose of the subgroup analyses is to assess the consistency of treatment effect across expected prognostic factors.

The ITT analysis set will be used in the subgroup analyses. The subgroup analyses will be based on values recorded on the eCRF (or vendor data if collected outside of eCRF).

HR and associated CIs will be calculated from an unstratified Cox proportional hazards model. The Cox models will be fit using SAS PROC PHREG with the EXACT method to control for ties, and the by statement to obtain HR and profile-likelihood 95% CI (RISKLIMITS = PL) for each subgroup level separately; refer to Section 4.2.1 for the analysis method and the corresponding primary censoring rules. The HRs and 95% CIs will be presented on a forest plot including the HR and 95% CI for the overall group.

Summaries of the number and percentage of participants experiencing an event for each subgroup will be provided along with the median by treatment group. Corresponding Kaplan-Meier plots of the survival distribution function will be presented and will include the number of participants at risk over time by subgroup level and treatment group.

4.4. Supportive secondary endpoint(s)

4.4.1. Investigator-Assessed PFS per RECIST v1.1

PFS will be assessed per RECIST v1.1 based on Investigator assessment as a secondary endpoint to serve as a sensitivity analysis for the PFS endpoint in the CR/PR Population. The same primary analysis methods as described for PFS as assessed by BICR will be utilized.

A table summarizing concordance and discordance between the number of study participants with PFS event per BICR and PFS event per Investigator will be provided in order to determine the discrepancy between the two endpoints. The number of participants where agreement on timing and occurrence as well as either timing or occurrence will also be provided. For study participants that had an agreement on occurrence of PFS BICR and Investigator but not timing, we will summarize whether BICR timing happened earlier or later than Investigator timing. This summary will be done separately for agreement on event and agreement for censoring. A similar summary will be done for participants that did not have an agreement on occurrence where the number of BICR events that occurred before or after Investigator censoring will be summarized as well as the number of BICR censorings that occurred before or after Investigator events. This table will be repeated to summarize the concordance and discordance between the BICR and Investigator methods for determining PD only rather than PFS events (excludes death events). In addition to the ITT Population all tables will also be summarized by Complete/Partial response as best response to induction chemotherapy.

4.4.2. BICR Assessed PFS per RECIST v1.1 and OS by PD-L1 status

For each PD-L1 subgroup, the analysis of BICR assessed PFS per RECIST v1.1 and OS will be performed as described in Section 4.3.5 for subgroups analyses. For each PD-L1 subgroup, the distribution of PFS and OS will be compared between the two treatment arms using an unstratified log-rank test.

4.4.3. Patient-Reported Outcomes

The EORTC QLQ-C30 and EORTC QLQ-LC13 will be collected in a coordinated fashion with imaging while participants remain on study treatment and following discontinuation of treatment, regardless of progression status. For participants who discontinue all study treatment, the EORTC QLQ-C30 and the EORTC QLQ-LC13 should be collected at the EOT Visit and the 30-day and 90-day Safety Follow-up Visits.

Scoring

The following PRO continuous variables will be summarized at each time point based on their scoring algorithms presented in the appendices.

- EORTC QLQ-C30: Global HRQoL (GHS/QoL scale), functional, and symptom scales and items (Section 6.2)
- EORTC-QLQ-LC13: symptom scales and items (Section 6.3)

For all PRO continuous variables, summary statistics will include: the number of available patients, means and 95% CIs, standard deviations, medians, minimums, maximums, first quartile Q1, and third quartile Q3. For categorical variables, the number of available patients, the frequency and percentage in each category will be displayed. Analyses will be summarized by treatment, unless otherwise specified. 95% CIs and 2-sided p-values will be presented. No adjustments for multiple testing or estimation will be used, so all p-values and 95% CIs will be considered descriptive/exploratory in nature.

Change from Baseline over Time

Summary statistics for observed values and changes from baseline will be provided for EORTC-QLQ-C30, sub-scales and items. This will also be done for QLQ-LC13 domain scores.

For individual items, change from baseline will be defined as described in Table 8.

Table 8 Item-level definition of change from baseline for EORTC QLQ-C30 EOT and QLQ-LC13

Definition	Description
Improved by 3+ response categories	For QLQ-C30 and QLQ-LC13: • For items in GHS/QoL* and functional scales: change from baseline by +3 or more response categories (e.g., from 1 "not at all" to 4 "very much") • For items in the symptom scales: change from baseline by -3 or more response categories (e.g., from 4 "very much" to 1 "not at all")
Improved by 2 response categories	For QLQ-C30 and QLQ-LC13: • For items in GHS/QoL* and functional scales: change from baseline by +2 response categories (e.g., from 1 "not at all" to 3 "quite a bit") • For items in symptom scales: change from baseline by -2 response categories (e.g., from 4 "very much" to 2 "a little")
Improved by 1 response category	For QLQ-C30 and QLQ-LC13: • For items in GHS/QoL* and functional scales: change from baseline by +1 response category (e.g., from 1 "not at all" to 2 "a little bit") • For items in symptom scales: change from baseline by -1 response category (e.g., from 3 "quite a bit" to 2 "a little")
No change	Remaining in the same response category as indicated at baseline
Worsened by 1 response category	For QLQ-C30 and QLQ-LC13: • For items in GHS/QoL* and functional scales: change from baseline by +1 response category (e.g., from 2 "a little bit" to 1 "not at all") • For items in symptom scales: change from baseline by -1 response category (e.g., from 2 "a little" to 3 "quite a bit")
Worsened by 2 response categories	For QLQ-C30 and QLQ-LC13: • For items in GHS/QoL* and functional scales: change from baseline by -2 response categories (e.g., from 3 "quite a bit" to 1 "not at all") For items in symptom scales: change from baseline by +2 response categories (e.g., from 2 "a little" to 4 "very much")
Worsened by 3+ response categories	For QLQ-C30 and QLQ-LC13: • For items in GHS/QoL* and functional scales: change from baseline by -3 response categories (e.g., from 4 "very much" to 1 "not at all") • For items in symptom scales: change from baseline by +3 response categories (e.g., from 1 "not at all" to 4 "very much")

* GHS/QoL scale occurs in QLQ-C30 only.

A mixed effects model for repeated measures (MMRM) will be performed adjusting for correlations across multiple time points within a participant and controlling for the baseline value. The MMRM model will be used to compare the average treatment effect while on study intervention and will include on-treatment visits and EOT. For each treatment group, an overall adjusted mean estimate will be derived that will estimate the average treatment effect over visits giving each visit equal weight along with the

corresponding 95% CI. In addition, an estimate of the treatment difference will be presented along with the 95% CI.

Adjusted means and 95% CI bars will be presented and will also be plotted over time. The analysis visits will include post-baseline visits, unless there is excessive missing data at a visit (defined as >50% of the expected reports are missing data).

