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NCT #: NCT03992131

STATISTICAL ANALYSIS PLAN

SEASTAR: A Phase 1b/2, Open-label, Parallel Arm Study to Assess the Safety, Tolerability, Pharmacokinetics, and Preliminary Efficacy of Oral Rucaparib in Combination with Other Anticancer Agents in Patients with a Solid Tumor

Arm A: rucaparib and lucitanib

PROTOCOL NUMBER:	CO-338-098
VERSION:	1.0
DATE FINAL:	10 September 2021
SPONSOR:	Clovis Oncology, Inc.
	[redacted]

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DocuSign Envelope ID: 5E70E8D8-99B8-4CCB-9D15-D470C5DE2254

TABLE OF CONTENTS

DocuSign Envelope ID: 5E70E8D8-99B8-4CCB-9D15-D470C5DE2254

LIST OF IN-TEXT TABLES

LIST OF APPENDICES

DocuSign Envelope ID: 5E70E8D8-99B8-4CCB-9D15-D470C5DE2254

ABBREVIATIONS AND SPECIALIST TERMS

AE(s)	adverse event(s)
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
$AUC_{0\text{-last}}$	last quantifiable concentration
BID	twice daily
CL/F	plasma clearance
C_{max}	maximum observed concentration
C_{min}	minimum concentration
CR	complete response
CRM	cohort review meeting
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating cell-free tumor DNA
DBP	diastolic blood pressure
DLT	dose limiting toxicity
DOR	duration of response
ECOG	Eastern Cooperative Oncology Group
MTD	maximum tolerated dose
NCI	National Cancer Institute
ORR	objective response per RECIST
PD	progressive disease
PK	pharmacokinetic(s)
PR	partial response
QD	once daily
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended Phase 2 dose
SAP	statistical analysis plan
SBP	Systolic blood pressure
SD	stable disease
SI	International System of Units
StD	standard deviation

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TEAE	treatment-emergent adverse event
T_{max}	time to maximum concentration
ULN	upper limit of normal

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1 INTRODUCTION

This SAP describes the data summaries and any statistical analyses to be performed to assess the safety, efficacy, and pharmacokinetics (PK) of rucaparib (CO-338) for Clovis Oncology, Inc sponsored clinical study CO-338-098, entitled "SEASTAR: A Phase 1b/2, Open-label, Parallel Arm Study to Assess the Safety, Tolerability, Pharmacokinetics, and Preliminary Efficacy of Oral Rucaparib in Combination with Other Anticancer Agents in Patients with a Solid Tumor."

This SAP addresses only the Phase 1b portion of Arm A of the study. The study reached the maximum rucaparib dose of 600 mg BID and a lucitanib dose of 6 mg QD. While the maximum tolerated dose (MTD) was not defined, the study was closed to further enrollment. The study will not continue to Phase 2 due to a change in priorities and no further clinical development of the lucitanib plus rucaparib combination is planned at this time. The analysis plan is therefore reduced from what was indicated in the protocol in order to support a abbreviated CSR. Results for Arm B of the Ph 1b part of the study are analyzed under a different SAP.

2 OVERALL STUDY DESIGN, OBJECTIVES, AND ENDPOINTS

2.1 STUDY DESIGN

For the Phase 1b portion of Arm A, the plan estimated 6 to 12 dose-escalation cohorts, with a minimum of 3 patients enrolled in each cohort, followed by an expanded evaluation of the recommended phase 2 dose (RP2D) in up to 10 additional patients. Dose escalation was to follow a 3+3 design.

The initial combination dose consisted of oral rucaparib 300 mg BID and oral lucitanib 4 mg QD, both administered continuously. In the initial program, the dose of rucaparib was to be escalated in 100 mg BID increments up to a maximum of 600 mg BID. A later protocol amendment allowed the final rucaparib dose to escalate from 400 to 600 mg BID. The dose of lucitanib was to be escalated in increments of 2 mg, up to a maximum dose of 10 mg QD.

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2.2 STUDY OBJECTIVES AND ENDPOINTS

Because this study was terminated early, not all endpoints from the protocol will be analyzed. Table 1 outlines the objectives and endpoints planned per protocol for Phase 1b of Arm A. The final column includes the analyses to be included in the CSR.

