Statistical Analysis Plan

Official Title of Study: Phase 2, Multi-Arm Study of Niraparib Administered Alone and in Combination with a PD-1 Inhibitor in Patients with Non-Small Cell Lung Cancer

Information Type: Reporting and Analysis Plan for PK

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Title:	Reporting and Analysis Plan for Phase 2, Multi-Arm Study of Niraparib Administered Alone and in Combination with a PD-1 Inhibitor in Patients with Non-Small Cell Lung Cancer

Compound Number: GSK3985771 (Niraparib), GSK4057190 (Dostarlimab)

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Description:

Subject: Oncology, Reporting and Analysis Plan

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Date

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Abbreviations

AUC(0-t)	Area under the plasma concentration-time curve from time 0 to the time of the last quantifiable concentration)
AUC(0-τ)	Area under the concentration-time curve over the dosing interval
AUCinf	Area under the concentration-time curve to infinity
CL, CL/F	Systemic, Apparent clearance
Cmax	Maximum observed concentration
Cmin	Minimum observed concentration
CPMS	Clinical Pharmacology Modeling and Simulation
CSR	Clinical Study Report
GCP	Good Clinical Practice
GSK	GlaxoSmithKline
h	Hour(s)
IB	Investigator's Brochure
ICH	International Council on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IV	Intravenous
kg	Kilogram(s)
L	Liter
μg	Microgram
mg	Milligram(s)
min	Minute(s)
mL	Milliliter(s)
PK	Pharmacokinetic(s)
Q3W	Every 3 weeks
Q6W	Every 6 weeks
RAP	Reporting and Analysis Plan
RP2D	Recommended Phase 2 dose
Vss, Vss/F	Volume distribution or apparent volume distribution at steady state

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1. INTRODUCTION

This reporting and analysis plan (RAP) details all planned analyses required for a Clinical Study Report of study 213352. This is an open-label, non-randomized, multi-center study designed to evaluate for the combination therapies including dostarlimab or niraparib or both in all histologies or squamous NSCLC.

For further information on the study design, see Protocol version 3.0 dated 31-May-2018.

The RAP was written by GSK CPMS. The execution of the RAP will be undertaken by staff of ICONplc.

All decisions regarding final analysis, as defined in this RAP document, have been made prior to Database Freeze of the study data.

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

Protocol Section	Change from Protocol	Rationale
N/A	N/A	N/A

2.2. Study Objective(s) and PK Related Endpoint(s)

Primary Objectives:

- To evaluate the efficacy of the combination of niraparib and a programmed cell death-1 (PD-1) inhibitor in chemotherapy-naïve and PD-1 inhibitor-naïve patients with locally advanced and metastatic non-small cell lung cancer (NSCLC) whose tumors have high programmed death ligand-1 (PD-L1) expression (Tumor Proportion Score [TPS] ≥ 50%), as assessed by objective response rate (ORR).
- To evaluate the efficacy of the combination of niraparib and a PD-1 inhibitor in chemotherapy-naïve and PD-1 inhibitor-naïve patients with locally advanced and metastatic NSCLC whose tumors express PD-L1 (TPS between 1 and 49%), as assessed by ORR.
- To evaluate the efficacy of single agent niraparib in patients with locally advanced and metastatic squamous NSCLC (sqNSCLC) who have been previously treated with both platinum-based chemotherapy and either PD-1 or PD-L1 inhibitor, as assessed by ORR.

Secondary Objectives

- To evaluate the safety and tolerability of single agent niraparib and of the combination of niraparib and a PD-1 inhibitor.
- To evaluate the following additional measures of clinical benefit of single agent niraparib and of the combination of niraparib and a PD-1 inhibitor:

  - Duration of response (DOR)
  - Disease control rate (DCR)
  - Progression-free survival (PFS)
  - Overall survival (OS)
- To evaluate the pharmacokinetics (PK) of niraparib following administration of single agent niraparib or the combination of niraparib and a PD-1 inhibitor.

Exploratory Objectives

- To explore blood and tumor-based biomarkers that predict sensitivity or resistance to single agent niraparib and to the combination of niraparib and a PD-1 inhibitor.

Pharmacokinetics (PK) Related Endpoint(s)

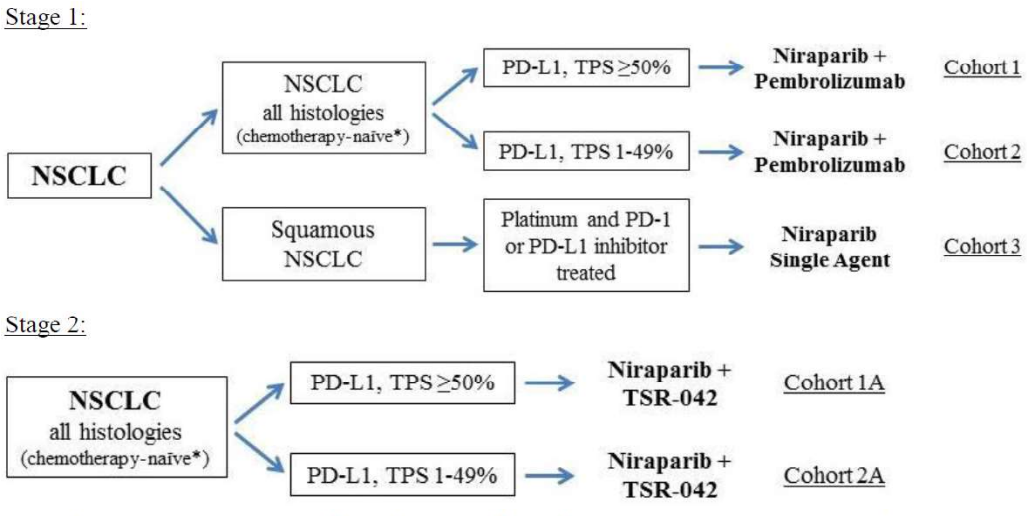
PK

Parameters of interest are AUC, minimum observed plasma or serum concentration (Cmin), maximum observed plasma or serum concentration (Cmax), time for maximum observed plasma or serum concentration (Tmax), clearance (CL), volume of distribution (Vss).

3. STUDY DESIGN

Study designs for Cohorts 1, 2 and 3 at Stage 1, and Cohorts 1A and 2A at stage 2 show in Figure 1.

Figure 1: Study Design



*Completion of treatment with chemotherapy and/or radiation as part of neoadjuvant/adjuvant therapy is allowed as long as therapy was completed at least 6 months prior to the diagnosis of metastatic disease

Abbreviations: NSCLC = non-small cell lung cancer; PD-1 = programmed cell death-1; PD-L1 = programmed death ligand-1; TPS = Tumor Proportion Score

4. SCHEDULE OF EVENTS

Schedules of events for PK can be found in Table 15 and 16 of the protocol as listed in the following.

Table 15: Pharmacokinetic Sampling: All Cohorts

Day 1 in Cycles 1, 2, 4, and 8 or 9[1]			
Time Point	**Cohort 1/1A**	**Cohort 2/2A**	**Cohort 3**
Pre-pembrolizumab dose (within 30 min)	X	X	
Post-pembrolizumab dose (30 min [- 5, + 20 min])[2]	X[3]	X[3]	
Pre-TSR-042 dose (within 30 min)	X	X	
Post-TSR-042 dose (30 min [- 5, + 20 min])[2]	X[3]	X[3]	
Pre-niraparib dose (within 30 min)	X[3, 4]	X[3, 4]	X
Post-niraparib dose (4 h ± 15 min)	X	X	X

Abbreviations: h = hours; min = minutes.
[1] Cycle 8 for niraparib and pembrolizumab (Cycle 9 for niraparib and TSR-042) or EOT if patient discontinues before Cycle 8 (Cycle 9 for niraparib and TSR-042)
[2] **From beginning of infusion**
[3] Post-pembrolizumab/TSR-042 dose and pre-niraparib dose can be the same blood draw.
[4] Niraparib will be administered upon completion of pembrolizumab or TSR-042 infusion (only Cohorts 1, 1A, 2, and 2A).

Table 16: Intensive Niraparib Pharmacokinetic Sampling: Subset of Patients in <u>All Cohorts</u>

	Cycle 1		Cycle 4	
Day of Procedure	**1**	**2**	**1**	**2**
Pre-niraparib dose[1]				
within 30 min	X		X	
Post-niraparib dose				
0.5 h (± 5 min)	X		X	
1 h (± 10 min)	X		X	
2 h (± 15 min)	X		X	
4 h (± 15 min)	X		X	
8 h (± 1h)	X		X	
24 h (± 3 h)		X		X

Abbreviations: h = hours; min = minutes; PD-1 = programmed cell death-1.
[1] Niraparib should be administered upon completion of PD-1 inhibitor infusion (applies only for Cohorts 1, 1A, 2, and 2A).

5. PLANNED ANALYSES

5.1. Independent Data Monitoring Committee (IDMC)

Reporting to the IDMC is to be handled by the study clinic and is outside the scope of this document.

5.2. Interim Analysis

There is no formal interim PK analysis planned for this study.

5.3. Final Analyses

All final, planned analyses identified in this RAP will be performed by ICONplc. following sponsor authorization of this RAP and unblinding of treatment (if prior to database lock unblinding of PK scientist(s) and programmer only).

6. ANALYSIS SETS

6.1. PK Analysis Set

The analysis set for the PK parameters will be the PK population. PK population are all patients who receive at least 1 dose of study treatment and have at least 1 PK sample.

7. GENERAL CONSIDERATIONS

PK parameters, statistics summary, and TFLs will follow GSK PK display standards (will be supplied in a separate document). All the required TFLs for PK are listed in the section 10 of this RAP.

7.1. Summary Statistics

For qualitative variables, the population size (N for sample size and n for available data) and the percentage (of available data) for each class of the variable will be presented. Serum concentrations and PK parameters will be summarized using descriptive statistics, including n, mean, standard deviation (SD), 95% CI (lower, upper), median, minimum, and maximum values. Additionally, geometric mean and geometric CV% will be included for Log transformed PK parameters, except for t_{max} and t_{min}. Only n, median, minimum, and maximum will be calculated for t_{max} and t_{min} (all other descriptive statistics will be reported as not determined [ND]).

