ImmunoGen, Inc.

Protocol #: IMGN853-0417

A Phase 3, Single Arm Study of Mirvetuximab Soravtansine in Platinum-Resistant, Advanced High-Grade Epithelial Ovarian, Primary Peritoneal, or Fallopian Tube Cancers with High Folate Receptor-Alpha Expression

Statistical Analysis Plan

Version 2.0
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LIST OF ABBREVIATIONS

Abbreviation or Specialist Term	Explanation
ADA	Anti-drug antibodies
AE	Adverse event
AIBW	Adjusted ideal body weight
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BICR	Blinded Independent Central Review
BOR	Best overall response
BRCA	Breast cancer susceptibility gene
C1D1	Cycle 1 Day 1
CA-125	Cancer antigen 125
CI	Confidence interval
CR	Complete response
CTCAE	Common Terminology Criteria for Adverse Events
DOR	Duration of response
ECG	Electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EOC	Epithelial ovarian cancer
EOS	End of Study
FRα	Folate receptor alpha
GCIG	Gynecologic Cancer Intergroup
IMGN	ImmunoGen
LOQ	Limit of Quantitation
MedDRA	Medical Dictionary for Regulatory Activities
MIRV	mirvetuximab soravtansine
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PK	Pharmacokinetics
PR	Partial response

Abbreviation or Specialist Term	Explanation
PROC	Platinum resistant ovarian cancer
PT	Preferred term
Q3W	Every 3 weeks
RECIST	Response Evaluation Criteria in Solid Tumors
RMST	Restricted mean survival time
SAE	Serious adverse event
SAP	Statistical analysis plan
SMQ	Standard MedDRA Query
SOC	System organ class
TBILI	Total bilirubin
TEAE	Treatment-emergent adverse event
TTR	Time to response
ULN	Upper limit of normal
WHO Drug	World Health Organization Drug Dictionary

1. INTRODUCTION

1.1. Background

This Statistical Analysis Plan (SAP) is based on Amendment 2 of Protocol IMGN853-0417, dated 28August2020.

A brief history of protocol amendments is presented in Table 1.

Table 1: History of Protocol Amendments

Version	Approval Date	Salient Changes (if any)*
Original Protocol	23October2019	N/A
Amendment 1	18December2019	Increased sample size from 91 to 105
Amendment 2	28August2020	N/A

*Changes expected to require accommodation in analysis plan.

This SAP will govern the analysis of study data. The plan for the primary efficacy analysis and all other analyses may be modified prior to final database lock. Any deviations from the SAP will be documented as such in the study report.

2. STUDY DESIGN

2.1. Protocol Objectives

2.1.1. Primary Objective

- To determine the efficacy of mirvetuximab soravtansine (MIRV) in patients with platinum resistant ovarian cancer (PROC) and high folate receptor-α (FRα) expression.

2.1.2. Secondary Objectives

2.1.2.1. Key Secondary Objectives:

- To determine the durability of response to MIRV in patients with PROC and high FRα expression.

2.1.2.2. Additional Secondary Objectives:

- To evaluate the safety and tolerability of MIRV.
- To further characterize the clinical activity of MIRV in patients with PROC and high FRα expression.

2.1.2.3. Exploratory Objectives

- [redacted]
- [redacted]

[redacted]

2.1.3. Study Endpoints

2.1.3.1. Primary Endpoint

- Objective response rate (ORR): includes best response of complete response (CR) or partial response (PR) as assessed by the Investigator.

2.1.3.2. Key Secondary Endpoint

- Duration of response (DOR), defined as the time from initial Investigator-assessed response (CR or PR) until PD as assessed by the Investigator.

2.1.3.2.1. Additional Secondary Endpoints:

- Treatment-emergent adverse events (TEAEs) and laboratory test results, physical examination, or vital signs.
- CA-125 response determined using the GCIG criteria defined in Protocol IMGN853-0417, Appendix C. CA-125 response per GCIG criteria will be determined programmatically.
- Progression-free survival (PFS): defined as the time from first dose of MIRV until Investigator-assessed radiological PD or death, whichever occurs first.
- Overall survival (OS), defined as the time from first dose of MIRV until the date of death. Patients alive at the time of analysis will be censored at the last date known to be alive.
- ORR, DOR, and PFS by blinded independent central review (BICR) will be summarized as sensitivity analysis.

2.1.3.3. Exploratory Endpoints

[redacted]

2.2. Study Overview

This study is designed to evaluate the efficacy and safety of MIRV in women with PROC and high FRα expression.

Eligible patients will receive MIRV 6 mg/kg AIBW Q3W until disease progression, unacceptable toxicity, withdrawal of consent, death, or until the Sponsor terminates the study (whichever comes first).

Tumor assessments, including radiological assessments by CT/MRI scans will be performed at Screening and subsequently every 6 (±1) weeks from C1D1 for the first 36 weeks then every 12 (±3) weeks until disease progression, death, the initiation of subsequent anticancer therapy, or patient's withdrawal of consent, whichever occurs first. CT/MRI scans will be collected for sensitivity analysis by blinded independent central review (BICR).

Patients who discontinue MIRV for reasons other than progressive disease (PD) will continue with tumor assessments until documentation of PD or the start of new anticancer therapy, whichever comes first.

All patients who discontinue MIRV will be followed for survival every 3 months (±1 month) until death, lost to follow-up, withdrawal of consent for survival follow-up, or End of Study (EOS), whichever comes first.