Table 1. Primary, Secondary, and Exploratory Objectives and Endpoints for Phase 1b

Primary Objectives	**Primary Endpoints**	**Included in CSR**
To evaluate the safety and tolerability of rucaparib in combination with lucitanib and to determine the MTD and/or the RP2D of the combination.	Incidence of AEs, clinical laboratory abnormalities, dose modifications, and blood pressure	Yes: AEs, some clinical laboratories, and dose modifications will be included
Secondary Objectives	**Secondary Endpoints**	
To characterize the PK of rucaparib and lucitanib when agents are co-administered.	Area under the curve from time zero to the last quantifiable concentration ($AUC_{0\text{-last}}$), maximum observed concentration (C_{max}), time to maximum concentration (T_{max}), and apparent plasma clearance (CL/F)	Not included in CSR
To evaluate the preliminary efficacy of rucaparib in combination with lucitanib in various solid tumors.	Objective response per RECIST v1.1 (ORR)	Yes
Exploratory Objectives	**Exploratory Endpoints**	
To assess tumor tissue biomarkers that correlate with response to the combination.	Not defined in protocol	Not included in CSR
To evaluate circulating cell-free tumor DNA (ctDNA) as a molecular marker of response to the combination.	Not defined in protocol	Not included in CSR
To evaluate biomarkers associated with resistance to the combination.	Not defined in protocol	Not included in CSR
To assess genomic changes over time in plasma and tumor samples.	Not defined in protocol	Not included in CSR
To determine steady-state exposure of rucaparib and lucitanib by sparse PK sampling.	Plasma concentration at trough (C_{min})	Yes

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2.3 SAMPLE SIZE JUSTIFICATION

For Arm A Phase 1b, it was estimated that up to 55 patients would be enrolled following a standard 3+3 design, dependent upon the occurrence of safety findings, specifically dose limiting toxicities (DLTs), observed at the different dose levels. Nineteen subjects were enrolled before the study was terminated.

3 GENERAL ANALYSIS CONVENTIONS

Quantitative variables will typically be summarized using frequencies and percentages for appropriate categorizations and may also be summarized using descriptive statistics. For variables summarized with descriptive statistics, the following will be presented: N, mean, standard deviation (StD), median, minimum, and maximum. Categorical variables will be presented using frequencies and percentages.

Baseline is defined as the last measurement on or prior to the first dose of rucaparib administration, unless otherwise specified.

All statistical analyses will be conducted with the SAS® System, Version 9.4 or higher.

3.1 ANALYSIS POPULATIONS

The following analysis populations are defined for the study:

Safety Population: All patients who have received at least 1 dose of rucaparib or lucitanib.

DLT-evaluable Population: All patients in Phase 1b who have either received at least 80% of the planned doses of rucaparib and lucitanib without having experienced a DLT or who experienced a DLT during Cycle 1. If a patient withdrew from the study without having met any of these criteria, then an additional patient was enrolled in that dose cohort.

Efficacy Population: All patients who have received at least 1 dose of rucaparib or lucitanib and who have measurable disease per RECIST v1.1 at baseline.

PK-Evaluable Population: all patients who have received at least one dose of rucaparib or lucitanib and have had at least one measurable concentration.

4 PATIENT DISPOSITION

Patient disposition will be summarized using frequency counts and the corresponding percentages. The number of patients in each analysis population, number of patients discontinued, and the primary reason for treatment discontinuation will be summarized.

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5 PROTOCOL DEVIATIONS

The number of patients with major protocol deviations (eg, inclusion or exclusion criteria) will be determined prior to data base lock and will be summarized with frequencies and percentages or provided in a patient listing.

Protocol deviations will not be used to exclude any patients from the efficacy analyses.

6 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

All demographics will be summarized for the safety population.

6.1 DEMOGRAPHICS

The demographic variables will be summarized with frequency tabulations and descriptive statistics. The demographic variables presented will include age, height, weight and sex using the following categorizations:

- Age (years): ≤ 50, 51-60, 61-70, 71-80, 81-90, > 90;
- Height (cm): ≤ 75, > 75-100, > 100-125, > 125-150, > 150-175, > 175;
- Weight (kg): ≤ 50, > 50-75, > 75-100, > 100-125, > 125-150, > 150
- Sex: Male, Female
- Race: American Indian or Alaskan Native, Asian, Black or African American, Native Hawaiian or Pacific Islander, White
- Ethnicity: Hispanic or Latino, Not Hispanic or Latino
- Baseline ECOG: 0,1

6.2 BASELINE CLINICAL CHARACTERISTICS

HRD status will be listed.

6.3 MEDICAL HISTORY

Medical history events will not be analyzed.

7 DOSE-LIMITING TOXICITIES

A summary of the number of DLTs by dose level and a patient listing of all DLTs will be provided for the patients in the DLT-evaluable population. A DLT for Arm A is defined at any of the following events occurring in Cycle 1, according to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0:

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- Grade 3 or greater febrile neutropenia (i.e., fever > 38.3°C with Absolute Neutrophil Count (ANC) < 1.0×10^9/L) of any duration;
- Grade 3 thrombocytopenia (platelets < 50×10^9/L) with significant bleeding or Grade 4 thrombocytopenia (platelets < 25×10^9/L) ≥ 5 days duration;;
- Grade 4 anemia (i.e., life-threatening consequences; urgent intervention indicated) or any anemia (regardless of grade or severity) requiring a blood transfusion;
- Hypertension, defined as systolic blood pressure [SBP] ≥ 160 mmHg and/or diastolic blood pressure [DBP] ≥ 100 mmHg, that does not resolve to ≤ Grade 2 within 14 days despite optimized antihypertensive therapy, or any Grade 4 hypertension (hypertension with life-threatening consequences);
- Any nonhematological AE ≥ Grade 3, with the exception of:
    - Nausea, vomiting, and diarrhea if well controlled by systemic medication and with duration ≤ 48 hrs;
    - Fatigue;
    - Hyponatremia;
    - Grade 3 alanine aminotransferase (ALT) or aspartate aminotransferase (AST) not accompanied by a concomitant increase in total bilirubin above the upper limit of normal (ULN). Note: any Grade 4 ALT/AST is a DLT.