Mean, median, minimum, and/or maximum concentrations that are below the limit of quantitation (BLQ) will be shown as NQ in the tables; if a mean concentration is BLQ, SD and CV% will be reported as NC. If n for a summary level is ≥3, all descriptive statistics will be presented; if n = 2, mean, minimum, and maximum will be presented and all other descriptive statistics will be reported as NC; if n = 1, the single available value will be presented for mean, minimum, and maximum, and all other descriptive statistics will be reported as NC.

7.2. Treatment Summarization

In general, data will be presented by Study Cohort and/or Stage for each analyte.

7.3. Precision

All PK concentrations will be reported and analyzed with the same precision as the source data provided by the bioanalytical laboratory regardless of how many significant figures or decimals the data carry. The PK concentrations will be reported with most applicable unit for each analyte, which need to be approved by the pharmacokineticist. Derived PK parameters will be rounded for reporting purposes in by-subject listings. The unrounded derived PK data will be considered the source data for the calculation of descriptive statistics and the statistical analysis. For most derived PK parameters, 3 significant digits will be used as the standard rounding procedure, with the following exceptions:

- Parameters directly derived from source data (e.g., C_{max}, C_{min}) will be reported and analyzed with the same precision as the source data.

- Parameters derived from actual elapsed sample collection times (e.g., t_{max}, t_{min}) will be reported with the same precision as the actual elapsed sampling time value. Actual elapsed time will be rounded to two decimal places in the source data.

For the reporting of descriptive statistics, the mean and median will be presented to one digit more precision while two more digits for standard deviation than the source data. The minimum and maximum will be presented to the same precision as the source data. Coefficient of variation will always be reported to 1 decimal place.

7.4. Reference Start Date and Study Day

Study Day will be calculated from the reference start date, and will be used to show start/stop day of assessments and events.

Reference start date is defined as the day of the first dose of study medication, (Day 1 is the day of the first dose of study medication), and will appear in every listing where an assessment date or event date appears.

- If the date of the event is on or after the reference date then: Study Day = (date of event – reference date) + 1.

- If the date of the event is prior to the reference date then: Study Day = (date of event – reference date).

In the situation where the event date is partial or missing, Study Day, and any corresponding durations will appear partial or missing in the listings.

7.5. Retest, Unscheduled Visits and Early Termination Data

Unscheduled measurements will not be included in summary statistics.

In the case of a retest of a scheduled assessment, the earliest available measurement for that scheduled time (i.e., the original assessment) will be used for summaries unless flagged as invalid.

Listings will include all scheduled, unscheduled, retest, and early discontinuation data.

7.6. Software Versions

All derivations, statistical analyses, summaries, and listings will be generated using SAS (SAS Institute, Inc., Cary, North Carolina). Noncompartmental PK parameter calculations will be performed using Phoenix® WinNonlin® (Certara L.P., Princeton, New Jersey). Graphics may be prepared using the same versions of SAS, or Phoenix WinNonlin. The versions of software will be noted in the report.

If the use of other software is warranted the final statistical report will detail what software was used.

8. PROTOCOL DEVIATIONS

8.1. Deviations Related to PK Analysis

Changes to the procedures or events, which may impact the quality of the PK data, will be considered significant protocol deviations and will be described within the clinical study report body text. These changes or events will include any circumstances that will alter the evaluation of the PK. Examples include, but may not be limited to, sample processing errors that lead to inaccurate bioanalytical results, inaccurate sampling times for predose samples, for example, after the corresponding doses, and/or inaccurate dosing on the day of PK sampling. In the case of a significant protocol deviation or event, PK data collected during the affected treatment period will be excluded from the study results. Other changes to the procedures or events which do not impact the quality of the PK data will not be considered significant protocol deviations. A common example of a non-significant protocol deviation is a missed blood sample or deviations from blood collection times.

9. PK ANALYSIS

PK analysis and drug concentration-time data will be conducted by non-compartmental methods under the direction of CPMS, Quantitative Sciences, GSK.

9.1. Plasma and Serum PK Concentrations

Mean or median concentrations will be calculated based on nominal sample times. For the calculation of mean concentration and/or time profiles, concentrations reported as being below the limit of quantitation (BLQ) defined as non-quantifiable (NQ) will follow the criteria defined in Non-compartmental Analysis (NCA) SOP GUI_51487 (5.0). For individual PK profiles:

- If one or more NQ values occur in a profile before the first measurable concentration, they will be assigned a value of zero concentration. Zero concentration value(s) before the first measurable concentration will be included in the linear plot and assigned a missing value in log-linear plot.
- If a single NQ value occurs between measurable concentrations in a profile, the NQ should generally be omitted (set to missing) in the derivation of pharmacokinetic parameters, statistical analysis, and the individual subject plots.
- If two or more NQ values occur in succession between measurable concentrations, the profile will be deemed to have terminated at the last measurable concentration prior to these NQs. For the purpose of individual subject plots, these NQs will be set to 0, and the subsequent measurable concentrations will be retained. For the derivation of pharmacokinetic parameters, these NQs and any subsequent measurable concentrations will be omitted (set to missing).
- NQs which occur after the last measurable concentration will be omitted (set to missing) in the derivation of pharmacokinetic parameters and from the individual subject plots.

For mean or median PK profiles:

- All NQ values will be set to zero except when an individual NQ falls between two quantifiable values, in which case it will be omitted from the calculation of mean or

median profiles. Measurable concentrations which follow more than one consecutive mid-profile NQ will be omitted (set to missing).

- The mean/median value at a time-point where one or more samples have NQ values will be reported (in tabular or graphical fashion) even if the mean or median value is below the LLQ of the assay. Zero concentration value(s) will be included in the linear plot and assigned a missing value in log-linear plot. Zero mean or median values will be included in summary tables.
- It should be noted that a high proportion of NQ values may affect the standard deviation (SD); if more than 30% of values are imputed, then SD will not be displayed. Any table of summary statistics for concentration-time data will report N (number of subjects in the analysis population), n (number of subjects with non-missing values) and number imputed (number of subjects with imputed values (i.e., NQ assigned zero concentration).

For Anomalous Concentration Values:

Individual concentrations deemed to be anomalous will be excluded from the pharmacokinetic analysis and median and mean profiles; such anomalous values will be identified (e.g., flagged by an asterisk or an appropriate footnote) in the data listings of the study report. Anomalous values are those that are inconsistent with known or expected pharmacokinetic behavior of the drug, and are not defined in a statistical outlier sense. Clear justification must be provided in the report for exclusion of any data.

9.2. PK Parameter Analysis

Where feasible, plasma and serum concentration-time data will be analyzed by NCA using the validated software program Phoenix WinNonlin (Phoenix WinNonlin Professional, Certara Inc., Mountain View, CA). The NCA parameters will not be reported to any greater accuracy than that of the observed concentration data. Default reporting in text and tables is 3 significant figures. All the analysis will follow the criteria listed in NCA SOP GUI_51487 (5.0). All calculations of non-compartmental parameters will be based on actual sampling times. The following PK parameters will be determined if data permit:

- Cmax, $C\tau$
- area under the plasma concentration-time curve including AUClast, AUCinf and AUC(0-τ)
- clearance (CL) or apparent CL (CL/F)
- steady-state volume of distribution (Vss) or apparent Vss (Vss/F)

All derived PK parameters will be listed. For each of these parameters the following summary statistics will be calculated for each dose level: median, minimum, maximum, arithmetic mean, 95% confidence interval for the arithmetic mean, standard deviation, coefficient of variation (CV = = $\sqrt{}$ (exp(SD2) - 1) * 100 [NOTE: SD = SD of log transformed data]), geometric mean, 95% confidence interval for the geometric mean and standard deviation of logarithmically transformed data. The first point, last point and number of points used in the determination of λz will be included on the listing of the derived parameters. All PK parameters will be reported to at least 3 significant digits, but to no more significant digits than the precision of the original data.

10. TABLE, FIGURE AND LISTING FOR THE STUDY

The scope of work is the following:

- Stage 1 Cohorts 1, 2 and 3: NCA analysis for niraparib (200 mg) at Cycle 1 and 4; The standard TFLs listed in Table 1;
- Stage 2 Cohorts 1A and 2A: NCA analysis for niraparib (200 mg) at Cycle 1 and 4; The standard TFLs listed in Table 1 are applied to both dostarlimab and niraparib, if applicable;

Table 1. Standard TFLs for PK Summary (from PK Statistical Display Standards)

Tables:

Example	Title	Macro
PK01	Summary of [Analyte] [Matrix] Pharmacokinetic Concentration-Time Data (units) {by Cohort and Stage}	pkct1
PK03	Summary of Derived [Analyte] [Matrix] Pharmacokinetic Parameters {by Cohort and Stage}	pkpt1
PK05	Summary of Derived [Analyte] [Matrix] Pharmacokinetic Parameters (log-transformed) {by Cohort and Stage}	pkpt3

Listings:

Display	Title	Macro
PK07	Listing of [Analyte] [Matrix] Pharmacokinetic Concentration-Time Data {by Cohort} (parallel)	pkcl1p
PK13	Listing of Derived [Analyte] [Matrix] [Primary/Secondary] Pharmacokinetic Parameters {by Cohort and Stage} (parallel)	pkpl1p

Figures:

Example	Title	Macro
PK19	Mean (+ SD) [Analyte] [Matrix] Concentration-Time Plots (Linear and Semi-log) {by Cohort and Stage}	pkcf4
PK20	Median (range) [Analyte] [Matrix] Concentration-Time Plots (Linear and Semi-log) {by Cohort and Stage}	pkcf5
PK24	Individual [Analyte] [Matrix] Concentration-Time Plots by Treatment {and/or Cohort}	pkcf6

11. REFERENCES

[1] Combined Statistical Displays Principles v1.docx (found on the IDSL library, under Supporting Documentation > Component > Statistical Displays>Compiled Statistical Display Principles)

[2] Non-Compartmental Analysis of Pharmacokinetic Data, CPMS Global (GUI_51487)

[3] Pharmacokinetic (PK) Concentration Analysis and Reporting Process Guidance

[4] Standards for the Handling of NQ Impacted PK Parameters

[5] PK Display Standards

Statistical Analysis Plan

Official Title of Study: Phase 2, Multi-Arm Study of Niraparib Administered Alone and in Combination with a PD-1 Inhibitor in Patients with Non-Small Cell Lung Cancer

NCT ID: NCT03308942

Other Identifiers: 213352, 3000-02-001

Date of Document: 02Jun2020

STATISTICAL ANALYSIS PLAN: Study 3000-02-001

Protocol Title:	Phase 2, Multi-Arm Study of Niraparib Administered Alone and in Combination with a PD1 inhibitor in Patients with Non-Small Cell Lung Cancer
Protocol Number:	3000-02-001
Protocol Version and Date:	Version 3.0, 31 May 31 2018 (amendment 2) Version 2.0, 05 September 2017 (Amendment 1) Version 1.0, 17 May 2017 (Original)
Study Phase:	Phase 2
Product Name:	Niraparib, Pembrolizumab, and TSR-042
Sponsor:	TESARO, Inc.
Analysis Plan Version and Date:	Version 0.8, 27 August 2019

SPONSOR SIGNATURES

Protocol Title: Phase 2, Multi-Arm Study of Niraparib Administered Alone and in Combination with a PD1 inhibitor in Patients with Non-Small Cell Lung Cancer

Protocol Number: 3000-02-001

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

Author

PPD, PhD
Director of Biostatistics
LLX Solutions, LLC

Signature: PPD
Date: 05/31/2020

Approver:

PPD, PhD
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Senior Medical Director,
Clinical Research, TESARO, Inc.