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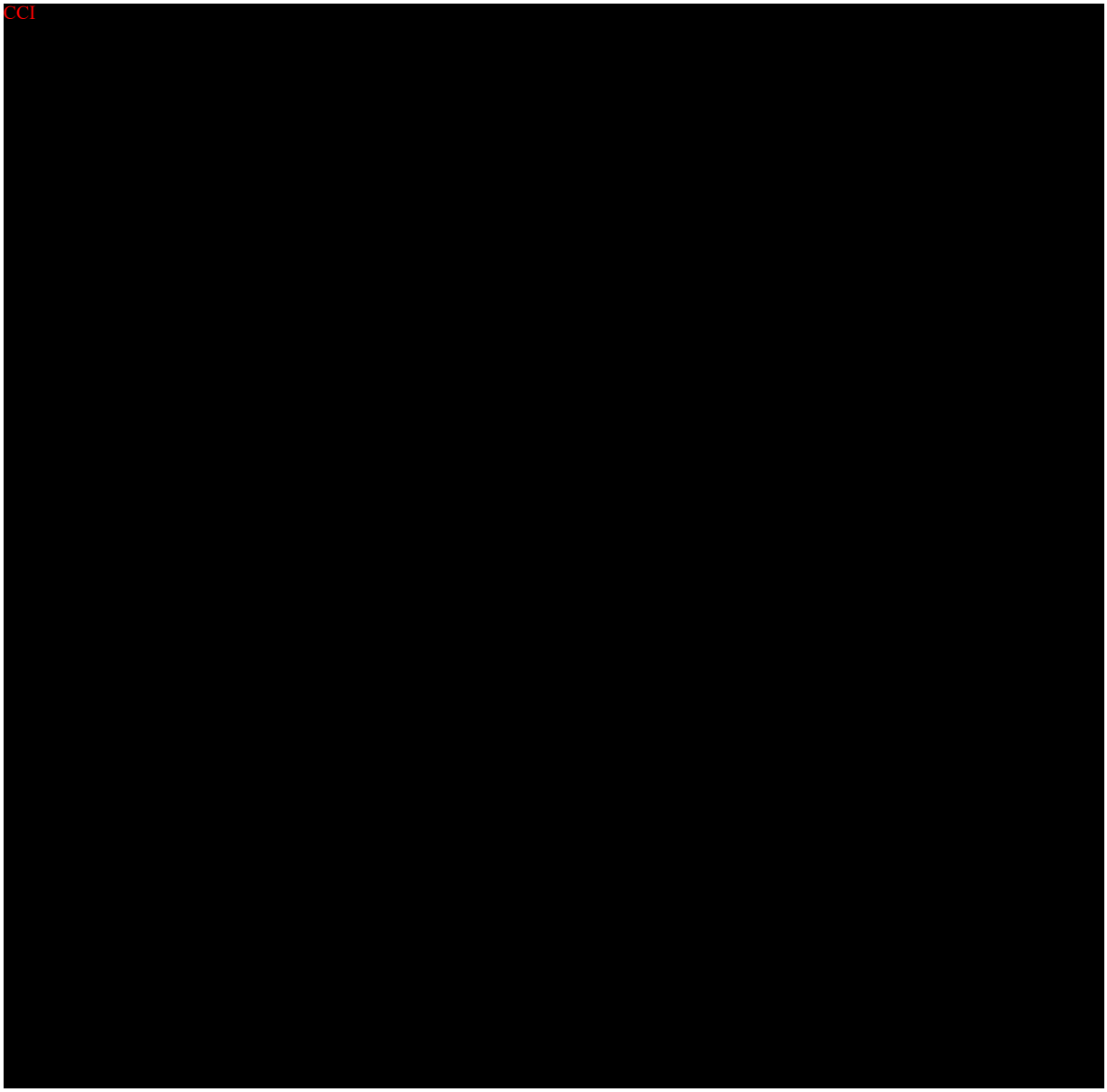

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Minimum Clinically Important Difference

The EORTC QLQ-C30 and the EORTC QLQ LC-13 scores were standardized to a scale ranging from 0-100 by linear transformation. The following categorical variables will be defined at each time point from the corresponding continuous variables according to the minimum clinically important difference (MCID) for the EORTC QLQ-C30: (Maringwa, 2011, Osoba, 1998):

Table 9 Definition of Response for the EORTC QLQ-C30 and the EORTC QLQ-LC13

Definition	Description
For functional scales and global HRQoL (GHS/QoL):	
• **Improved**	change from baseline ≥ 10 points
• **Stable**	-10 points < change from baseline < 10 points
• **Worsened***	change from baseline ≤ -10 points
For symptom scales	
• **Improved**	change from baseline ≤ -10 points
• **Stable**	-10 points < change from baseline < 10 points
• **Worsened***	change from baseline ≥ 10 points

* or "Patient was too ill" is answered as the reason for not completing the QLQ-C30 form at visit not included due to information not being collected.

The number and proportions of participants in each category will be presented over time.

Compliance

This section covers all PRO endpoints including the ones listed in Section 4.5.3 through Section 4.5.7.

For each HRQoL questionnaire, the overall compliance and compliance by visit will be summarized. The overall participant compliance rate for each PRO endpoint is defined for each randomised treatment group as: Total number of participants with an evaluable baseline and at least one evaluable follow-up questionnaire, divided by the total number of participants expected to have completed at least a baseline questionnaire multiplied by

100. When calculating the overall participant compliance rate the following terms are defined:

An expected form = a questionnaire that is expected to be completed at a scheduled assessment time, i.e. a questionnaire from a participant who is alive and has not withdrawn from the study at the scheduled assessment time.

A received form = a questionnaire received back.

An evaluable form = a received questionnaire with a completion date and at least one subscale that is non-missing.

Reasons for non-completion will be summarized, if available in the ePRO.

The target compliance for each instrument is 90%. Additionally, an overall study level compliance rate across all PRO endpoints will be calculated. This will be the total number of all evaluable forms across all participants, all timepoints, and all PRO instruments, divided by the total number of expected forms across all participants, all timepoints and all PRO instruments. This proportion is then multiplied by 100 to become a percentage. PRO instruments analyzed in the supplemental SAP will not be included in this calculation.

Participant compliance over time is calculated separately for each scheduled assessment (including baseline) as the number of participants providing an evaluable assessment at that assessment divided by the number of participants expected to have provided an assessment.

The following estimates will be provided to characterize the number of expected forms:

- PRO assessment forms expected
- PRO assessment forms not expected – due to lost to follow-up
- PRO assessment forms not expected – due to timepoint not yet reached
- PRO assessment forms not expected – due to EOT taking place earlier
    - This reason will also be summarized by baseline brain metastases status
- PRO assessment forms not expected – due to death
- PRO assessment forms not expected – due to other reasons

The evaluable forms will be characterized by estimating the following:

- All questions completed (i.e., fully completed, not completion rates for individual items)
- Sufficient number of questions (i.e., at least one subscale) completed[1]

[1] The number of forms with *enough items to enable the score to be calculated* will be included in the tables reporting absolute scores and changes from baseline for each visit.