8 STUDY DRUG EXPOSURE AND COMPLIANCE

The following variables will be summarized:

- Duration of treatment (days)
- Duration of treatment (months)
- Number of cycles started
- Number of dose reductions
- Number of treatment interruptions
- Dose intensity

Duration of treatment will be calculated as 1+ the number of days from earliest study drug start date to date of last study drug discontinuation. Dose intensity will be calculated as the actual dose received divided by the assigned dose amount. Descriptive statistics and frequencies/percentages for appropriate categorizations will be used to summarize study drug exposure variables.

9 PRIOR AND CONCOMITANT MEDICATIONS

Prior and concomitant medications will not be analyzed in the CSR.

10 EFFICACY ANALYSIS

Efficacy analyses will be performed using the efficacy population.

DocuSign Envelope ID: 5E70E8D8-99B8-4CCB-9D15-D470C5DE2254

Overall objective response to treatment according to RECIST v1.1 as assessed by the investigator will be listed along with target lesion measurements and response, non-target lesion response, and assessment of new lesions. Confirmation of a complete response (CR) or partial response (PR) is a response that is maintained and documented on a subsequent tumor assessment no less than 4 weeks after initial response. Duration of response (DOR) will also be calculated as the time from the date that a confirmed PR or CR is first recorded until the first date that progressive disease (PD) is documented per RECIST v1.1. Duration of stable disease (SD) will be calculated from the start of treatment to the first PD if the subject had a best response of SD.

A listing of all tumor scan details collected in the clinical database, including assessment of objective response and DOR will be provided.

11 EXPLORATORY ANALYSIS

Only the PK exploratory endpoint will be analyzed in the CSR. In all patients with at least one PK sample collected, the trough plasma rucaparib and lucitanib PK data (C_{min}), summary statistics of C_{min} (N, mean, SD, minimum, median, max, CV%), and the mean (±SD) concentration versus time plot will be reported.

12 PHARMACOKINETIC ANALYSIS

The secondary PK analytical plan and analyses will be included in a separate PK report.

13 SAFETY ANALYSIS

The safety analyses will be performed using the safety population.

13.1 ADVERSE EVENTS

AEs will be classified using the MedDRA v. 24.0 classification system. The severity of the toxicities will be graded according to the National Cancer Institute (NCI) CTCAE v5.0 whenever possible. TEAEs are defined as AEs with onset date on or after the date of first dose of study medication until the date of the last study medication dose plus 28 days. Adverse events will be considered treatment-emergent if all or part of the date of onset of the AE is missing and it cannot be determined if the AE meets the definition for treatment-emergent.

The number and percentage of patients who experienced TEAEs for each system organ class and preferred term will be presented. Multiple instances of the TEAE in each system organ class and multiple occurrences of the same preferred term are counted only once per patient. The number and percentage of patients with at least one TEAE will also be summarized.

The incidence of TEAEs will also be summarized by relationship to study drug according to the following categories: “treatment-related,” or “not treatment-related” for each study drug.

DocuSign Envelope ID: 5E70E8D8-99B8-4CCB-9D15-D470C5DE2254

If a patient experiences multiple occurrences of the same AE with different relationship categories, the patient will be counted once, as a relationship category of treatment-related.

If a patient experiences multiple occurrences of the same AE with different toxicity grades, the patient will be counted once for the maximum (most severe) toxicity grade. AEs with a missing toxicity grade will be presented in the summary table with a toxicity grade of "Missing." For each toxicity grade, the number and percentage of patients with at least one TEAE of the given grade will be summarized.

Separate tables will be presented including but not limited to:

- All TEAEs;
- TEAEs by CTCAE grade;
- Grade 3 or greater TEAEs;
- Treatment-related TEAEs will be included in the following three categories of relatedness: related to rucaparib, related to lucitanib and related to either study drug. Relatedness will be analyzed, overall and by categories: CTCAE grade, grade 3 or greater, serious TEAEs, resulting in dose reduction, resulting in dose interruption, resulting in dose discontinuation, outcome of death;
- Serious TEAEs;
- TEAEs with an outcome of death;
- TEAEs leading to discontinuation of rucaparib only, lucitanib only, or either study drug;
- TEAEs resulting in interruption of rucaparib only, lucitanib only, or either study drug; and
- TEAEs resulting in reduction, delay, or interruption of rucaparib only, lucitanib only, or either study drug.