Signature: PPD
Date:

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TABLES

LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
AESI	adverse event of special interest
ALK	anaplastic lymphoma kinase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
BMI	body mass index
BOR	best overall response
CI	confidence interval
CBC	complete blood count
CR	complete response
CT	computed tomography
CTCAE	common terminology criteria for adverse events
ECOG	Easter Cooperative Oncology Group
eCRF	electronic case report form
EGFR	epidermal growth factor receptor
EOS	end of study
EOT	end of treatment
FDA	US Food and Drug Administration
LLN	lower limit of normal
MedDRA	medical dictionary for regulatory activities
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PD	progressive disease
PD-1	programmed cell death-1
PD-L1	programmed death-ligand 1
PFS	progression-free survival
PK	pharmacokinetics
PO	oral(ly)

Abbreviation	Definition
PR	partial response
PT	preferred term
Q1	first quartile
Q3	third quartile
QD	once daily
RECIST	response evaluation criteria in solid tumors
RRs	standard of care response rate
RRt	target response rate
SAE	serious adverse event
SAP	statistical analysis plan
SOC	system organ class
SD	stable disease or standard deviation
sqNSCLC	squamous non-small cell lung cancer
TEAE	treatment-emergent adverse event
TPS	tumor proportion score
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
WHO	World Health Organization

1 INTRODUCTION

This statistical analysis plan (SAP) provide the detailed statistical methods to be used for analyses and data presentation for reporting efficacy, safety, non-compartmental Pharmacokinetics of investigational drug niraparib for TESARO study protocol 3000-02-01.

The pharmacokinetics and exposure-response analyses will be provided in a separate document. The exploration of blood and tumor-based biomarkers that predict sensitivity or resistance to niraparib will also be detailed in a separate document. This document has been prepared according to Study Protocol Amendment 2 dated 31 May 2018.

2 STUDY DESIGN OVERVIEW

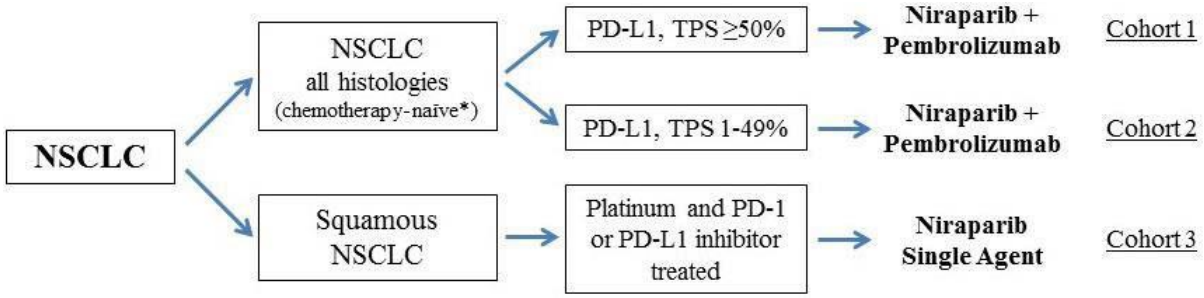
2.1 Overall Study Design

This is a multicenter, open-label, multi-arm Phase 2 study to evaluate the efficacy and safety of single agent niraparib in patients with locally advanced and metastatic squamous non-small cell lung cancer (sqNSCLC) and of the combination of niraparib and a PD-1 inhibitor in locally advanced and metastatic non-small cell lung cancer (NSCLC) all histologies patients.

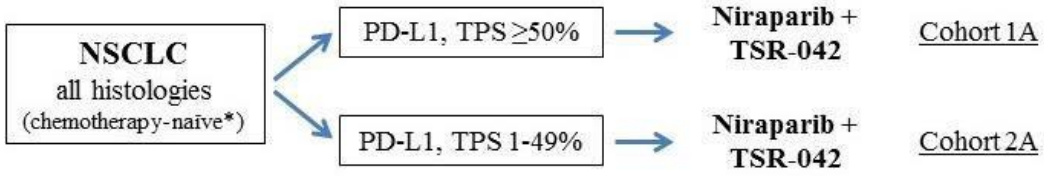
The study has 2 stages, each of which will evaluate separate cohorts of different cancer patients with a sample size that is deemed statistically significant to determine whether further examination may be warranted in the individual indications. In Stage 1, Cohorts 1 and 2 will receive niraparib plus the PD-1 inhibitor pembrolizumab, and Cohort 3 will receive niraparib alone. In Stage 2, Cohorts 1A and 2A will receive niraparib plus the PD-1 inhibitor TSR-042. The study design is presented graphically in Figure 1.

Figure 1 Study Design

Stage 1:



Stage 2:



*Completion of treatment with chemotherapy and/or radiation as part of neoadjuvant/adjuvant therapy is allowed as long as therapy was completed at least 6 months prior to the diagnosis of metastatic disease

Abbreviations: NSCLC = non-small cell lung cancer; PD-1 = programmed cell death-1;
PD-L1 = programmed death ligand-1; TPS = Tumor Proportion Score

Cohorts 1 and 1A: Locally advanced and metastatic NSCLC patients (all histologies) with no prior systemic chemotherapy or PD-1/PD-L1 inhibitor treatment, whose tumors have high PD-L1 expression (TPS ⩾ 50%), and no known epidermal growth factor receptor (EGFR) sensitizing mutation and/or ROS-1 or anaplastic lymphoma kinase (ALK) translocations will receive combination of niraparib and a PD-1 inhibitor (pembrolizumab or TSR-042). *Completion of treatment with chemotherapy and/or radiation as part of neoadjuvant/adjuvant therapy is allowed as long as therapy was completed at least 6 months prior to the diagnosis of metastatic disease.*

Cohorts 2 and 2A: Locally advanced and metastatic NSCLC patients (all histologies) with no prior systemic chemotherapy or PD-1/PD-L1 inhibitor treatment, whose tumors have PD-L1 expression (TPS between 1% and 49%) and no known EGFR sensitizing mutation and/or ROS-1 or ALK translocations, will receive combination of niraparib and a PD-1 inhibitor (pembrolizumab or TSR-042). *Completion of treatment with chemotherapy and/or radiation as part of neoadjuvant/adjuvant therapy is allowed as long as therapy was completed at least 6 months prior to the diagnosis of metastatic disease.*

Cohort 3: Locally advanced and metastatic sqNSCLC patients who have been previously treated with both platinum and either PD-1 or PD-L1 inhibitor will receive single agent niraparib.

This study will consist of a Screening Period (Day -21 to Day -1), a Treatment Period, an End of Treatment (EOT) Period occurring within 7 days of the decision to discontinue treatment for any reason, a Safety Follow-up Visit occurring 30 + 7 days after the last dose of study drug, and a Follow-up Assessment occurring every 90 ± 14 days, which will continue until death or the end of study data collection (a minimum of 6 months after the enrollment of the last patient, provided that this allows the opportunity for completion of all 90-day follow-up assessments).

The schedules of assessments for cohorts are presented in Table 1 and Table 2.

Table 1: Schedule of Events for Cohort 1, 1A, 2, 2A

Cycle/Visit	**Screening**	**Cycle 1**			**Subsequent Cycles**	**EOT**	**Safety Follow-Up**	**Follow-Up Assessment**
Day of Procedure	**-21 to -1**	**1**	**8**	**15**	**Cycle n, Day 1**		**30 + 7 days post-treatment**	**(every 90 ± 14 days)**
Informed consent	X							
Inclusion/exclusion criteria review	X	X						
Demographics	X							
Medical, surgical, cancer, smoking, and medication history	X							
Archival FFPE tumor tissue	X[1]							
Blood sample for ctDNA	X				X[2]	X		
Blood sample for CTC		X						
Blood sample for PK		X[3, 4]			X[3, 4]			
Tumor assessment	X[5]	First on-study imaging assessment should be performed 9 weeks (63 ± 7 days) after first dose. Subsequent tumor imaging will be performed every 9 weeks (63 ± 7 days) until Week 72 and every 12 weeks (84 ± 7 days) thereafter[6]				If patient discontinues treatment for a reason other than progression, death, withdrawal of consent, or loss to follow-up, imaging should continue every 9 weeks (63 ± 7 days) until Week 72 and every 12 weeks (84 ± 7 days) thereafter[6]		
Clinical laboratory assessments								
CBC	X	X[7]	X	X	X	X	X	X[8]

Cycle/Visit	**Screening**	**Cycle 1**			**Subsequent Cycles**	**EOT**	**Safety Follow-Up**	**Follow-Up Assessment**
Day of Procedure	**-21 to -1**	**1**	**8**	**15**	**Cycle n, Day 1**		**30 + 7 days post-treatment**	**(every 90 ± 14 days)**
Serum chemistry	X	X[7]		X	X	X	X	X[8]
Pregnancy test[9]	X							
Urinalysis	X							
TSH, T3 or FT3, and FT4	X[10]				X[10]	X[10]	X[10]	
ECG	X					X		
Physical examination	X					X		
Symptom-directed physical examination		X		X	X		X	
Vital signs and weight	X	X			X	X	X	
Height	X							
ECOG performance status	X	X			X	X		
Concomitant medications/procedures[11]		Recorded from first dose of study drug through Safety Follow-up						
AE monitoring[12]	X	X	X	X	X	X	X[13]	X[13]
Pembrolizumab treatment administered[14] (Stage 1 only)		X			X			
TSR-042 treatment administered (Stage 2 only)		X			X[15]			
Niraparib treatment dispensed/collected		X			X	X		
Survival/AESI (regardless of causality) and study-drug related SAEs								

Cycle/Visit	Screening	Cycle 1			Subsequent Cycles	EOT	Safety Follow-Up	Follow-Up Assessment
Day of Procedure	**-21 to -1**	**1**	**8**	**15**	**Cycle n, Day 1**		**30 + 7 days post-treatment**	**(every 90 ± 14 days)**
(Telephone assessment allowed)								X[16]

Abbreviations: AE = adverse event; AESI = Adverse Event of Special Interest, CBC = complete blood count; CTC = circulating tumor cell; ctDNA = circulating tumor DNA; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; FFPE = formalin fixed paraffin embedded; FT3 = free triiodothyronine; FT4 = free thyroxine; ICF = informed consent form; PK = pharmacokinetics; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; T3 = triiodothyronine; TSH = thyroid-stimulating hormone.