- Insufficient number of questions completed

The percentage of forms received and the reasons for forms not received back will be reported at each visit. To ensure the representativeness of the reported HRQoL data, a comparison of baseline characteristics for compliant vs. non-compliant patients will be performed if compliance is considered inadequate.

4.4.4. Time to Deterioration

Time to Deterioration (TTD) in lung symptoms is defined as the time from randomization to first onset of ≥10 point increase from baseline with confirmation by a second adjacent ≥10 point increase in the same symptom domain for any of the three symptoms: dyspnea, chest pain, and cough, on the EORTC QLQ-LC13 (Mazieres, 2019). The composite endpoint 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.

TTD in lung symptoms will be analyzed following a similar approach for PFS as described in Section 4.2.2. TTD of each symptom, as well as GHS/QoL, physical functioning, and role functioning from QLQ-C30 will also be analyzed individually. If no deterioration is observed, censoring will occur at the date of the last QLQ-LC13/QLQ-C30 assessment. If there is an incomplete baseline assessment or no post-baseline assessment, censoring will occur on the date of randomization.

4.4.5. Safety and Tolerability

Safety will be evaluated based on the incidence of AEs, SAEs, treatment discontinuations or dose interruptions or dose reductions due to AEs, AESIs, changes in ECOG performance status, changes in clinical laboratory results (hematology, chemistry, coagulation, liver function, 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 (MedDRA). The severity of AEs will be graded utilizing the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0.

Analyses for safety and tolerability endpoints are described in Section 4.6 .

4.4.6. Drug Concentration Analyses

Plasma concentrations of niraparib will be listed for each participant and summarized (when appropriate) by planned time point. A box plot of niraparib concentrations by planned time point will be presented. Details of the planned displays are provided in the OPS document.

4.4.7. CNS-PFS by BICR per RANO-BM

CNS-PFS is defined as the time from the date of randomization to the date of first documented progression in the CNS as determined by BICR using RANO-BM criteria or

until death (whichever occurs first). Fine and Gray's competing risk model will be fitted with first documented progression in CNS as event (coded as 1) and first documented progression in other region (non-CNS) including death by any cause as competing event (coded as 2). Patients with no documented progression at any region will be censored (coded as 0). SAS PROC PHREG will be used to fit Fine and Gray model. If data is available, explanation of CNS progression and competing events will be summarized by treatment group using frequency and percentages. This summary will be done overall as well as by Isolated (CNS progression per RANO-BM, due to new brain lesions only, progression of existing brain lesions only, worsening of clinical status only and multiple reasons) versus Concurrent (BICR RECIST and CNS progression per RANO-BM, due to new brain lesion only, progression of existing brain lesion only, worsening of clinical status only and multiple reasons). BICR RECIST and RANO-BM scans that occur on different days but during the same visit will also be considered as Concurrent PDs. The SHR and accompanying 95% CI will be presented.

4.5. Tertiary/Exploratory Endpoint(s) Analyses

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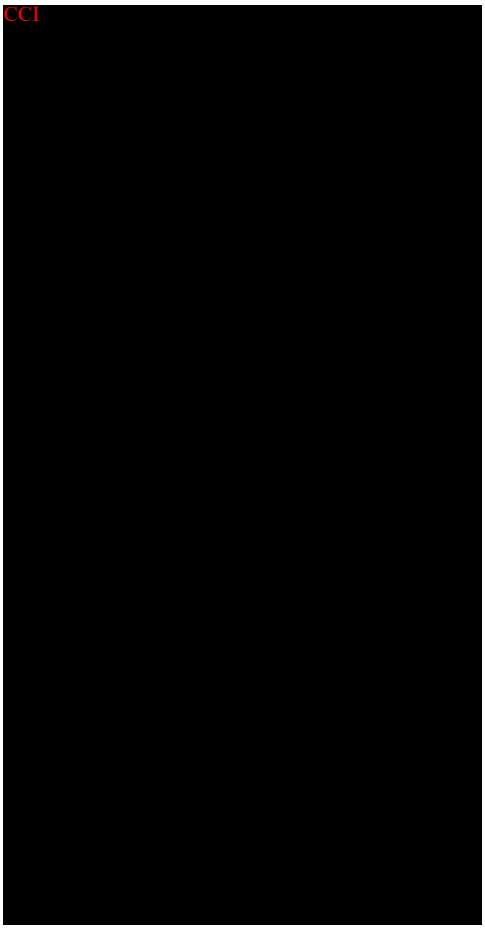

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4.6. (Other) Safety Analyses

The safety analyses will be based on the Safety Analysis Set, unless otherwise specified.

Due to sponsor's decision on November 16, 2023, to discontinue pembrolizumab after 35 cycles, information related to AE, dosing, and other parameters may not have been collected for such patients that had subsequent anticancer therapy of pembrolizumab only as it was not considered part of study treatment.

4.6.1. Extent of Exposure

Extent of exposure to niraparib/placebo and pembrolizumab (post-randomization) will be summarized overall and separately.

The number and percentage of participants at the starting prescribed dose by cycle will be summarized.

Exposure parameters as defined in Table 12 will be summarized descriptively. In addition, the number and percentage of participants who have a niraparib/placebo dose reduction, dose interruption or missed dose will be summarized. Additionally, the number and percentage of participants who have pembrolizumab dose interruption or missed dose will be summarized. Note that any mention of dose in the calculation below refers only to non-zero doses as some sites may enter no dose as a dose with value 0 in dosing records.

Table 12 Exposure Parameters for Niraparib/Placebo, Pembrolizumab

Parameter	Niraparib/Placebo	Pembrolizumab	Overall Combination Study Treatment
Number of treatment cycles initiated	CCI	# of pembrolizumab cycles initiated (infusion started)	# of cycles where either pembrolizumab or niraparib initiated.
Duration of treatment (Unit: months)		[Date of last pembrolizumab infusion+20 – first pembrolizumab infusion+1]/30.4375.*	(Max [date of last niraparib/placebo dose, pembrolizumab infusion+20)]-min(date of first niraparib/placebo dose, first pembrolizumab infusion) + 1)/ 30.4375*
Cumulative dose (Unit: mg)		Sum of all pembrolizumab doses infused.	NA
Actual dose intensity (Unit: mg/day)		Cumulative dose/pembrolizumab treatment duration (days)	NA

Parameter	Niraparib/Placebo	Pembrolizumab	Overall Combination Study Treatment
Intended dose (Unit: mg/day)	CCI [redacted]	200 mg/21-day cycle (9.52 mg/day)	NA
Relative dose intensity (Unit: %)	CCI [redacted]	100* (Actual dose intensity/intended dose)	NA
Abbreviations: NA=not applicable.			