13.2 CLINICAL LABORATORY EVALUATIONS

Clinical laboratory evaluations include the continuous variables for hematology, chemistry, and urinalysis. The laboratory values will generally be presented in International System (SI) units. The on-treatment period will be defined as the time from earliest first dose to 28 days after the last dose of rucaparib or lucitanib, whichever is last. Hematology, chemistry and urinalysis values collected will be listed. Descriptive summaries, and all chemistry and urinalysis parameters, mentioned in the protocol will not be included in the analysis.

13.3 VITAL SIGNS

The on-treatment period will be defined as the time from first dose to 28 days after the last dose of study drug. Blood pressure measurements (systolic and dystolic) collected during the on-treatment period will be included in the summary tables. The blood pressure measurements collected after the on-treatment period will only be presented in the data listings.

DocuSign Envelope ID: 5E70E8D8-99B8-4CCB-9D15-D470C5DE2254

The summary of blood pressure data will include descriptive statistics (N, mean, StD, minimum, median, and maximum) of the maximum, minimum, and last value during the on-treatment period. Summaries using descriptive statistics (N, mean, StD, minimum, median, and maximum) of the change from baseline to the maximum, minimum, and last value during the on-treatment period will also be given. The data will be presented separately for each treatment group and overall.

14 STATISTICAL / ANALYTICAL ISSUES

14.1 HANDLING OF DROPOUTS OR MISSING DATA

All data will be used to their maximum possible extent, but without any imputations for missing data.

14.2 POOLING OF CENTERS IN MULTI-CENTER STUDIES

All centers will be pooled for analysis.

14.3 MULTIPLE COMPARISON / MULTIPLICITY

No statistical comparisons will be performed.

14.4 EXAMINATION OF SUBGROUPS

Analyses of primary and secondary endpoints may be analyzed by starting dose. No additional subgroup analyses will be performed.

14.5 INTERIM ANALYSES AND DATA MONITORING

No formal interim analyses occurred outside standard Cohort Review Meetings (CRM). CRMs were held for the first 4 dose cohorts.

14.6 ANALYSIS INCLUDED ON CT.GOV

Because enrollment was halted early with less than 20 subjects enrolled, only the primary endpoint will be included in CT.gov analyses

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15 REFERENCES

1. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228-47.

DocuSign Envelope ID: 5E70E8D8-99B8-4CCB-9D15-D470C5DE2254

16 APPENDICES

Appendix 1 Response Evaluation Criteria in Solid Tumors

The RECIST guidelines (Version 1.1) are described in Eisenhauer (2009)[1] and at http://www.eortc.be/Recist/Default.htm. A short summary is given below.

Measurable Disease:

Tumor lesions: measurable lesions are defined as those that can be accurately measured in at least 1 dimension (longest diameter to be recorded) with the following:

- A minimum size of 10 mm by CT scan (CT scan thickness no greater than 5 mm).
- A minimum size of 10 mm caliper measurement by clinical exam (lesions that cannot be accurately measured with calipers should be recorded as nonmeasurable).
- A minimum size of 20 mm by chest X-ray.

All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Malignant lymph nodes: to be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be not greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Nonmeasurable Disease:

All other lesions (or sites of disease), including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis), as well as truly nonmeasurable lesions, are considered nonmeasurable disease. Lesions considered truly nonmeasurable include leptomeningeal disease, ascites, pleural/pericardial effusions, inflammatory breast disease, lymphangitic involvement of skin and lung, and abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Bone Lesions

Bone lesions, cystic lesion, and lesions previously treated with local therapy require particular comment. Bone scan, PET scan, or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.

Lytic bone lesions or mixed lytic–blastic lesions with identifiable soft tissue components that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.

DocuSign Envelope ID: 5E70E8D8-99B8-4CCB-9D15-D470C5DE2254

Blastic bone lesions are nonmeasurable.

Cystic Lesions

Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor nonmeasurable) because they are, by definition, simple cysts.

Cystic lesions thought to represent cystic metastases can be considered as measurable lesions if they meet the definition of measurability described above. However, if noncystic lesions are present in the same patient, these are preferred as target lesions.

Lesions with Prior Local Treatment

Tumor lesions situated in a previous irradiated area or in an area subjected to other locoregional therapy are usually not considered measurable unless there has been demonstrated progression in the lesion.

Target Lesions

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

Nontarget Lesions

RECIST criteria require unequivocal quantification of the changes in tumor size for adequate interpretation of the sum of target lesions. Consequently, when the boundaries of the primary are difficult to delineate, this tumor should not be considered a target lesion.

Guidelines for Evaluation of Measurable Disease

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

DocuSign Envelope ID: 5E70E8D8-99B8-4CCB-9D15-D470C5DE2254

Evaluation of Target Lesions	
Complete Response	Disappearance of all target lesions. Any pathological lymph nodes (whether target or nontarget) must have reduction in short axis to < 10 mm.
Partial Response	At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD.
Stable Disease	Neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.
Progressive Disease	At least a 20% increase in the sum of the LD 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. The appearance of one or more new lesions is also considered progression.