[1] An archival FFPE tumor tissue specimen, which may have been collected at any time prior to Screening, should be submitted for exploratory biomarker analysis within 30 days of the patient's first dose. If no archival FFPE tumor tissue is available, a tumor tissue biopsy should be obtained before Cycle 1/Day 1.

[2] Required for Cycle 2/Day 1 only.

[3] Blood sample for niraparib and pembrolizumab PK will be collected on Cycle 1/Day 1, Cycle 2/Day 1, Cycle 4/Day1, and Cycle 8/ Day 1 (or EOT if patient discontinues before Cycle 8) in all patients in Cohorts 1 and 2. Blood samples for PK assessment of niraparib will be collected in Cycle 1/Day 1, Cycle 2/Day 1, Cycle 4/Day 1, and Cycle 9/Day 1 (or EOT if patient discontinues before Cycle 9) in all patients in Cohorts 1A and 2A. Blood sample for TSR-042 will be collected on Cycle 1/Day 1, Cycle 2/Day 1, Cycle 4/Day1, and Cycle 9/ Day 1 (or EOT if patient discontinues before Cycle 9). See Table 15 of protocol for detailed schedule.

[4] Intensive niraparib PK sampling will be collected only for a subset of patients (N = 8/cohort) in Cycle 1 and Cycle 4. See Section 8.3 and Table 16 of protocol for detailed schedule. Patients in this subset will be instructed to hold their niraparib dose, which will be taken in clinic on specified days for PK sampling.

[5] Scans performed prior to the signing of the ICF as part of routine clinical management are acceptable for use as initial tumor imaging if they are of diagnostic quality and are performed within 28 days prior to first dose date

[6] For details on tumor assessment per RECIST v1.1 see Section 7.3.1, Section 8.2, and Appendix C of protocol. All radiographic images/scans at the specified time points as well as any unscheduled images/scans should be archived by the study sites for potential future evaluation.

[7] If screening assessments were performed within 72 hours of Day 1, repeat testing is not required.

[8] CBC and serum chemistry at the Follow-up Assessment should be conducted only on Day 90 post-treatment to assess for possible AESI (Section 7.1.6 of protocol).

[9] Serum pregnancy test for women of childbearing potential within 72 hours of first dose of study treatment. If the serum pregnancy result is not available before dosing, a urine pregnancy test may be performed.

[10] Blood samples for TSH, T3 or FT3, and FT4 are to be collected at screening, every 6 weeks from Cycle 1/Day 1, and at EOT. Blood samples for TSH, T3 or FT3, and FT4 should be collected at 30-day post-treatment Safety Follow-up only if assessment is clinically indicated.

[11] Any new anticancer treatment started during the study should also be collected.

Cycle/Visit	Screening	Cycle 1			Subsequent Cycles	EOT	Safety Follow-Up	Follow-Up Assessment
Day of Procedure	**-21 to -1**	**1**	**8**	**15**	**Cycle n, Day 1**		**30 + 7 days post-treatment**	**(every 90 ± 14 days)**

[12]Collection of AEs begins when the ICF is signed.

[13]AEs are required to be captured through 30 days after cessation of study treatment (Section 7.1.3 of protocol). However, SAEs are required to be captured through 90 days after cessation of study treatment (or to a minimum of 30 days post-treatment if the patient starts alternate anticancer therapy) (Section 7.1.5 of protocol), and any pregnancies that occur within 180 days post-treatment are to be captured. AESIs should be collected until study closeout, regardless of causality (Section 7.1.6 of protocol).

[14]Pembrolizumab should be administered once every 21 days (200 mg intravenous) on Day 1 of each cycle. Pembrolizumab may be administered up to 3 days before or after the scheduled Day 1 of each cycle after Cycle 1 due to administrative reasons. On days where pembrolizumab is administered, it should be administered before niraparib.

[15]TSR-042 will be administered at a dose of 500 mg on Day 1 every 3 weeks in Cycles 1 through 4, followed by 1,000 mg every other cycle (every 6 weeks) thereafter, beginning on Cycle 5 Day 1. On days where TSR-042 is administered, it should be administered before niraparib.

[16]Patients will be followed until study closeout for survival status, AESI (regardless of causality), and study-drug related SAEs (Section 7.1.6 of protocol).

Table 2: Schedule of Events for Cohort 3

Cycle/Visit:	**Screening**	**Cycle 1**			**Subsequent Cycles**	**EOT**	**Safety Follow-Up**	**Follow-Up Assessment**
Day of Procedure	**-21 to -1**	**1**	**8**	**15**	**Cycle n, Day 1**		**30 + 7 days post-treatment**	**(every 90 ± 14 days)**
Informed consent	X							
Inclusion/exclusion criteria review	X	X						
Demographics	X							
Medical, surgical, cancer, smoking, and medication history	X							
Archival tumor tissue	X[1]							
Blood sample for ctDNA	X				X[2]	X		
Blood sample for CTC		X						
Blood sample for PK		X[3, 4]			X[3, 4]			
Tumor assessment	X[5]	First on-study imaging assessment should be performed 6 weeks (42 ± 7 days) after first dose. Subsequent tumor imaging will be performed every 6 weeks (42 ± 7 days) until Week 24 (6 months). After Week 24, tumor imaging will be performed every 9 weeks (63 ± 7 days) until Week 52 (12 months) and every 12 weeks (84 ± 7 days) thereafter[6]				If patient discontinues treatment for a reason other than progression, death, withdrawal of consent, or loss to follow-up, imaging should continue every 6 weeks (42 ± 7 days) until Week 24 (6 months), then every 9 weeks (63 ± 7 days) until Week 52 (12 months) and every 12 weeks (84 ± 7 days) thereafter[6]		
Clinical laboratory assessments								
CBC	X	X[7]	X	X	X	X	X	X[8]
Serum chemistry	X	X[7]		X	X	X	X	X[8]
Pregnancy test[9]	X							
Urinalysis	X							
ECG	X					X		
Physical examination	X					X		

Cycle/Visit:	**Screening**	**Cycle 1**			**Subsequent Cycles**	**EOT**	**Safety Follow-Up**	**Follow-Up Assessment**
Day of Procedure	**-21 to -1**	**1**	**8**	**15**	**Cycle n, Day 1**		**30 + 7 days post-treatment**	**(every 90 ± 14 days)**
Symptom-directed physical examination		X		X	X		X	
Vital signs and weight	X	X			X	X	X	
Height	X							
ECOG performance status	X	X			X	X		
Concomitant medications/procedure[10]		Recorded from first dose of study drug through Safety Follow-up						
AE monitoring[11]	X	X	X	X	X	X	X[12]	X[12]
Niraparib treatment dispensed/collected		X			X	X		
Survival/AESI (regardless of causality) and study-drug related SAEs (telephone assessment allowed)								X[13]

Abbreviations: AE = adverse event; AESI = Adverse Event of Special Interest; CBC = complete blood count; CTC = circulating tumor cell; DNA = deoxyribonucleic acid; ctDNA = circulating tumor DNA; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; FFPE = formalin fixed paraffin embedded; ICF = informed consent form; PK = pharmacokinetics; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event

[1] An archival FFPE tumor tissue specimen, which may have been collected at any time prior to Screening, should be submitted for exploratory biomarker analysis within 30 days of the patient's first dose. If diagnosis was made by cytology and archival FFPE tissue is not available, patient will not need to provide tumor tissue.

[2] Required for Cycle 2/Day 1 only.

[3] Blood sample for niraparib PK will be collected on Cycle 1/Day 1, Cycle 2/Day 1, Cycle 4/Day 1, and Cycle 8/Day 1 (or EOT if patient discontinues before Cycle 8). See Table 15 of protocol for detailed schedule.

[4] Intensive niraparib PK sampling will be collected only for a subset of patients (N = 8/cohort) on Cycle 1 and Cycle 4. See Section 8.3 and Table 16 of protocol for detailed schedule. Patients in this subset will be instructed to hold their niraparib dose, which will be taken in clinic on specified days for PK sampling.

[5] Scans performed prior to the signing of the ICF as part of routine clinical management are acceptable for use as initial tumor imaging if they are of diagnostic quality and are performed within 28 days prior to first dose date.

[6] For details on tumor assessment per RECIST v1.1 see Section 7.3.1, Section 8.2 and Appendix C of protocol. All radiographic images/scans at the specified time point as well as any unscheduled images/scans should be archived by the study sites for potential future evaluation.

[7] If screening assessments were performed within 72 hours of Day 1, repeat testing is not required.