*Date of last pembrolizumab infusion + 20 is ensured to not exceed cut-off/death date

4.6.2. Adverse Events

All adverse events (AEs) and serious adverse events (SAEs) will be collected from the signing of the main study ICF until 30 days after the last dose of study treatment. Any SAEs assessed as related to study participation or related to study treatment will be collected and reported until study closeout. MDS or AML, along with other secondary cancers (new malignancies other than MDS or AML) will be collected until death or loss to follow-up. Pneumonitis will be collected through 90 days after the last dose of study treatment (or until the start of alternate anticancer therapy, whichever occurs first).

AEs will be recorded using standard medical terminology and graded by the investigator according to the NCI-CTCAE, Version 5.0. For AE reporting, the verbatim term used in the eCRF by Investigators to identify adverse events will be coded using the latest version of Medical Dictionary for Regulatory Affairs (MedDRA) coding dictionary. All AEs that are Grade 3 and above will also be summarized.

All treatment-emergent adverse events (TEAEs), whether serious or non-serious, will be reported from the start of study treatment until 30 days (unless otherwise stated) after the last dose of study treatment, until the participant withdraws consent for study participation, or until the participant starts subsequent anticancer therapy, whichever occurs first. Serious related immune related adverse events (irAE) beyond 30 days after the last dose of study treatment until study closure will also be summarized.

A high-level overview of TEAEs will be presented in a summary table. This table will include the numbers and percentages of participants who had:

- Any TEAE
- Any study intervention-related TEAE
    - Related to niraparib/placebo
    - Related to niraparib/placebo only

  - Related to pembrolizumab
  - Related to pembrolizumab only
  - Related to both niraparib/placebo and pembrolizumab
- Any serious TEAE
- Any study intervention-related serious TEAE
  - Related to niraparib/placebo
  - Related to niraparib/placebo only
  - Related to pembrolizumab
  - Related to pembrolizumab only
  - Related to both niraparib/placebo and pembrolizumab
- Any TEAE with CTCAE Toxicity Grade >=3
- Any study intervention-related TEAE with CTCAE Toxicity Grade >=3
  - Related to niraparib/placebo
  - Related to niraparib/placebo only
  - Related to pembrolizumab
  - Related to pembrolizumab only
  - Related to both niraparib/placebo and pembrolizumab
- Any TEAE leading to study intervention interruption/reduction/delay
  - TEAE leading to niraparib/placebo interruption
  - TEAE leading to niraparib/placebo dose reduction
  - TEAE leading to pembrolizumab infusion interrupted
  - TEAE leading to pembrolizumab infusion delay
- Any TEAE leading to permanent discontinuation of either treatment
- Any TEAE leading to permanent discontinuation of niraparib/placebo
- Any TEAE leading to permanent discontinuation of pembrolizumab
- Any TEAE leading to permanent discontinuation of both niraparib/placebo and pembrolizumab
- Any TEAE resulting in death
- Any study intervention-related TEAE resulting in death
  - Related to niraparib/placebo
  - Related to pembrolizumab

The following TEAE tables will be provided summarizing the frequency and percentage of participants experiencing adverse events:

- TEAEs by System Organ Class (SOC) and Preferred Term (PT)
- TEAEs by PT (sorted by frequency)
- Common TEAEs with a frequency ≥ 5% in either treatment group by PT
- Related TEAEs by SOC and PT (Overall and separately for study intervention, niraparib/placebo and pembrolizumab)
- Treatment-emergent SAEs by SOC and PT
- Related Treatment-emergent SAEs by SOC and PT (separately for study intervention, niraparib/placebo and pembrolizumab)
- Related Treatment-emergent SAEs by PT (separately for study intervention, niraparib/placebo and pembrolizumab)
- TEAEs by SOC, PT, and maximum grade
- Related TEAEs by SOC, PT, and maximum grade (separately for study intervention, niraparib/placebo and pembrolizumab)
- Grade ≥3 TEAEs by SOC and PT
- Grade ≥3 TEAEs by PT (sorted by frequency)
- Related Grade ≥3 TEAEs by SOC and PT (separately for study intervention, niraparib/placebo and pembrolizumab)
- TEAEs resulting in death by SOC and PT
- Related TEAEs resulting in death by SOC and PT
- TEAEs resulting in niraparib/placebo dose interruption by SOC and PT
- TEAEs resulting in niraparib/placebo dose reduction by SOC and PT
- TEAEs leading to pembrolizumab infusion interruption by SOC and PT
- TEAEs leading to pembrolizumab infusion delay by SOC and PT
- TEAEs leading to permanent discontinuation of study treatment
- TEAEs leading to permanent discontinuation of niraparib/placebo by SOC and PT
- TEAEs leading to permanent discontinuation of pembrolizumab by SOC and PT
- Related TEAEs leading to permanent discontinuation of study treatment

Tables structured as listings will be provided for the following:

- By patient listing of all AEs
- SAEs resulting in death
- Non-fatal SAEs
- TEAEs resulting in niraparib/placebo drug interruption or dose reduction
- TEAEs resulting in pembrolizumab infusion interruption or delay
- TEAEs resulting in permanent discontinuation of study intervention (niraparib/placebo or pembrolizumab)

- AESIs (Section 4.6.2.1)
- AEMIs (Section 4.6.2.2)
- Immune-related adverse events (irAEs) (Section 4.6.2.3)
- Mapping of AE reported term to PT

Additional adverse event summaries may be provided for the purposes of disclosure summaries and will be described in the OPS.

When summarizing TEAEs by maximum grade, the following algorithms for counting the participant will be used:

- **Preferred term row**: Participants experiencing the same TEAE preferred term several times with different grades will only be counted once with the maximum grade.
- **SOC term row:** Participants experiencing the same TEAE SOC several times with different grades will only be counted once with the maximum grade.
- **Any event row:** Each participant with at least one adverse event will be counted only once at the maximum grade no matter how many events they have.

The relationship of each TEAE to the study intervention will be summarized as assessed by the Investigator. A study intervention-related TEAE is defined as a TEAE for which the investigator classifies the relationship to either niraparib/placebo or pembrolizumab as RELATED. A worst-case scenario approach will be taken to handle missing relatedness data, i.e., the summary table will include events considered RELATED to either niraparib/placebo or pembrolizumab or with missing relationship to either study intervention. Summaries will also be generated by relationship to individual components of the study intervention (niraparib/placebo and pembrolizumab separately). The imputation for a missing relationship will take place prior to determining the most related TEAE within a SOC or PT for a given participant.