Abbreviations: LD = longest diameter; PD = progressive disease.

Evaluation of Nontarget Lesions	
Complete Response	Disappearance of all nontarget lesions and normalization of tumor marker level.
Stable Disease/Incomplete Response	Persistence of 1 or more nontarget lesion(s) or/and maintenance of tumor marker level above the normal limits.
Progressive Disease	Appearance of 1 or more new lesions and/or unequivocal progression of existing nontarget lesions.

If tumor markers are initially above the institutional ULN, they must normalize for a patient to be considered a complete responder.

Evaluation of Best Overall Response

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

Evaluation of Best Overall Response			
Target Lesions	**Nontarget Lesions**	**New Lesions**	**Overall Response**
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR

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Evaluation of Best Overall Response			
Target Lesions	**Nontarget Lesions**	**New Lesions**	**Overall Response**
CR	Not evaluated	No	PR
PR	Non-PD or not evaluated	No	PR
SD	Non-PD or not evaluated	No	SD
Not Evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR	=	complete response
NE	=	not evaluable.
PD	=	progressive disease
PR	=	partial response
SD	=	stable disease

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having symptomatic deterioration. Every effort should be made to document the objective progression, even after discontinuation of treatment.

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of CR depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspiration/biopsy) prior to confirming the complete response status.

Confirmatory Measurement/Duration of Response

Confirmation

If a complete response (CR) or partial response (PR) is noted, confirmatory scans should be performed at least 4 weeks after response was first documented.

Duration of Overall Response

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

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

DocuSign Envelope ID: 5E70E8D8-99B8-4CCB-9D15-D470C5DE2254

Duration of Stable Disease

Stable disease (SD) is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

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STATISTICAL ANALYSIS PLAN

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Arm B: rucaparib and IMMU-132 (sacituzumab govitecan)

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DocuSign Envelope ID: C5C0CC40-0C12-4FE4-8920-9B989A36B1BA

TABLE OF CONTENTS

DocuSign Envelope ID: C5C0CC40-0C12-4FE4-8920-9B989A36B1BA

LIST OF IN-TEXT TABLES

LIST OF APPENDICES

DocuSign Envelope ID: C5C0CC40-0C12-4FE4-8920-9B989A36B1BA

ABBREVIATIONS AND SPECIALIST TERMS

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ANC	absolute neutrophil count
AST	aspartate aminotransferase
ALT	alanine aminotransferase
BID	twice daily
C_{EOI}	concentration at the end of infusion
C_{min}	minimum concentration
CRM	cohort review meeting
CR	complete response
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating cell-free tumor DNA
DLT	dose limiting toxicity
ECG	electrocardiogram
GCSF	granulocyte colony-stimulating factor
IMMU-132	sacituzumab govitecan
MTD	maximum tolerated dose
NCI	National Cancer Institute
ORR	objective response per RECIST
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PK	pharmacokinetic(s)
PR	partial response
RP2D	Recommended Phase 2 dose
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SAP	statistical analysis plan
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SI	International System of Units
StD	standard deviation
TEAE	treatment-emergent adverse event
ULN	upper limit of normal

DocuSign Envelope ID: C5C0CC40-0C12-4FE4-8920-9B989A36B1BA

1 INTRODUCTION

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2 OVERALL STUDY DESIGN, OBJECTIVES, AND ENDPOINTS

2.1 STUDY DESIGN

For the Phase 1b portion of Arm B, the plan estimated 6 to 12 dose-escalation cohorts, with a minimum of 3 patients enrolled in each cohort, followed by an expanded evaluation of the recommended phase 2 dose (RP2D) in up to 10 additional patients. Dose escalation was to follow a 3+3 design.

The initial combination dose consists of oral rucaparib 300 mg twice daily (BID), administered continuously, in combination with IV IMMU-132 6 mg/kg administration on Day 1 and Day 8 of a 21-day cycle. The dose of rucaparib was to be escalated in 100 mg BID increments up to a maximum of 600 mg BID. The dose of IMMU-132 was to be escalated in increments of 2 mg/kg, up to a maximum dose of 10 mg/kg.

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2.2 STUDY OBJECTIVES AND ENDPOINTS

Because this study was halted before phase 1b was complete, not all endpoints from the protocol will be analyzed. Table 1 outlines the objectives and endpoints planned per protocol for Phase 1b of Arm B. The final column includes the analyses to be included in the CSR.