Cycle/Visit:	**Screening**	**Cycle 1**			**Subsequent Cycles**	**EOT**	**Safety Follow-Up**	**Follow-Up Assessment**
Day of Procedure	**-21 to -1**	**1**	**8**	**15**	**Cycle n, Day 1**		**30 + 7 days post-treatment**	**(every 90 ± 14 days)**

[8] CBC and serum chemistry at the Follow-up Assessment should be conducted only on Day 90 post-treatment to assess for possible AESI (Section 7.1.6 of protocol)

[9] Serum pregnancy test for women of childbearing potential within 72 hours of first dose of study treatment. If the serum pregnancy result is not available before dosing, a urine pregnancy test may be performed.

[10] Any new anticancer treatment started during the study should also be collected.

[11] Collection of AEs begins when the ICF is signed.

[12] AEs are required to be captured through 30 days after cessation of study treatment (Section 7.1.3 of protocol). However, SAEs are required to be captured through 90 days after cessation of study treatment (or to a minimum of 30 days post-treatment if the patient starts alternate anticancer therapy) (Section 7.1.5 of protocol), and any pregnancies that occur within 180 days post-treatment are to be captured. AESIs should be collected until study closeout, regardless of causality (Section 7.1.6 of protocol).

[13] Patients will be followed until study closeout for survival status, AESI (regardless of causality), and study-drug related SAEs (Section 7.1.6 of protocol).

2.2 Sample Size

The null hypothesis for this study is H0: ORR ≤ Standard of Care Response Rate (RRs) vs. the alternative hypothesis: ORR ≥ Target Response Rate (RRt) for all cohorts. RRs and RRt for each cohort are specified in Table 3 below.

As different study drugs will be used in Stage 1 and Stage 2, the sample size for each stage was calculated separately for Cohort 1 and Cohort 2. Sample size calculation was based on the primary efficacy endpoint ORR for each cohort assuming a 1-sided alpha level of 0.10 and 80% power.

For Cohorts 1, 2, and 3, the number of patients in Stage 1 was determined based on Simon's 2-stage design. The sample size for Stage 2 (Cohorts 1A and 2A) was calculated based on a 1-stage design. Once enrollment for Stage 1 is completed, Stage 2 enrollment will start. Stage 1 data will be used to determine if further enrollment for Stage 2 is warranted. (Following a cross-program review and decision to move forward with other studies, the Sponsor has decided that Cohort 3 will close to any further enrollment as of Protocol Amendment 2.) The total sample size for this study will range from 59 to 142.

The criteria for rejecting the alternative hypothesis and declaring the experiment treatment as not efficacious at the end of Stage 1 and Stage 2 are listed in Table 4 below. For each cohort, if the number of responders by the end of Stage 1 is the same or less as defined by the criterion, the cohort will be terminated. For a cohort that proceeds to Stage 2, if the total number of responders by the end of Stage 2 is the same or less than the criterion, the alternative hypothesis will be rejected and the experimental treatment will be considered not efficacious for the indication in the cohort, unless the clinical judgment suggests otherwise.

Table 3: Sample Size by Cohort

Cohort No.	Cohort Description	Target RR	SoC RR	Sample Size		
				1st Stage	2nd Stage	Total
1/1A	NSCLC (chemotherapy-naïve, PD-L1 TPS ≥ 50%)	65%	45%	16	36	52
2/2A	NSCLC (chemotherapy-naïve, PD-L1 TPS 1-49%)	50%	33.5%	20	47	67
3	SqNSCLC: Platinum and PD-1/PD-L1- treated	20%	9%	23	0	23

Abbreviations: NSCLC = non-small cell lung cancer; PD-1 = programmed cell death-1; PD-L1 = programmed death ligand-1; RR = response rate; SoC = standard of care; SqNSCLC = squamous non-small cell lung cancer; TPS = tumor proportion score.

Table 4: Criteria for Considering Treatment Efficacious by Cohort and Stage

Cohort No.	Cohort Description	Stage 1 Criteria*	Stage 2 Criteria*
1/1A	NSCLC (chemotherapy-naïve, PD-L1 TPS ≥ 50%)	8	20‡
2/2A	NSCLC (chemotherapy-naïve, PD-L1 TPS 1-49%)	7	20‡
3	SqNSCLC: Platinum and PD-1 or PD-L1-treated	2	NA

Abbreviations: NA = not applicable; NSCLC = non-small cell lung cancer; PD-1 = programmed cell death-1; PD-L1 = programmed death ligand-1; SqNSCLC = squamous non-small cell lung cancer; TPS = tumor proportion score. * Number of patients with responses (CR/PR) ‡ Not including stage 1 responders.

2.3 Randomization and Blinding

This is an open-label study and patients will not be randomized.

3 STUDY OBJECTIVES

3.1 Primary Objectives

The primary objectives of this study are:

- To evaluate the efficacy of the combination of niraparib and a PD-1 inhibitor in chemotherapy-naïve and PD-1 inhibitor-naïve patients with locally advanced and metastatic NSCLC whose tumors have high PD-L1 expression (TPS ≥ 50%), as assessed by objective response rate (ORR)
- To evaluate the efficacy of the combination of niraparib and a PD-1 inhibitor in chemotherapy-naïve and PD-1inhibitor-naïve patients with locally advanced and metastatic NSCLC whose tumors express PD-L1 (TPS between 1 and 49%) as assessed by ORR
- To evaluate the efficacy of single agent niraparib in patients with metastatic sqNSCLC who have been previously treated with both platinum-based chemotherapy and either PD-1 or PD-L1 inhibitor, as assessed by ORR

3.2 Secondary Objectives

The secondary objectives of the study are as follows:

- To evaluate the safety and tolerability of single agent niraparib and of the combination of niraparib and a PD-1 inhibitor

- To evaluate the following additional measures of clinical benefit of single agent niraparib and of the combination of niraparib and a PD-1 inhibitor:
    - Disease control rate (DCR)
    - Duration of response (DOR)
    - Progression-Free Survival (PFS)
    - Overall Survival (OS)

4 STUDY ENDPOINTS AND EVALUATIONS

4.1 Efficacy Endpoints

4.1.1 Primary Efficacy Endpoint

The primary efficacy endpoint is objective response rate (ORR), defined as the proportion of patients with a confirmed best overall response (BOR) of complete response (CR) or partial response (PR) in the analysis population (See Section 6). Tumor assessments after the initiation of further anticancer therapy are excluded for the assessment of BOR.

Response to treatment will be determined based on investigator evaluation of radiographic images according to RECIST v1.1. If CR or PR is observed, tumor imaging for confirmation of response needs to be performed at the earliest 28 days after the first indication of response, but no later than 35 days after the response.

Confirmed BOR will be determined based on the RECIST v1.1. For a confirmed response, the tumor assessment date for the first recorded CR or PR will be considered as the date CR/PR achieved.

All final efficacy analyses for response rate will be based on the confirmed response. Confirmation of response is not required for the purpose of determining if the study should continue enrolling stage 2 patients.

4.1.2 Secondary Efficacy Endpoints

4.1.2.1 Disease Control Rate

Disease control rate (DCR) is defined as the proportion of patients with a best overall response of CR, PR or SD.

4.1.2.2 Duration of Response

Duration of Response (DOR) is defined as the time from first documented CR or PR until the subsequently documented disease progression or death, whichever occurs earlier.

DOR will be calculated as shown below for responders only using the censoring rules specified in Table 5.

$$DOR\ (months) = \frac{\text{Date of PD/Death/Censoring} - \text{ Date of First recorded CR or PR } + 1}{30.4375}$$

Table 5: Censoring Rules for DOR

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

* Cohort 1, 1A, 2, and 2A: On-study tumor imaging requires an assessment every 9 weeks (63 ± 7 days) until Week 72, every 12 weeks (84 ± 7 days) after Week 72 from start of protocol treatment until progression or start of subsequent anticancer treatment.

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Cohort 3: On-study tumor imaging requires assessment every 6 weeks (42 ± 7 days) until Week 24; every 9 weeks (63 ± 7 days) after Week 24 until Week 52, and then every 12 weeks ((84 ± 7 days) from start of protocol treatment until progression or start of subsequent anticancer treatment.

4.1.2.3 Progression Free Survival (PFS)

PFS defined as the time from the date of first dose to the date of disease progression or death due to any cause, whichever occurs earlier.

PFS will be calculated as shown below using the censoring rules specified in Table 6.

$$PFS(months) = \frac{\text{Date of PD/Death/Censoring} - \text{ Date of First Dose } + 1}{30.4375}$$

Table 6: Censoring Rules for PFS

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

* Cohort 1, 1A, 2, and 2A: On-study tumor imaging requires an assessment every 9 weeks (63 ± 7 days) until Week 72, every 12 weeks (84 ± 7 days) after Week 72 from start of protocol treatment until progression or start of subsequent anticancer treatment.
.
Cohort 3: On-study tumor imaging requires assessment every 6 weeks (42 ± 7 days) until Week 24; every 9 weeks (63 ± 7 days) after Week 24 until Week 52, and then every 12 weeks ((84 ± 7 days) from start of protocol treatment until progression or start of subsequent anticancer treatment.

4.1.2.4 Overall Survival

Overall survival (OS) is defined as the time from date of first dose to the date of death due to any cause. Patients without documented death at the time of the final analysis will be censored at the last known alive date.

The date of last known alive date will be derived for patients not known to have died at the analysis cut-off date using the latest complete date among the following:

- Patient assessment dates (blood sampling [laboratory], vital signs, ECGs, tumor assessment)
- Start and end date of AEs
- Start and end date of study treatment
- Start and end date of subsequent anti-cancer therapies administered after study treatment discontinuation
- Date of study discontinuation for reasons other than lost-to-follow-up
- Last date of contact recorded on the survival follow-up
- Any assessment date after the analysis cut-off date will not be applicable.