4.6.2.1. Adverse Events of Special Interest

The following will be considered adverse events of special interest (AESI) for niraparib for the purpose of analyses: MDS, AML, Secondary cancers (new malignancies other than MDS or AML) and Pneumonitis. Table 13 outlines the AESIs with the criteria of mapping MedDRA PTs for each AESI using Standardized MedDRA Queries (SMQs), High Level Terms (HLTs), and/or PTs.

Table 13 Adverse Events of Special Interest

Group Term	MedDRA Criteria for Selection of Preferred Terms
AESI: MDS/AML event	Myelodysplastic syndrome SMQ (Narrow) Leukaemias acute myeloid (HLT)

Group Term	MedDRA Criteria for Selection of Preferred Terms
AESI: Malignant tumour SMQ (other than MDS/AML)	Haematological malignant tumours SMQ (Narrow), Non-haematological malignant tumours SMQ (Narrow)., excluding terms not reflecting a new malignancy, e.g., signs or symptoms of malignancies, disease progression of existing cancer
AESI: Pneumonitis	Lower respiratory tract inflammatory and immunologic conditions (HLT)

Abbreviations: MedDRA = medical dictionary for regulatory activities; PT = preferred term; SMQ = Standardized MedDRA Query.

Note: The list of MedDRA PTs will be provided by the GSK Safety Evaluation and Risk Management (SERM) group prior to database release (DBR) based on the most up-to-date MedDRA version.

Each AESI will be summarized by grouped term and PT and will include the numbers and percentages of participants who experienced:

- AESI
- Grade ≥3 AESI
- Serious AESI
- AESI related to niraparib/placebo
- AESI resulting in discontinuation of niraparib/placebo
- AESI resulting in death

Additional data collected for AESIs will be presented in patient narratives and will be further specified in the OPS.

4.6.2.2. Adverse Events of Medical Interest

Adverse events of medical interest (AEMI) will also be grouped for analysis and will be summarized in a similar manner as the AESIs. All AEMI will be additionally summarized for Grade 3 and 4 events, all SAEs, AEs leading to death, leading to treatment discontinuation, and leading to dose interruption and reduction. Table 14 outlines all the grouped events including the criteria of mapping MedDRA PTs for each group using Standardized MedDRA Queries (SMQs), High Level Terms (HLTs), and/or PTs.

Table 14 Adverse Events of Medical Interest

Group Term	MedDRA Criteria for Selection of Preferred Terms
Thrombocytopenia events	Haematopoietic thrombocytopenia SMQ (Broad)
Anemia events	Haematopoietic erythropenia SMQ (Broad)

Group Term	MedDRA Criteria for Selection of Preferred Terms
Leukopenia events	Haematopoietic leukopenia SMQ (Narrow)
Neutropenia events	Selected PTs related to neutropenia in the Haematopoietic leukopenia SMQ (Narrow)
Pancytopenia events	Haematopoietic cytopenias affecting more than one type of blood cell (SMQ Broad)
Hypertension events	Hypertension SMQ (Narrow)

Abbreviations: MedDRA = medical dictionary for regulatory activities; PT = preferred term; SMQ = Standardized MedDRA Query.

Note: The list of MedDRA PTs will be provided by the GSK SERM group prior to DBR based on the most up-to-date MedDRA version.

4.6.2.3. Immune-Related Adverse Events (irAEs)

Immune-related adverse events (irAEs) within 30 days after treatment ended, are identified as any Grade 2 or greater AE related to pembrolizumab according to a pre-specified search strategy which will be provided by the GSK Safety Evaluation and Risk Management (SERM) group prior to DBR based on the most up-to-date MedDRA version. Any irAEs that began after the treatment-emergent period will be summarized separately. The irAEs will be identified by a list of GSK custom MedDRA queries (CMQ). irAEs will be summarized by irAE type and PT and will include the numbers and percentages of participants who experienced:

- irAEs,
- Grade ≥3 irAEs
- Serious irAEs
- irAEs resulting in interruption of pembrolizumab
- irAEs resulting in discontinuation of pembrolizumab
- irAEs resulting in death

4.6.2.4. Common Adverse Events/Relative Risk

Adverse events will be evaluated by PT using the relative risk assessment for the niraparib treatment arm versus the placebo arm. The relative risk and 95% CI will be provided for AEs reported in ≥1% of participants in either treatment arm. A similar table will be provided for Grade ≥3 AEs reported in ≥1% of participants in either treatment arm. Tables will be sorted by the decreasing frequency of PT.

Plots of the relative risk and 95% CI will also be generated. The criteria for inclusion in the plots will include AEs reported in ≥10% of participants in either treatment arm. A similar plot will be generated for Grade ≥3 AEs reported in ≥5% of participants in either treatment arm. Plots will be sorted by the decreasing magnitude of relative risk estimate.

4.6.3. Additional Safety Assessments

4.6.3.1. Deaths

All deaths will be summarized based on the number and percentage of participants. There will be an overall summary in addition to a summary that will classify participants by time of death relative to the last dose of medication (>90 days, 31-90 days or ≤30 days) and will summarize the primary cause of death. A supportive listing will be generated on participants who died.

4.6.3.2. Pregnancies

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 recorded as an AE or SAE as described in the protocol. If participants become pregnant while on the study, the information will be included in the narratives.

4.6.3.3. Laboratory Data

Laboratory evaluations including the analyses of chemistry, hematology, coagulation, thyroid function and routine urinalysis laboratory tests and other screening tests will be summarized based on GSK Core Data Standards and will be further described in the OPS document. Liver function laboratory tests will be included with chemistry lab tests.

Descriptive statistics (n, mean, standard deviation, median, quantiles, minimum and maximum) will be used to summarize change from baseline in observed value at each scheduled visit. This summary will be performed both overall and for each treatment group. A distribution boxplot of hematology and chemistry laboratory test values over time will be presented.

Summaries of worst-case grade increase from baseline grade will be provided for all the lab tests that are gradable by CTCAE v5.0. These summaries will display the number and percentage of participants with a maximum post-baseline grade increasing from their baseline grade (e.g., Increase to Grade 1, Increase to Grade 2, Increase to Grade 3, Increase to Grade 4) and maximum grade increase subtotals (e.g., Increase to Grades 1 to 4, Increase to Grades 2 to 4, Increase to Grades 3 to 4). Participants with missing baseline value are to be assumed to have a Grade 0 at baseline. For laboratory tests that are graded for both low and high values, summaries will be done separately and labelled by direction, e.g., sodium will be summarized as hyponatremia and hypernatremia separately.

For lab tests that are not gradable by CTCAE v5.0, summaries of worst-case changes from baseline with respect to normal range will be generated. Decreases to low, changes to normal or no changes from baseline, and increases to high will be summarized for the worst-case post-baseline. If a participant has a decrease to low and an increase to high during the same time interval, then the participant is counted in both the “To Low” categories and the “To High” categories.