Table 1. Primary, Secondary, and Exploratory Objectives and Endpoints for Phase 1b

Primary Objectives	**Primary Endpoints**	**Included in CSR**
To evaluate the safety and tolerability of rucaparib in combination with IMMU-132 and to determine the maximum tolerated dose (MTD) and/or the RP2D of the combination.	Incidence of AEs, clinical laboratory abnormalities, dose modifications, and listings of ECGs and vital signs	AEs, some clinical laboratories, and dose modifications will be included
Secondary Objectives	**Secondary Endpoints**	
To characterize the PK of IMMU-132 and its metabolites when rucaparib and IMMU-132 agent are co-administered.	Plasma concentration at trough (C_{min}) and at the end of infusion (C_{EOI})	Not included in CSR
To evaluate the preliminary efficacy of rucaparib in combination with IMMU-132 in various solid tumors.	Objective response per RECIST v1.1 (ORR)	Included in the CSR
Exploratory Objectives	**Exploratory Endpoints**	
To assess tumor tissue biomarkers that correlate with response to the combination.	Not defined in protocol	Not included in CSR
To evaluate circulating cell-free tumor DNA (ctDNA) as a molecular marker of response to the combination.	Not defined in protocol	Not included in CSR
To evaluate biomarkers associated with resistance to the combination.	Not defined in protocol	Not included in CSR
To assess genomic changes over time in plasma and tumor samples.	Not defined in protocol	Not included in CSR
To determine steady-state exposure of rucaparib by sparse PK sampling.	Not defined in protocol	Not included in CSR
To evaluate the development of anti-drug antibodies (ADAs).	Not defined in protocol	Not included in CSR

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2.3 SAMPLE SIZE JUSTIFICATION

For Arm B Phase 1b, it was estimated that up to 55 patients would be enrolled following a standard 3+3 design, dependent upon the occurrence of safety findings, specifically DLTs, observed at the different dose levels. 6 subjects were enrolled before the study was halted.

3 GENERAL ANALYSIS CONVENTIONS

Quantitative variables will typically be summarized using frequencies and percentages for appropriate categorizations and may also be summarized using descriptive statistics. For variables summarized with descriptive statistics, the following will be presented: N, mean, standard deviation (StD), median, minimum, and maximum. Categorical variables will be presented using frequencies and percentages.

Baseline is defined as the last measurement on or prior to the first dose of rucaparib administration, unless otherwise specified.

All statistical analyses will be conducted with the SAS® System, Version 9.4 or higher.

3.1 ANALYSIS POPULATIONS

The following analysis populations are defined for the study:

Safety Population: All patients who have received at least 1 dose of rucaparib or IMMU-132.

DLT-evaluable Population: All patients in Phase 1b who have either received at least 80% of the planned doses of rucaparib and both planned infusions of IMMU-132 without having experienced a DLT or who experienced a DLT during Cycle 1. If a patient withdrew from the study without having met any of these criteria, then an additional patient was enrolled in that dose cohort.

Efficacy Population: All patients who have received at least 1 dose of rucaparib or IMMU-132 and who have measurable disease per RECIST v1.1 at baseline.

4 PATIENT DISPOSITION

Patient disposition will be summarized using frequency counts and the corresponding percentages. The number of patients in each analysis population, number of patients discontinued, and the primary reason for treatment discontinuation will be summarized.

DocuSign Envelope ID: C5C0CC40-0C12-4FE4-8920-9B989A36B1BA

5 PROTOCOL DEVIATIONS

Protocol deviations will not be analyzed in Arm B of the SEASTAR study.

6 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

All demographic will be summarized for the safety population.

6.1 DEMOGRAPHICS

The demographic variables will be summarized with frequency tabulations and descriptive statistics. The demographic variables presented will include age, height, weight and sex using the following categorizations:

- Age (years): ≤ 50, 51-60, 61-70, 71-80, 81-90, > 90;
- Height (cm): ≤ 75, > 75-100, > 100-125, > 125-150, > 150-175, > 175;
- Weight (kg): ≤ 50, > 50-75, > 75-100, > 100-125, > 125-150, > 150
- Sex: Male, Female

6.2 BASELINE CLINICAL CHARACTERISTICS

No baseline disease characteristics will be analyzed in the CSR.

6.3 MEDICAL HISTORY

In a change from the protocol, medical history events will not be analyzed.

7 DOSE-LIMITING TOXICITIES

A summary of the number of DLTs by dose level and a patient listing of all DLTs will be provided for the patients in the DLT-evaluable population. A DLT is defined at any of the following events occurring in Cycle 1, according to CTCAE version 5.0:

- Grade 3 or greater febrile neutropenia (i.e., fever > 38.3°C with Absolute Neutrophil Count (ANC) < 1.0 × 109/L) of any duration;
- Grade 3 or 4 neutropenia lasting more than 7 days despite granulocyte colony-stimulating factor (GCSF) administration; Grade 3 thrombocytopenia (platelets < 50 × 10^9/L) with significant bleeding or Grade 4 thrombocytopenia (platelets < 25 × 10^9/L) ≥ 5 days duration;
- Grade 4 anemia (i.e., life-threatening consequences; urgent intervention indicated) or any anemia (regardless of grade or severity) requiring a blood transfusion;
- Any nonhematological AE ≥ Grade 3, with the exception of:

DocuSign Envelope ID: C5C0CC40-0C12-4FE4-8920-9B989A36B1BA

  - Nausea, vomiting, and diarrhea if well controlled by systemic medication and with duration ≤ 48 hrs;
  - Fatigue;
  - Grade 3 alanine aminotransferase (ALT) or aspartate aminotransferase (AST) not accompanied by a concomitant increase in total bilirubin above the upper limit of normal (ULN). Note: any Grade 4 ALT/AST is a DLT.
- Any Grade 3 or greater infusion-related reaction that fails to resolve within 4 hours despite optimal medical management.