OS will be calculated as:

$$OS(months) = \frac{\text{Date of Death/Censoring} - \text{ Date of First Dose } + 1}{30.4375}$$

4.2 Safety Evaluations

The safety evaluations include:

- Treatment emergent adverse events (TEAEs)
- Extent of exposure
- Clinical laboratory assessments
  - Hematology (including CBC and coagulation)
  - Chemistry (including thyroid function tests)
  - Urinalysis
- Serum or urine pregnancy testing
- Vital signs
- Physical examination findings
- ECG

4.3 Other Evaluations

Other evaluations include:

- Demographics and baseline characteristics (including NSCLC History)
- Medical history
  - General medical history
  - Other cancer History
  - Surgical history
  - Prior blood disorders
  - Smoking history
- Medication use/procedures
  - Prior medications and concomitant medications
  - Prior anticancer treatment for primary cancer
  - Subsequent anticancer treatment for primary cancer
  - Growth factors
  - Transfusions
  - Concomitant Procedures
  - Concomitant radiotherapy
- ECOG Performance status
- Drug accountability (Niraparib)
- Pembrolizumab Administration

- TSR-042 Administration
- Niraparib dose modification

5 PLANNED ANALYSES

5.1 Changes from planned Analyses in the Protocol

5.2 Interim Analyses

Confirmation of response is not required for the purpose of determining if the study should continue enrolling stage 2 patients. Therefore, there will be no formally interim conducted for the study

5.3 Final Analyses and Reporting

All final planned analyses per protocol and this SAP will be performed after database lock. All final efficacy analyses for response rate will be based on the confirmed response.

6 ANALYSIS POPULATIONS AND APPLICATIONS

Statistical analysis and data tabulation will be performed using the following analysis populations unless specified otherwise:

6.1 Modified Intent-to-Treat Population

Modified intent-to-treat (mITT) population includes all patients who received any study drug and did not withdraw consent prior to having at least one post-baseline tumor assessment. The modified ITT population will be the primary analysis population for the efficacy analyses.

6.2 Pharmacokinetic Population

Pharmacokinetic (PK) population includes patients who have at least one of measurable niraparib concentration.

6.3 Safety Population

Safety population includes patients who receive at least one dose of either study medications. The safety population will be the primary analysis population for the safety analyses.

6.4 Application of Analysis Populations

The analysis population(s) that will be used for creating the summary table(s) of each type is provided in Table 7. All data will be presented in listings for the Enrolled population. A patient will be considered enrolled when the patient has been consented, screened, and all eligibility criteria have been confirmed in the electronic case report form (eCRF).

Table 7: Application of Analysis Populations for Tables and Graphs

Type	Safety	mITT	PK*
Disposition	X		X
Demographics and baseline characteristics	X	X	
Protocol deviations	X		
Medical and disease history	X		
Prior and concomitant medications	X		
Summary and analyses on efficacy endpoints		X	
Summary statistics on PK			
Safety evaluations	X		
Extent of Exposure	X		

* The PK analyses will be provided in a separate document.

7 STATISTICAL CONSIDERATIONS

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

All summaries and analyses for demographics, baseline characteristics, and safety data will be done by cohort and overall separately for

- Stage 1 Receiving Combination of Niraparib and Pembrolizumab
- Stage 1 Receiving Niraparib only Treatment
- Stage 2 Receiving Combination of Niraparib and TSR-042

The summaries and analyses of efficacy data will be provided by stage and cohort.

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

7.1 General Statistical Procedures

The descriptive statistics for continuous variables will be the mean, median, standard

deviation (SD), quartiles (Q1, Q3), minimum, maximum, and number of patients.

Frequency distributions for all categorical variables will be presented using counts and percentages.

7.2 Patient Enrolment and Disposition

7.2.1 Patient Enrollment

Number of patients will be provided for each analysis population. The denominators for percentages are number of enrolled. A patient is considered as enrolled when the patient has been consented, screened, and all eligibility criteria have been confirmed in the electronic case report form (eCRF).

Enrollment information will be provided in a data listing.

7.2.2 Patient Disposition

Patient disposition will be summarized for the Safety population. The summary will present frequency distribution for patients completing the study and discontinuing from the study overall and by reason for discontinuation.

Additionally, the frequency distribution will be provided by reason for discontinuation as applicable for each cohort

- for patients discontinuing treatment niraparib
- for patients discontinuing treatment pembrolizumb
- for patients discontinuing treatment TSR-042

The denominators for calculating the percentages will be based on number of patients for each cohort and overall in the Safety population.

Patient disposition will be provided in a data listing.

7.2.3 Protocol Deviations

A protocol deviation (PD) is any failure to comply with the study protocol as approved by the relevant regulatory authority, ethics committee and/or institutional review board, whether planned or unplanned.

PD will be assessed and classified as important or significant. A protocol deviation is classified as an important PD if there is the potential to:

- Impact the completeness, accuracy, and/or reliability of the study data, or

- Affect a subject's rights, safety, or well-being.

Important protocol deviations require review to confirm whether they are significant. The following are PDs that will always be considered important according to TESARO SOP 1000-00021-CLN:

- Failure to obtain informed consent for participation in the clinical trial
- Enrollment of ineligible subject
- Subject developed withdrawal criteria during the study but was not withdrawn
- Subject received incorrect treatment
- Incorrect or non-compliant dosing of a subject, i.e. dosing that is inconsistent with the protocol
- Administration of an excluded concomitant treatment to a trial subject
- Incorrect cohort assignment

A protocol deviation is classified as a significant PD if it has been confirmed to:

- Adversely impact the completeness, accuracy, and/or reliability of the study data
- Affect a subject's rights, safety, or well-being.

The TESARO medical monitor in conjunction with other study team members as appropriate may determine any PD not listed above to be important or significant based on his/her assessment of (potential) impact. Additionally, a PD could be "downgraded." In this case, the rationale for the change should be documented by the TESARO medical monitor.

Criteria for important and/or significant PDs may be updated as needed throughout the course of the clinical trial.

All PDs will be identified and finalized prior to database lock.

Number and percentage of patients with important or significant protocol deviations will be summarized, further by type of deviation. The denominators for calculating the percentages will be based on number of patients.

All protocol deviations will be listed.

7.3 Demographic and Other Pre-treatment Variables

7.3.1 Demographics/Baseline Characteristics and Non-small Cell Lung Cancer History

7.3.1.1 Demographics/Baseline Characteristics

Patient demographics and baseline characteristics include:

- Age (years) calculated as (date of screening - date of birth) / 365.25 if date of birth is reported, or age as reported on the eCRF will be used
- Age categories (18 to <65, 65 to <75, ⩾75; and ⩾65)
- Race (American Indian/Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, White, and Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported, and Unknown)
- Baseline weight (in kilograms; if weight is reported in pounds, convert to kilograms by dividing by 2.2)
- Baseline height (in centimeters; if height is reported in inches, convert to centimeters by multiplying by 2.54)
- Baseline body mass index (BMI) (kg/m2), calculated using the patient's height and weight [BMI (kg/m2) = weight (kg) / height (m)2]
- ECOG performance status at baseline
- Smoking status (Current Smoker, Former Smoker, Never Smoked, Unknown)
- If female, childbearing status (Childbearing potential, Non-childbearing potential)

Continuous data will be summarized for both Safety and mITT populations, using descriptive statistics.

Categorical data will be summarized with frequency distributions using counts and percentages of patients in each category. The denominators for calculating the percentages will be based on the number of patients in both Safety and mITT populations.

Demographics and baseline characteristics will be provided in a listing.

7.3.1.2 Non-small Cell Lung Cancer Disease History

The following NSCLC disease history will be collected.

- date of original diagnosis
- overall cancer stage of original diagnosis
- date of first diagnosis of advanced or recurrent or metastatic disease
- stage of first advanced or recurrent or metastatic disease
- histology at diagnosis
- EGFR mutation, KRAS mutation, BRAF mutation, BRCA1/BRCA2 mutation, ALK translocation, and ROS1 translocation.

Time from original diagnosis and time from first diagnosis of advanced or recurrent or metastatic disease to the date of first dose, stages of cancer, histology, mutations and translocations will be summarized using descriptive statistics for continuous variables and frequency distribution for categorical variables.

A data listing will be provided for NSCLC history.

7.3.1.3 PD-L1 Test Results

The PD-L1 test results will be summarized for location of testing, PD-L1 IHC assay, and PD-L1 status as collected on CRF, and percent of TPS.

The PD-L1 test results will be provided data listings.

7.3.2 Medical History

7.3.2.1 General Medical History

The medical history will be coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA). The frequency count and percentage of patients experiencing any medical conditions will be tabulated by MedDRA SOC and PT for each analysis population. The denominators for calculating the percentages will be based on number of patients in the Safety population.

A data listing of medical history will be provided.

7.3.2.2 Other Cancer History, Surgery History, and Prior Blood Disorders

Prior blood disorders will be coded using current version of MedDRA and summarized by MedDRA SOC, PT and CTCAE grade. Additionally, they will also be summarized by event collected on CRF and CTCAE grade.

Other cancer history will be summarized by the types listed on the CRF as well.

Data listings will be provided separately for other cancer history, surgery, and prior blood disorders.

7.3.3 Medication Use/Procedures

All medications will be coded using the current version of World Health Organization (WHO) Drug Dictionary (WHO-DD). The count and percentage of patients who took prior/concomitant medications will be provided using therapeutic class and WHO Drug preferred name. The denominators for calculating percentages will be based on the number of patients in each cohort of the Safety population. For the summary tables, if a patient has taken a prior or concomitant medication/subsequent treatment more than once, the patient

will be counted only once for the medication/treatment.

Prior medications are defined as medications received prior to the first dose of either study drugs. Concomitant medications are defined as medications received during the treatment period.

Prior and subsequent anticancer treatments for primary cancer will be summarized for the following information:

- agent name listed on CRF
- reason for administration
- number of anticancer treatments (categorical)
- number of anticancer treatments (categorical) in neoadjuvant, adjuvant, metastatic and other settings
- time since the end of last anticancer treatment (months)
- best response of last anticancer treatment
- reason for discontinuation
- treatment ongoing (only for subsequent)

The denominators for calculating the percentages will be based on number of patients in each cohort of safety population.

Number of patients receiving transfusions will be summarized by the type of transfusions. For each type of transfusion, number of units transfused will be presented in the table.

All medications, prior and subsequent anticancer treatments, and transfusions will be provided in data listings. In addition, separate listings will be provided for:

- Growth factors
- Concomitant Procedures
- Concomitant radiotherapy

7.4 Analysis of Efficacy Data

7.4.1 Primary Efficacy Data

The primary efficacy variable is objective response rate (ORR), defined as the proportion of patients with a confirmed best overall response of complete response (CR) or partial response

(PR) in the analysis population. Tumor assessments after the initiation of further anticancer therapy are excluded for the assessment of best overall response.