The determination of the worst-case post-baseline lab values will consider both planned and unscheduled assessments. Participants with missing baseline values are assumed to have a normal/Grade 0 baseline value. The percentages are based on the number of participants in the treatment group with post-baseline data.

Summaries of hepatobiliary laboratory events including possible Hy's law cases will be provided in addition to what has been described above. Possible Hy's law cases, based on laboratory parameters, are defined as any elevated alanine aminotransferase (ALT) ≥3×upper limit of normal (ULN) and total bilirubin ≥2×ULN (for participants with known Gilbert's syndrome these criteria only apply if total bilirubin ≥2xULN and ≥2x baseline value) or ALT ≥3×ULN and INR >1.5, if INR measured. Total bilirubin ≥2×ULN can be within 28 days following the ALT elevation and if direct bilirubin is available on the same day, it must be ≥35% of total bilirubin.

An e-DISH plot of maximum post baseline total bilirubin versus maximum post baseline ALT will be created. A similar plot will also be produced for maximum post-baseline total bilirubin versus maximum post baseline AST. GSK Core Data Standards will be used to summarize data specific to participants who meet the protocol specified liver stopping or monitoring events that are specified in the study protocol and will be further described in the OPS.

4.6.3.4. Vital Signs

Values of vital signs (weight, temperature, pulse rate, respiratory rate, and systolic and diastolic blood pressure) as well as the change from baseline will be summarized by scheduled visit using n, mean, median, standard deviation, minimum and maximum. These descriptive statistics will be provided both overall and by treatment arm. A distribution boxplot of blood pressure values over time will be presented.

In addition, summaries of grade increase in systolic blood pressure (SBP) and diastolic blood pressure (DBP) will be provided separately. These summaries will display the number and percentage of participants with any grade increase, increase to Grade 2 and increase to Grade 3 for worst-case post-baseline only. The grade definition for SBP (mmHg) is: Grade 0 (<120), Grade 1 (120-139), Grade 2 (140-159), Grade 3 (>=160). The grade definition for DBP (mmHg) is: Grade 0 (<80), Grade 1 (80-89), Grade 2 (90-99), Grade 3 (>=100). The summaries will be produced for worst-case post-baseline only.

The determination of the worst-case post-baseline vital signs will consider both planned and unscheduled assessments. Participants with missing baseline values are assumed to have a normal/Grade 0 baseline value. The percentages are based on the number of participants in the treatment group with baseline and post-baseline data.

4.6.3.5. Performance Status

The ECOG shift from baseline to highest post-baseline score (including all post-baseline scheduled and unscheduled visits through safety follow-up) will be summarized both overall and by treatment group.

4.6.3.6. COVID-19

Since the study has taken place during the COVID-19 pandemic, analyses will be performed to assess the impact of COVID-19 on the trial. Summary statistics will be provided with regard to participants who had suspected, probable, or confirmed COVID-19 assessment (case diagnosis), as well as whether they had the test performed and the exact results of that test. Incidence of COVID-19 as reported as an AE and SAE as well as incidence of treatment discontinuation due to AE of COVID-19 infection will also be summarized (as part of the AE, SAE and treatment discontinuation summaries).

4.6.3.7. Long-term Safety

To evaluate long-term safety, a subset analysis of AE incidence for study participants who have been randomized and treated for 6 months, 1 year, 2 years or 3 or more years will be performed. This subset analysis will be in the form of a summary using frequency and percentage.

4.6.4. Interim Analyses

No formal efficacy or futility interim analyses will be conducted. The Independent Data Monitoring Committee (IDMC) will make recommendations for discontinuation or modification of the study based on ongoing reviews of safety data according to the IDMC Charter.

4.7. Changes to the Protocol Defined Statistical Analysis Plan

The protocol defined the following objective "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" which will be changed such that total scores for the instruments will no longer be calculated and evaluated. Thus, the wording in Table 2 was changed such that "total and" was deleted.

4.8. Outputs to Regenerate at Final Database Lock

The following outputs are proposed to be regenerated at final Database Lock (DBL) date only for participants who are still in the study between the final analysis DCO date/ and date of final DBL, i.e., post-DCO period (PDP).

- Summary of Subject Disposition (All Screened Population– PDP)
- Summary of Demographic Characteristics (ITT Population - PDP)
- Summary of Baseline Characteristics (ITT Population - PDP)
- Summary of Advanced/Metastatic NSCLC Cancer History and Biomarker Status (Safety Population - PDP)
- Summary of Prior Anticancer Therapy (Safety Population - PDP)
- Summary of Induction Therapy (Safety Population - PDP)
- Summary of Treatment Duration (Safety Population - PDP)
- Summary of Treatment-Emergent Adverse Events (Safety Population - PDP)
- Summary of All Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Safety Population - PDP)
- Summary of All Treatment-Emergent Adverse Events by Overall Frequency (Safety Population – PDP)
- Summary of Common (>=5%) Treatment-Emergent Adverse Events in Either Treatment Arm by Overall Frequency (Safety Population – PDP)
- Summary of Common (>=5%) Non-Serious Treatment-Emergent Adverse Events in Either Treatment Arm by System Organ Class and Preferred Term (Number of Subjects and Occurrences) (Safety Population – PDP)
- Summary of Study Treatment-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Safety Population - PDP)
- Summary of Study Treatment-Related Non-Serious Treatment-Emergent Adverse Events by Overall Frequency (Safety Population – PDP)
- Summary of Grade >=3 Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Safety Population - PDP)
- Summary of Study Treatment-Related Grade >=3 Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Safety Population - PDP)

- Summary of Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences) (Safety Population - PDP)
- Summary of Study Treatment-Related Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Safety Population - PDP)
- Summary of Study Treatment-Related Serious Treatment-Emergent Adverse Events by Overall Frequency (Safety Population – PDP)
- Summary of Treatment-Emergent Adverse Events Resulting in Death by System Organ Class and Preferred Term (Safety Population - PDP)
- Summary of Study Treatment-Related Treatment-Emergent Adverse Events Resulting in Death by System Organ Class and Preferred Term (Safety Population - PDP)
- Summary of Treatment-Emergent Adverse Events Leading to Permanent Discontinuation of Niraparib/Placebo by System Organ Class and Preferred Term (Safety Population - PDP)
- Summary of Treatment-Emergent Adverse Events Leading to Permanent Discontinuation of Pembrolizumab by System Organ Class and Preferred Term (Safety Population - PDP)
- Summary of Treatment-Emergent Adverse Events of Special Interest by Group Category and Preferred Term (Safety Population - PDP)
- Summary of Deaths (Safety Population - PDP)
- Listing of Reasons for Study Withdrawal (PDP)
- Listing of Treatment – Niraparib/Placebo (PDP)
- Listing of Treatment – Pembrolizumab (PDP)
- Listing of All Adverse Events (PDP)

It is expected that less than 5% of PFS/OS events will occur between the final analysis DCO date and date of final DBL, efficacy outputs will not be re-generated.