8 STUDY DRUG EXPOSURE AND COMPLIANCE

The following variables will be summarized:

- Duration of treatment (days)
- Number of dose reductions
- Number of dose interruptions

Duration of treatment will be calculated as 1+ the number of days from earliest study drug start date to date of last study drug discontinuation. Descriptive statistics and frequencies/percentages for appropriate categorizations will be used to summarize study drug exposure variables.

9 PRIOR AND CONCOMITANT MEDICATIONS

Prior and concomitant medications will not be analyzed in the CSR.

10 EFFICACY ANALYSIS

Efficacy analyses will be performed using the efficacy population.

Overall objective response to treatment according to RECIST v1.1 as assessed by the investigator will be listed along with target lesion measurements and response, non-target lesion response, and assessment of new lesions. Confirmation of a complete response (CR) or partial response (PR) is a response that is maintained and documented on a subsequent tumor assessment no less than 4 weeks after initial response and will be indicated on the listing. Duration of response will also be calculated as the time from the date that a confirmed PR or CR is first recorded until the first date that progressive disease (PD) is documented per RECIST v1.1. Duration of stable disease (SD) will be calculated from the start of treatment to the first PD if the subject had a best response of SD.

A listing of all tumor scan details collected, including ORR, in the clinical database will be provided.

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11 EXPLORATORY ANALYSIS

No exploratory endpoints will be analyzed in the CSR.

12 PHARMACOKINETIC ANALYSIS

PK analyses, including the secondary endpoint, will no longer be included in the CSR due to the early termination of the study.

13 SAFETY ANALYSIS

The safety analyses will be performed using the safety population.

13.1 ADVERSE EVENTS

Adverse events (AEs) will be classified using the MedDRA classification system. The severity of the toxicities will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0 whenever possible. Treatment-emergent adverse events (TEAEs) are defined as AEs with onset date on or after the date of first dose of study medication until the date of the last study medication dose plus 28 days. Adverse events will be considered treatment-emergent if all or part of the date of onset of the AE is missing and it cannot be determined if the AE meets the definition for treatment-emergent.

The number and percentage of patients who experienced TEAEs for each system organ class and preferred term will be presented. Multiple instances of the TEAE in each system organ class and multiple occurrences of the same preferred term are counted only once per patient. The number and percentage of patients with at least one TEAE will also be summarized.

The incidence of TEAEs will also be summarized by relationship to study drug according to the following categories: “treatment-related,” or “not treatment-related” for each study drug. If a patient experiences multiple occurrences of the same AE with different relationship categories, the patient will be counted once, as a relationship category of treatment-related.

If a patient experiences multiple occurrences of the same AE with different toxicity grades, the patient will be counted once for the maximum (most severe) toxicity grade. AEs with a missing toxicity grade will be presented in the summary table with a toxicity grade of “Missing.” For each toxicity grade, the number and percentage of patients with at least one TEAE of the given grade will be summarized.

Separate tables will be presented including but not limited to:

- All TEAEs;
- TEAEs by CTCAE grade;
- Grade 3 or greater TEAEs;

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- Treatment-related TEAEs, overall and by categories: CTCAE grade, grade 3 or greater, resulting in dose reduction, resulting in dose interruption, resulting in dose discontinuation, outcome of death;
- Serious TEAEs;
- TEAEs with an outcome of death;
- TEAEs leading to discontinuation of study medication;
- TEAEs resulting in interruption of study medication; and
- TEAEs resulting in reduction, delay, or interruption of study medication.

13.2 Clinical Laboratory Evaluations

Clinical laboratory evaluations include the continuous variables for hematology, chemistry, and urinalysis. The laboratory values will generally be presented in International System (SI) units. The on-treatment period will be defined as the time from earliest first dose to 28 days after the last dose of rucaparib or IMMU-132, whichever is last. Hematology values collected will be listed. Descriptive summaries, and all chemistry and urinalysis parameters, mentioned in the protocol will not be included in the analysis.

13.3 Vital Signs

Vital signs will not be analyzed in this study.

14 Statistical / analytical issues

14.1 Handling of Dropouts or Missing Data

All data will be used to their maximum possible extent, but without any imputations for missing data.

14.2 Pooling of Centers in Multi-Center Studies

All centers will be pooled for analysis.

14.3 Multiple Comparison / Multiplicity

No statistical comparisons will be performed.