Number of responders, ORR, and its two-sided 80% and 95% binomial exact (Clopper-Pearson) confidence interval will be reported for each cohort.

7.4.2 Secondary Efficacy Data

DCR will be analyzed using the same methods for ORR for each cohort.

For each cohort, time-to-event variables (DOR, PFS, and OS) will be summarized in a descriptive manner using Kaplan-Meier method including median and its 95% confidence interval (CI), progression rates and their 95% CI at 3 months, 6 month, 9 months, 12 months, and 15 months. In addition, Kaplan-Meier curves will also be presented for time-to-event variables.

The above efficacy data will be provided in listings.

7.5 Analysis of Safety Data

7.5.1 Adverse Events

Adverse events will be classified into a standardized terminology MedDRA system organ classifications (SOC) and preferred terms (PT). Severity of AEs will be assessed by investigators according to CTCAE (v4.03).

A treatment-emergent AE (TEAE) will be defined as any new AE that begins, or any preexisting condition that worsens in severity during the treatment period, which is after the earlier date of first dose of niraparib, pembrolizumab or TSR-042 as applicable.

AEs that were possibly or definitely related to study drug niraparib or pembrolizumab or TSR-042 will be defined to be related to the study drugs while unrelated and unlikely related AEs will be defined as “not related”. AEs with the closest relationship to study drugs will be used for summary.

Adverse events of special interest (AESI) will be collected and summarized.

- Patients who received pembrolizumab will be monitored for AESI caused by abnormal hepatic tests with an elevated AST or ALT value that is $\geqslant 3 \times$ ULN concurrent with an elevated total bilirubin value that is $\geqslant 2 \times$ ULN and, at the same time, an alkaline phosphatase value that is $< 2 \times$ ULN
- Patients who received niraparib will be monitored for
    - MDS and AML

  - New malignancy information, i.e., any malignancy identified after the start of study medication
  - Pneumonitis
  - Embryo-fetal toxicity
- Regarding AESIs for TSR-042, no AESIs have been reported to date, therefore all serious AEs will be reasonably considered as AESI for patients who received TSR-042.

The number and percentage of patients who experienced an AE will be summarized. The denominator for calculating the percentages will be based on the number of patients in each cohort of the safety population.

The following types of summaries will be provided:

- Overview of TEAEs
- TEAEs by SOC and PT
- by SOC, PT, and Maximum CTCAE toxicity grade
  - TEAE
  - CTCAE Grade 3 or Greater TEAEs
- TEAEs by PT in descending frequency
- Drug-related TEAEs by SOC, PT, and Relationship to study drug
- by SOC, PT, Relationship to study drug, and Maximum CTCAE toxicity grade
  - Drug-related TEAEs
  - Drug-related CTCAE Grade 3 or Greater TEAEs
- by PT in descending frequency
  - Drug-related TEAEs by PT in descending frequency
  - Niraparib-related TEAEs by PT in descending frequency
  - Pembrolizumab-related TEAEs by PT in descending frequency
  - TSR-042-related TEAEs by PT in descending frequency
- Treatment emergent SAE by SOC and PT
- Drug-related treatment emergent SAE by SOC, PT, and Relationship to study drug
- TEAEs leading to study drug interruption, reduction, and discontinuation
  - TEAEs leading to study drug interruption by SOC, PT, and Interrupted Drug
  - TEAEs leading to study drug reduction by SOC, PT, and Reduced Drug
  - TEAEs leading to study discontinuation by SOC, PT, and Discontinued Drug
- Drug-Related TEAEs leading to study drug discontinuation SOC, PT,

Relationship to Drug, and Discontinued Drug
- TEAEs leading to death by SOC and PT
- Most commonly reported TEAEs (i.e., those events reported by ⩾5% of all patients

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

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

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

All AEs will be provided in a data listing.

7.5.2 Study Drug Exposure and Compliance

The following study drug exposure and compliance parameters will be summarized:

- Duration of study drug exposure in months is defined as

$$\frac{\max(\text{Date of last dose of niraparib} + 1, \text{Date of last dose of pembrolizumab} + 21) - \min(\text{Date of first dose of niraparib}, \text{Date of first dose of pembrolizumab})}{30.4375}$$

- niraparib exposure parameters
    - Duration of niraparib exposure in months defined as

$$\frac{\text{Date of last dose of niraparib} - \text{Date of first dose of niraparib} + 1}{30.4375}$$

    - Number of cycles initiated as continuous variable
    - Number of cycles initiated as a categorical variable (1 cycle, 2 cycles, etc.)
    - Number of patients with at least one dose escalation
    - Number of patients with at least one dose interruption
    - Number of patients with at least one dose reduction

- Number of patients with at least one missed dose
- Starting dose for niraparib
- Cumulative niraparib dosage (mg) received defined as sum of all niraparib dose received. This will be derived using pill count data (dispensed - returned), whenever available. If the returned pill count data is not available for a particular cycle, the dosing data along with dosing modifications will be used to compute cumulative dose for that cycle.
- Actual dose intensity (mg/day) for niraparib defined as

$$\frac{\text{Cumulative niraparib dosage (mg) received}}{\text{\# of cycle initated} \times \text{\# planned dosing days per cycle}}$$

- Intended dose intensity (mg/day) for niraparib defined as

$$\frac{\text{Intended dose (mg) at first cycle} \times \text{\# of planned niraparib dosing days per cycle}}{\text{\# planned dosing days per cycle}}$$

- pembrolizumab exposure parameters
  - Duration of pembrolizumab exposure in months defined as

$$\frac{\text{Date of last dose of pembrolizumab} - \text{Date of first dose of pembrolizumab} + 21}{30.4375}$$

  - Cumulative pembrolizumab dosage (mg) received defined as sum of all pembrolizumab dose received
  - Actual dose intensity (mg/wk) for pembrolizumab defined as

$$\frac{\text{Cumulative pembrolizumab dosage (mg) received}}{\text{Duration of pembrolizumab exposure (wk)}}$$

  - Intended dose intensity (mg/wk) for pembrolizumab defined as

$$\frac{200\ (\text{mg})}{3\ (\text{wk})} = 66.7\ (\text{mg/wk})$$

  - Relative dose intensity (%) for pembrolizumab defined as

$$\frac{\text{Actual dose intensity}}{\text{Intended dose intensity}} \times 100\%$$

- TSR-042 exposure parameters
    - Duration of TSR-042 exposure in months defined as

$$\frac{(\text{Date of last dose of TSR042} - \text{Date of first dose of TSR042} + 21) \text{ for the first cycles} + (\text{Date of last dose of TSR042} - \text{Date of first dose of TSR042} + 42) \text{ for applicable Cycle 5 or later}}{30.4375}$$

    - Cumulative TSR-042 dosage (mg) received defined as sum of all TSR-042 dose received
    - Actual dose intensity (mg/wk) for TSR-042 defined as

$$\frac{\text{Cumulative TSR042 dosage (mg) received}}{\text{Duration of TSR042 exposure (wk)}}$$

    - Intended dose intensity (mg/wk) for TSR042 defined as

$$\frac{500\ (\text{mg})}{3\ (\text{wk})}\ (or\ \frac{1000\ (\text{mg})}{6\ (\text{wk})}) = 166.7\ (\text{mg/wk})$$

    - Relative dose intensity (%) for TSR-042 defined as

$$\frac{\text{Actual dose intensity}}{\text{Intended dose intensity}} \times 100\%$$

Study drug exposure parameters will be summarized using descriptive statistics. Details of study drug administration, dose modifications and duration of exposure will be listed.

7.5.3 Clinical Laboratory Evaluations

Clinical laboratory assessments (CBC, serum chemistry, TSH, T3 or FT3, and FT4) will be summarized by visit in descriptive nature. Descriptive statistics will be provided for continuous laboratory data and associated change from baseline. Frequency distribution will be provided for categorical laboratory.

Baseline and post-baseline results will be converted to SI units and categorized as low, normal, or high relative to the normal range. Shift tables will be done by visit for each cohort.

In addition, the worst toxicity grades for selected laboratory tests as listed in Appendix B will be determined for each patient based on worst abnormal high and abnormal low lab values. The shift table from baseline CTCAE grade to the worst NCI CTC grade will be provided.

Corrected calcium will be derived using the following formula:

$$\text{Corrected calcium (mmol/L)} = 0.02 * (40 - \text{normal albumin (g/L)}) + \text{serum calcium (mmol/L)}$$

Unless otherwise specified, for frequency laboratory tables, the denominators for calculating the percentages will be based on the number of patients with non-missing values at each visit in the Safety population of each cohort.

For shift table from baseline to post-baseline visit, the denominators for calculating the percentages will be based on the number of patients with non-missing values at both baseline and each post-baseline analysis visit in the Safety population of each cohort.

Liver function tests post baseline will be summarized at any post baseline by the following categories.

- ALT ⩾ 3×ULN, ALT ⩾ 5×ULN, ALT ⩾ 10×ULN, ALT ⩾ 20×ULN
- AST ⩾ 3×ULN, AST ⩾ 5xULN, AST ⩾ 10×ULN, AST ⩾ 20×ULN
- (ALT or AST) ⩾ 3×ULN, (ALT or AST) ⩾ 5×ULN, (ALT or AST) ⩾ 10×ULN, (ALT or AST) ⩾ 20×ULN
- Total bilirubin ⩾ 2×ULN
- Concurrent ALT ⩾ 3×ULN and total bilirubin ⩾ 2×ULN
- Concurrent AST ⩾ 3×ULN and total bilirubin ⩾ 2×ULN
- Concurrent (ALT or AST) ⩾ 3×ULN and total bilirubin ⩾ 2×ULN
- Concurrent (ALT or AST) ⩾ 3×ULN and total bilirubin ⩾ 2×ULN and ALP > 2×ULN
- Potential Hy's law: Concurrent (ALT or AST) ⩾ 3×ULN and total bilirubin ⩾ 2×ULN and ALP ⩽ 2×ULN or missing

Concurrent measurements are those occurring on the same date

Urinalysis is only collected at screening. The data will be provided in a listing. Other laboratory data will also be provided in data listings.

7.5.4 Vital Signs

Vital signs (systolic and diastolic blood pressure, pulse, temperature, and weight) will be summarized by visit. Actual values and changes from baseline will be summarized at each visit. Baseline is defined as the last observation prior to start of the first dose of study drug(s).