5. SAMPLE SIZE DETERMINATION

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6. SUPPORTING DOCUMENTATION

6.1. Appendix 1: Abbreviations and Trademarks

6.1.1. List of Abbreviations

Abbreviation	Description
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AML	Acute Myeloid Leukemia
BICR	Blinded Independent Central Review
BMI	Body Mass Index
BoR	Best overall Response
CI	Confidence Interval
CNS	Central Nervous System
CNS-PFS	Progression Free Survival in Central Nervous System
CCI [redacted]	
COVID-19	Coronavirus Disease 2019
CSR	Clinical Study Report
CR	Complete Response
CTCAE	Common Term Criteria for Adverse Events
CCI [redacted]	
DBF	Database Freeze
DBL	Database Lock

Abbreviation	Description
DBP	Diastolic Blood Pressure
DBR	Database Release
DCO	Data Cut-off
DNA	Deoxyribonucleic Acid
CCI [redacted]	
eCRF	Electronic Case Record Form
e-DISH	Evaluation of Drug-Induced Serious Hepatotoxicity
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]	
CCI [redacted]	
FH	Fleming-Harrington
GSK	GlaxoSmithKline
HLGT	High Level Group Terms
HLT	High Level Terms
HMG-CoA	3-hydroxy-3-methyl-glutaryl-coenzyme A
HR	Hazard Ratio
CCI [redacted]	
HRQoL	Health-Related Quality of Life
IA	Interim Analysis
ICF	Informed Consent Form

Abbreviation	Description
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
irAE	Immune-related Adverse Events
IRT	Interactive Response Technology
ITT	Intent-to-Treat
IV	Intravenous
KM	Kaplan-Meier
MCID	Minimum Clinically Important Difference
MDS	Myelodysplastic Syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model Repeated Measures
NA	Not Applicable
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
NE	Not Evaluable
NSCLC	Non-Small Cell Lung Cancer
NSQ	Non-squamous
OPS	Output and Programming Specification
CCI [redacted]	
OS	Overall Survival
PBO	Placebo
PD	Progressive Disease
PD-L1	Programmed cell death-ligand 1
PFS	Progression Free Survival

Abbreviation	Description
CCI [redacted]	
CCI [redacted]	
PK	Pharmacokinetic
popPK	Population Pharmacokinetic
PR	Partial Response
PRES	Posterior Reversible Encephalopathy Syndrome
PRO	Patient-Reported outcome
CCI [redacted]	
PT	Preferred Term
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
REML	Restricted Maximum Likelihood
RMST	Restricted Mean Survival Time
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Stable disease
SDF	Survival Distribution Function
SERM	Safety Evaluation and Risk Management
SMQ	Standardized MedDRA Queries
SoA	Schedule of Activities

Abbreviation	Description
SOC	System Organ Class
SQ	Squamous
TC	Tumor Cell
TEAEs	Treatment-Emergent Adverse Events
TFSW	Time-to-First Symptom Worsening
CCI [redacted]	
TTD	Time to Deterioration
CCI [redacted]	
ULN	Upper Limit of Normal
VAS	Visual Analogue Scale

6.1.2. Trademarks

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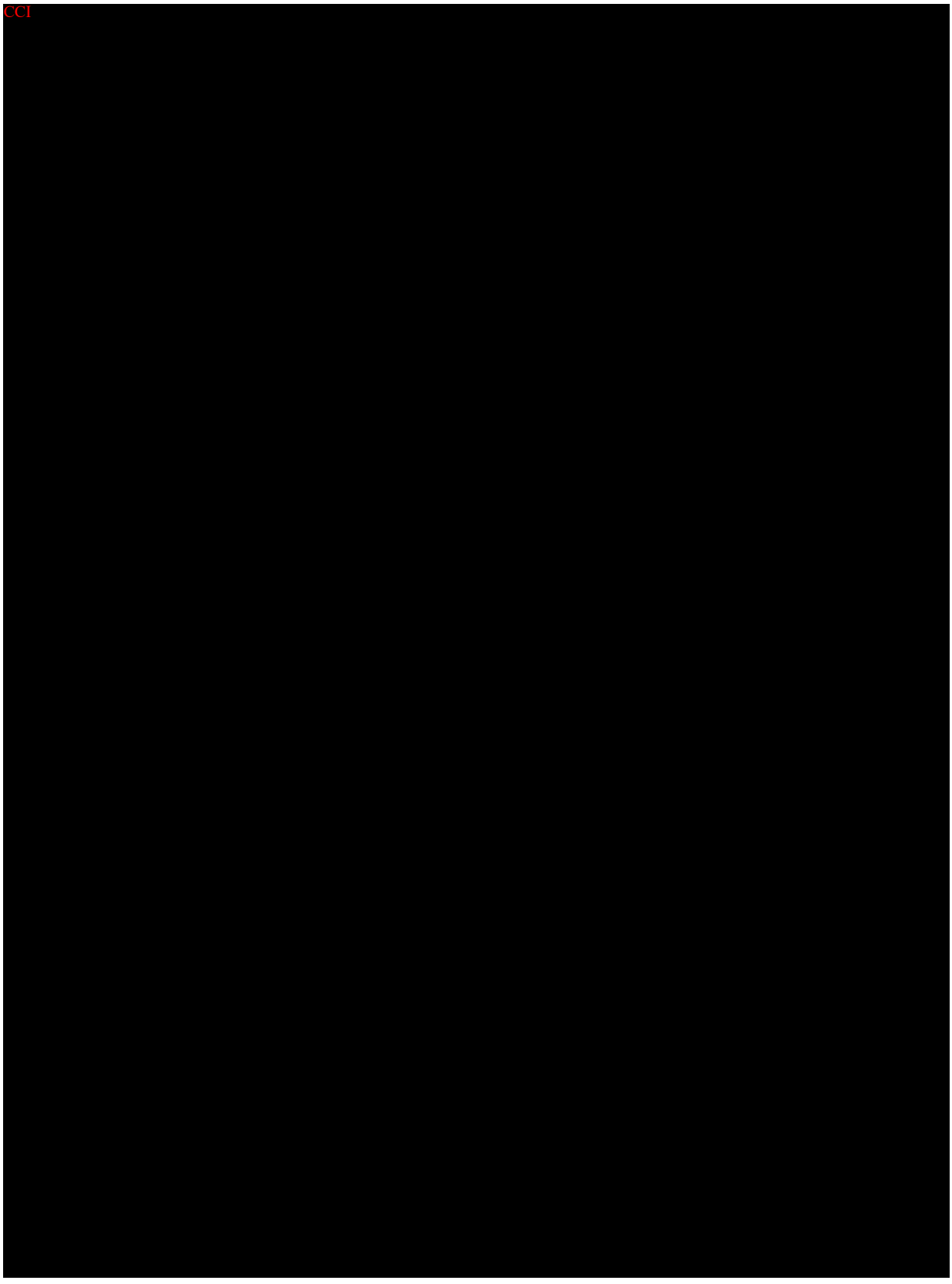