14.4 Examination of Subgroups

Analyses of primary and secondary endpoints may be analyzed by starting dose. No additional subgroup analyses will be performed.

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14.5 INTERIM ANALYSES AND DATA MONITORING

No formal interim analyses were planned outside standard Cohort Review Meetings (CRM). CRMs were held for the first 2 dose cohorts and the decision was made to forgo exploration of any other dose cohorts.

DocuSign Envelope ID: C5C0CC40-0C12-4FE4-8920-9B989A36B1BA

15 REFERENCES

1. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228-47.

DocuSign Envelope ID: C5C0CC40-0C12-4FE4-8920-9B989A36B1BA

16 APPENDICES

Appendix 1 Response Evaluation Criteria in Solid Tumors

The RECIST guidelines (Version 1.1) are described in Eisenhauer (2009)[1] and at http://www.eortc.be/Recist/Default.htm. A short summary is given below.

Measurable Disease:

Tumor lesions: measurable lesions are defined as those that can be accurately measured in at least 1 dimension (longest diameter to be recorded) with the following:

- A minimum size of 10 mm by CT scan (CT scan thickness no greater than 5 mm).
- A minimum size of 10 mm caliper measurement by clinical exam (lesions that cannot be accurately measured with calipers should be recorded as nonmeasurable).
- A minimum size of 20 mm by chest X-ray.

All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Malignant lymph nodes: to be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be not greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Nonmeasurable Disease:

All other lesions (or sites of disease), including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis), as well as truly nonmeasurable lesions, are considered nonmeasurable disease. Lesions considered truly nonmeasurable include leptomeningeal disease, ascites, pleural/pericardial effusions, inflammatory breast disease, lymphangitic involvement of skin and lung, and abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Bone Lesions

Bone lesions, cystic lesion, and lesions previously treated with local therapy require particular comment. Bone scan, PET scan, or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.

Lytic bone lesions or mixed lytic–blastic lesions with identifiable soft tissue components that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.

DocuSign Envelope ID: C5C0CC40-0C12-4FE4-8920-9B989A36B1BA

Blastic bone lesions are nonmeasurable.

Cystic Lesions

Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor nonmeasurable) because they are, by definition, simple cysts.

Cystic lesions thought to represent cystic metastases can be considered as measurable lesions if they meet the definition of measurability described above. However, if noncystic lesions are present in the same patient, these are preferred as target lesions.

Lesions with Prior Local Treatment

Tumor lesions situated in a previous irradiated area or in an area subjected to other locoregional therapy are usually not considered measurable unless there has been demonstrated progression in the lesion.

Target Lesions

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

Nontarget Lesions

RECIST criteria require unequivocal quantification of the changes in tumor size for adequate interpretation of the sum of target lesions. Consequently, when the boundaries of the primary are difficult to delineate, this tumor should not be considered a target lesion.

Guidelines for Evaluation of Measurable Disease

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

DocuSign Envelope ID: C5C0CC40-0C12-4FE4-8920-9B989A36B1BA

Evaluation of Target Lesions	
Complete Response	Disappearance of all target lesions. Any pathological lymph nodes (whether target or nontarget) must have reduction in short axis to < 10 mm.
Partial Response	At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD.
Stable Disease	Neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.
Progressive Disease	At least a 20% increase in the sum of the LD 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. The appearance of one or more new lesions is also considered progression.

Abbreviations: LD = longest diameter; PD = progressive disease.

Evaluation of Nontarget Lesions	
Complete Response	Disappearance of all nontarget lesions and normalization of tumor marker level.
Stable Disease/Incomplete Response	Persistence of 1 or more nontarget lesion(s) or/and maintenance of tumor marker level above the normal limits.
Progressive Disease	Appearance of 1 or more new lesions and/or unequivocal progression of existing nontarget lesions.

If tumor markers are initially above the institutional ULN, they must normalize for a patient to be considered a complete responder.

Evaluation of Best Overall Response

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

Evaluation of Best Overall Response			
Target Lesions	**Nontarget Lesions**	**New Lesions**	**Overall Response**
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR

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Evaluation of Best Overall Response			
Target Lesions	**Nontarget Lesions**	**New Lesions**	**Overall Response**
CR	Not evaluated	No	PR
PR	Non-PD or not evaluated	No	PR
SD	Non-PD or not evaluated	No	SD
Not Evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR	=	complete response
NE	=	not evaluable.
PD	=	progressive disease
PR	=	partial response
SD	=	stable disease

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having symptomatic deterioration. Every effort should be made to document the objective progression, even after discontinuation of treatment.

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of CR depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspiration/biopsy) prior to confirming the complete response status.

Confirmatory Measurement/Duration of Response

Confirmation

If a complete response (CR) or partial response (PR) is noted, confirmatory scans should be performed at least 4 weeks after response was first documented.

Duration of Overall Response

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

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

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Duration of Stable Disease

Stable disease (SD) is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.