7.5.5 Electrocardiogram

ECG summaries will present frequency table analysis of ECG interpretation (normal vs abnormal - NCS, abnormal - CS) by stage and overall for baseline and end of treatment. The shift table from Baseline to end of treatment will also be provided.

A separate summary will be provided for ECG measurements including heart rate, PR interval, QT interval, RR interval, and QRS complex.

QTc will be used for the data analysis and interpretation. Commonly used techniques including Bazett's (QTcB) and Fridericia's (QTcF) methods are applied. QTcF will be used for the primary QT evaluation. A summary of the number and percentage of patients with QTc interval exceeding some predefined upper limit (e.g., >450 ms, >480 ms, >500 ms) will be provided. A summary of the number and percentage of patients with change from baseline in QTc interval exceeding some predefined upper limit (e.g., >30 ms, >60 ms) will be provided.

Furthermore, a summary will also provide the number and percentage of patients for

1. maximum post-baseline QRS interval ≥ 120 ms,
2. heart rate ≤ 50 bpm and decrease from baseline ≥ 20 bpm or ≥ 120 bpm and increase from baseline ≥ 20 bpm
3. PR interval >=220 ms and increase from baseline ≥ 20 ms.

Detailed ECG results will be provided in a data listing.

7.5.6 Physical Examinations

Physical examinations will be provided in a data listing only.

7.5.7 ECOG Performance Status

Summary of ECOG performance status will present frequency distribution for each category. The denominators for calculating the percentages will be based on the number of patients without missing values.

Details on ECOG status will be provided in a data listing.

8 DEFINITIONS AND CONVENTIONS FOR DATA HANDLING

As a general rule, missing data values are not imputed unless otherwise specified below and, in presentation of categorical variables, unknown and missing data may be presented as a separate category in some case and the denominator will include unknown or missing values

as appropriate.

8.1 Definition of Baseline

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

8.2 Analysis Visit Window

For safety parameters including clinical laboratory data, measurements collected from unscheduled visits will not be included in the by-visit summary tables but will be included in the listings.

8.3 Efficacy Data Handling

See Section 4.1.

8.4 Safety Data Handling

For all safety data, only observed data will be used for analyses, and missing data will not be imputed.

8.4.1 Handling of Repeated Clinical Laboratory Tests

The last repeat of laboratory results will be used in the summary tables for that visit. All the laboratory test results (original test results and repeated results) will be included in the data listings.

8.4.2 Handling of Partial Dates for AEs

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

- If the day of the month is missing, the onset day will be set to the first day of the month unless it is the same month and year as study treatment. In this case, the onset date will be assumed to be the date of treatment.
- If the onset day and month are both missing, the month and day will be assumed to be January 1 unless the event occurred in the same year as the study treatment. In this case, the event onset will be set to the day of treatment to conservatively report the event as treatment-emergent.
- A completely missing onset date will be set as the day of treatment. If the resulting onset date is after a reported date of resolution, the onset date will be set equal to the date of resolution.

- Imputation of partial dates is used only to determine whether an event is treatment-emergent; data listings will present the partial date as recorded in the eCRF.

8.4.3 Handling of Partial Dates for Medications

A medication with a completely missing start date will be considered a prior medication. A medication with a completely missing stop date will be considered a concomitant medication.

When determining prior or concomitant medications, partial start dates of prior and concomitant medications will be assumed to be the earliest possible date consistent with the partial date. Partial stop dates of prior and concomitant medications will be assumed to be the latest possible date consistent with the partial date. In the case of completely missing stop date, medication will be assumed to be ongoing. In the case of complete missing start date, medication will be assumed to be prior medication.

9 REFERENCE

Simon R. Optimal two-stage designs for phase II clinical trials. Control Clin Trials. 1989;10(1):1-10.

10 APPENDICES

Appendix A. Response Criteria by Response Evaluation Criteria in Solid Tumors (RECIST), v1.1

Evaluation of Target Lesions

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

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

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

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

Evaluation of Non-Target Lesions

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

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of 1 or more nontarget lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of 1 or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of “non-target” lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Investigator).

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 progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Table 8: RECIST Response for Patients with Measurable Disease

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	> 4 weeks Confirmation**
CR	Non-CR/Non-PD	No	PR	> 4 weeks Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/Not evaluated	No	PR	
SD	Non-CR/Non-PD/Not evaluated	No	SD	Documented at least once > 4 weeks from baseline**
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; PD = progressive disease; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease

* See RECIST v1.1 publication for further details on what is evidence of a new lesion.

** Only for nonrandomized trials with response as primary endpoint.

*** In exceptional circumstances, unequivocal progression in nontarget lesions may be accepted as disease progression.

Note: Patients 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.

Appendix B. Common Terminology Criteria for Adverse Events v4.03 (CTCAE)

Table 9: Common Terminology Criteria for Adverse Events v4.03 (CTCAE)

Lab Test	Std. Unit	CTCAE v4.0 SOC	CTCAE v4.0 Term	Grade 1	Grade 2	Grade 3	Grade 4
Hemoglobin	g/L	Blood and lymphatic system disorders	Anemia	<LLN - 100 g/L	<100 - 80g/L	<80 g/L	-
ALT	U/L	Investigations	Alanine aminotransferase increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
ALP	U/L	Investigations	Alkaline phosphatase increased	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
AST	U/L	Investigations	Aspartate aminotransferase increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
Bilirubin	umol/L	Investigations	Blood bilirubin increased	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 - 10.0 x ULN	>10.0 x ULN
CD4	10e9/L	Investigations	CD4 lymphocytes decreased	<LLN - 0.5 x 10e9 /L	<0.5 - 0.2 x 10e9 /L	<0.2 x 0.05 - 10e9 /L	<0.05 x 10e9 /L
Cholesterol	mmol/L	Investigations	Cholesterol high	>ULN - 7.75 mmol/L	>7.75 - 10.34 mmol/L	>10.34 - 12.92 mmol/L	>12.92 mmol/L
CPK (creatinine phosphor-kinase)	-	Investigations	CPK increased	>ULN - 2.5 x ULN	>2.5 - 5 x ULN	>5 - 10 x ULN	>10 x ULN
Creatinine	umol/L	Investigations	Creatinine increased	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 - 6.0 x ULN	>6.0 x ULN
Lymphocytes	10e9/L	Investigations	Lymphocyte count decreased	<LLN - 0.8 x 10e9/L	<0.8 - 0.5 x 10e9 /L	<0.5 - 0.2 x 10e9 /L	<0.2 x 10e9 /L
Neutrophils	10e9/L	Investigations	Neutrophil count decreased	<LLN - 1.5 x 10e9 /L	<1.5 - 1.0 x 10e9 /L	<1.0 - 0.5 x 10e9 /L	<0.5 x 10e9 /L
Platelets	10e9/L	Investigations	Platelet count decreased	<LLN - 75.0 x 10e9 /L	<75.0 - 50.0 x 10e9 /L	<50.0 - 25.0 x 10e9 /L	<25.0 x 10e9 /L
Amylase	-	Investigations	Serum amylase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN	>2.0 - 5.0 x ULN	>5.0 x ULN
Leukocytes	10e9/L	Investigations	White blood cell decreased	<LLN - 3.0 x 10e9 /L	<3.0 - 2.0 x 10e9 /L	<2.0 - 1.0 x 10e9 /L	<1.0 x 10e9 /L

Table 9: Common Terminology Criteria for Adverse Events v4.03 (CTCAE)

Lab Test	Std. Unit	CTCAE v4.0 SOC	CTCAE v4.0 Term	Grade 1	Grade 2	Grade 3	Grade 4
Calcium (corrected)	mmol/L	Metabolism and nutrition disorders	Hypercalcemia	>ULN - 2.9 mmol/L	>2.9 - 3.1 mmol/L	>3.1 - 3.4 mmol/L	>3.4 mmol/L
Glucose	mmol/L	Metabolism and nutrition disorders	Hyperglycemia	Fasting glucose >ULN - 8.9 mmol/L	Fasting glucose >8.9 - 13.9 mmol/L	>13.9 - 27.8 mmol/L	>27.8 mmol/L
Potassium	mmol/L	Metabolism and nutrition disorders	Hyperkalemia	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L	>6.0 - 7.0 mmol/L	>7.0 mmol/L
Magnesium	mmol/L	Metabolism and nutrition disorders	Hypermagnesemia	>ULN - 1.23 mmol/L	-	>1.23 - 3.30 mmol/L	>3.30 mmol/L
Sodium	mmol/L	Metabolism and nutrition disorders	Hypernatremia	>ULN - 150 mmol/L	>150 - 155 mmol/L	>155 - 160 mmol/L	>160 mmol/L
Albumin	g/L	Metabolism and nutrition disorders	Hypoalbuminemia	<LLN - 30 g/L	<30 - 20 g/L	<20 g/L	-
Calcium (corrected)	mmol/L	Metabolism and nutrition disorders	Hypocalcemia	<LLN - 2.0 mmol/L	<2.0 - 1.75 mmol/L	<1.75 - 1.5 mmol/L	<1.5 mmol/L
Glucose	mmol/L	Metabolism and nutrition disorders	Hypoglycemia	<LLN - 3.0 mmol/L	<3.0 - 2.2 mmol/L	<2.2 - 1.7 mmol/L	<1.7 mmol/L
Potassium	mmol/L	Metabolism and nutrition disorders	Hypokalemia	<LLN - 3.0 mmol/L	<LLN - 3.0 mmol/L	<3.0 - 2.5 mmol/L	<2.5 mmol/L
Magnesium	mmol/L	Metabolism and nutrition disorders	Hypomagnesemia	<LLN - 0.5 mmol/L	<0.5 - 0.4 mmol/L	<0.4 - 0.3 mmol/L	<0.3 mmol/L
Sodium	mmol/L	Metabolism and nutrition disorders	Hyponatremia	<LLN - 130 mmol/L	-	<130 - 120 mmol/L	<120 mmol/L
Phosphate	mmol/L	Metabolism and nutrition disorders	Hypophosphatemia	<LLN - 0.8 mmol/L	<0.8 - 0.6 mmol/L	<0.6 - 0.3 mmol/L	<0.3 mmol/L