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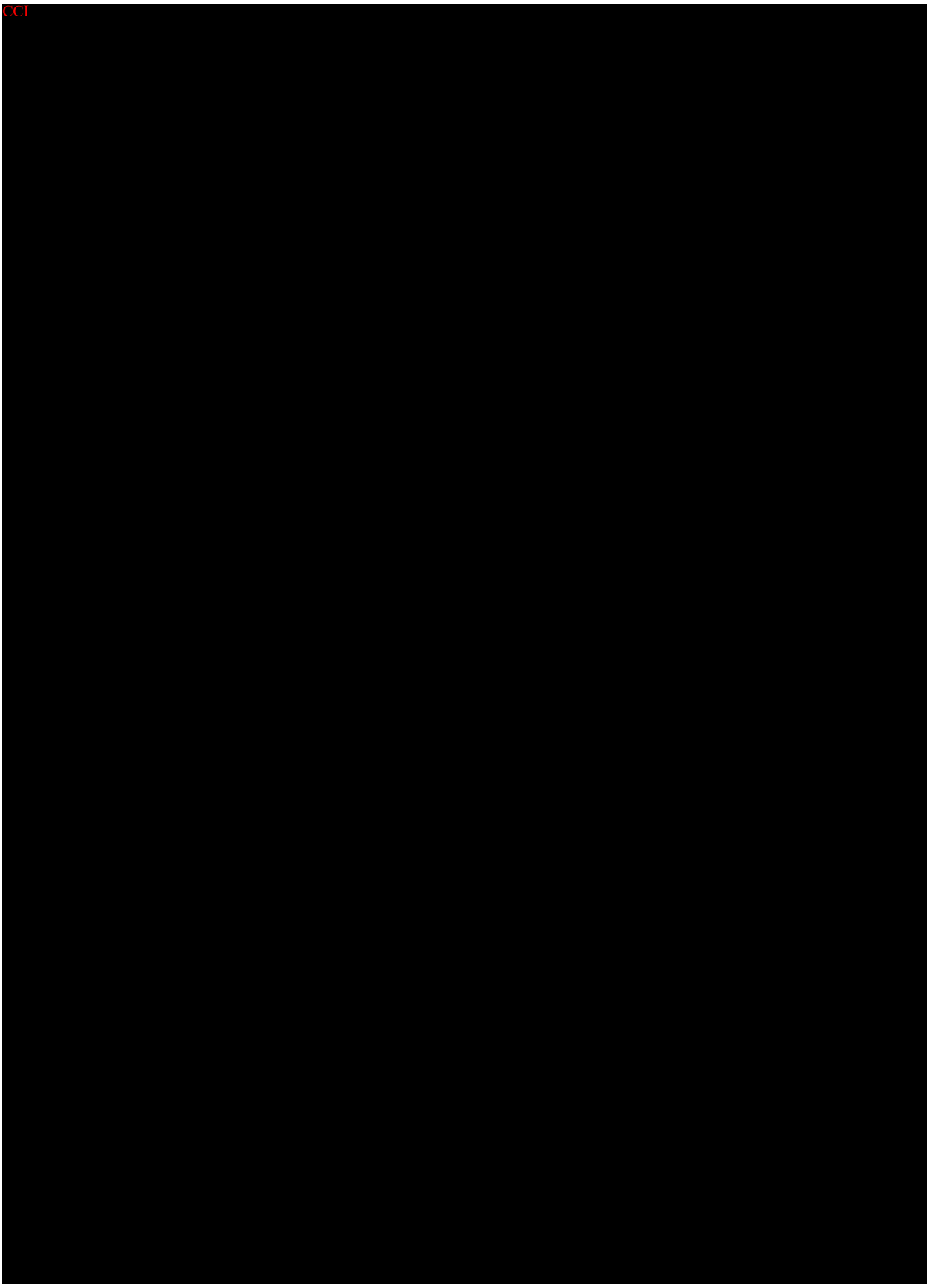

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6.4. Appendix 4: MedDRA Preferred Terms for AESIs, AEMIs and irAEs

The list of preferred terms corresponding to AESIs, AEMIs, and irAEs is provided in a separate document. This list will be provided by the GSK Safety Evaluation and Risk Management (SERM) group prior to DBR based on the most up-to-date MedDRA version.

6.5. Appendix 5: Population Pharmacokinetic (PopPK) Analysis

Niraparib plasma concentration-time data may be analyzed by popPK methods using a nonlinear mixed-effects modelling approach.

The key objective of this analysis is:

- Estimate niraparib individual PK parameters using the current popPK model developed for niraparib.

Niraparib plasma concentration-time data may be analyzed by popPK methods using a nonlinear mixed-effects modeling approach. Previously combined niraparib popPK data may be merged with the data from Study 213400 in order to provide a pooled NONMEM input dataset.

The analysis will use the then-current popPK model for niraparib to generate *post hoc* PK parameter estimates for the individual participants in Study 213400 using the updated dataset with the added Study 213400 data by employing an evaluation-only (MAXEVAL=0) run in NONMEM, if data permit. A study-specific residual error term may be used. Based on the individual *post hoc* parameter estimates, dosing information, and sample collection times, drug concentrations at the time of sample collection may be predicted for each participant.

Model evaluation will consist of comparison of model-predicted and observed concentrations. If a poor model fit is encountered with this method, the addition of covariates that are not yet included in the then-current popPK model, including study-specific effects, will be explored. If a poor model fit persists, more thorough covariate modelling and analysis may be pursued. Failing to obtain a good model fit after this line of inquiry, inter-individual random effects on the parameters may be re-evaluated after the inclusion of data from Study 213400.

The results of this analysis may be provided as an appendix to the CSR or in a separate report.

Details of the popPK methodology will be provided in a separate modeling and simulation analysis plan.

6.6. Appendix 6: Exposure-Response Analysis

If deemed appropriate and if data permit, exposure-response relationships between niraparib (e.g., concentration, Cmax, or AUC) and clinical activity and/or toxicity (e.g., PFS, AESIs) may be explored using population methods. If data permit, the effects of covariates may be explored.

The results of this analysis may be provided as an appendix to the clinical study report or in a separate report.

Details of the exposure-response analysis methodology will be provided in a separate modeling and simulation analysis plan.

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