2.2.1. Study Population

All patients must have confirmed diagnosis of high-grade serous EOC, primary peritoneal cancer, or fallopian tube cancer. Patients must also have the following:

- Patients must have at least 1 lesion that meets the definition of measurable disease by RECIST v1.1 (radiologically measured by the Investigator).
- Patients must have received at least 1 but no more than 3 prior systemic lines of anticancer therapy, including at least 1 line of therapy containing bevacizumab, and for whom single-agent therapy is appropriate as the next line of treatment.
- Patient's tumor must be positive for FRα expression as defined by the Ventana FOLR1 (FOLR-2.1) CDx assay.

See Protocol IMGN853-0417, Section 3.1 for a complete list of the inclusion/exclusion criteria.

2.2.2. Power and Sample Size

The primary endpoint of this study is ORR as assessed by the investigator. The study is designed to test the null hypothesis that the ORR is 12% (Eisenhauer 2009, Pujade-Lauraine 2014). The ORR will be estimated using the efficacy evaluable population as defined in Section 3.12.3.

Approximately 110 patients will be enrolled so that a total of 105 patients will be efficacy evaluable. A sample size of 105 efficacy evaluable patients achieves 90% power to detect a difference in ORR of 12% (24% vs 12%) using a one-sided binomial test. The target significance level (one-sided α level) is 0.025. The actual significance level achieved by this test is 0.0242. These results assume that the ORR is 12% under the null hypothesis and 24% under the alternative hypothesis.

2.2.3. Treatment Randomization and Blinding

Randomization and blinding are not applicable in this single-arm, open-label study.

2.2.4. Assessment Schedule

See Protocol IMGN853-0417, Table 2 for study schedule of assessments.

2.3. Interventions

2.3.1. Clinical Trial Material

MIRV will be administered at 6 mg/kg AIBW as an IV infusion following preparation as outlined in the Pharmacy Manual on day 1 of every 3-week cycle.

The protocol provides additional details in Protocol IMGN853-0417, Section 5.4.

3. GENERAL ANALYTICAL CONSIDERATIONS

3.1. Data Sources

Data will be captured using validated, electronic data capture (EDC) systems. Data will be documented in various source documents (eg, the patient medical chart) and then manually entered into the clinical trial database. Protocol IMGN853-0417, Section 11 provides additional details regarding data recording and handling.

3.2. Definition of Baseline

Study Day 1 (ie, Cycle 1 Day 1) will be designated as the first day a patient receives MIRV. The baseline value is defined as the last non-missing value on or before the date of first dose of MIRV.

3.3. Missing Data

Partial dates are allowed in the clinical database for subsequent anti-cancer therapy start date, adverse event (AE) onset and resolution dates, concomitant medication start and stop dates, and concomitant procedure dates. An entry for the year is required in the clinical database for each of these dates. Only the month and day may be entered as unknown. Prior anticancer systemic therapy start and stop dates and subsequent anticancer therapy stop date allows for unknown dates in the clinical database. Dates from these forms will be reported in listings as collected. Every effort will be made to query missing dates.

For records with missing AE onset date, the following procedure will be employed for use in determining whether the AE is treatment emergent:

- AE onset dates with missing day and non-missing month will be assumed to occur on the first day of the non-missing month, except for AEs occurring in the first month of dosing, in which case the date will be the first day of dosing.

- AE onset dates with missing month will be assumed to occur on the first day of the non-missing year (ie, January 1), except for AEs occurring in the first year of dosing, in which case the date will be the first day of dosing.

For records with a missing medication start and/or stop date, the following procedure will be employed for use in determining whether the medication is prior or concomitant:

- Medication start dates with a missing day and non-missing month will be assumed to occur on the first day of the non-missing month, except for medications occurring in the first month of dosing, in which case the date will be the first day of dosing.
- Medication start dates with missing month will be assumed to occur on the first day of the non-missing year (ie, January 1), except for medications occurring in the first year of dosing, in which case the date will be the first day of dosing.
- Medications that are not ongoing and have a medication stop date with a missing day and non-missing month will be assumed to occur on the last day of the non-missing month.
- Medications that are not ongoing and have a medication stop date with a missing month will be assumed to occur on the last day of the non-missing year (ie, December 31).

For records with a missing procedure date, the following procedure will be employed for use in determining whether the procedure is prior or concomitant:

- Procedure dates with a missing day and non-missing month will be assumed to occur on the first day of the non-missing month, except for procedures occurring in the first month of dosing, in which case the date will be the first day of dosing.
- Procedure dates with missing month will be assumed to occur on the first day of the non-missing year (ie, January 1), except for procedures occurring in the first year of dosing, in which case the date will be the first day of dosing.

For records with a missing prior anti-cancer systemic therapy start and/or stop date, and/or disease progression date from prior therapy, the following procedure will be employed for use in calculating the platinum-free interval (PFI):

- If the stop date of prior platinum therapy is completely missing OR only the year is available, the PFI will be set as missing.
- If both year and month of stop date of prior platinum therapy are available and only day is missing, the stop date will be imputed by the first day of the month.
- If the disease progression date from prior platinum therapy is completely missing OR only the year is available, the PFI will be set as missing.
- If both year and month of disease progression date from prior platinum therapy are available and only day is missing, the date of disease progression will be imputed by the last day of the month.

For records with a missing subsequent anti-cancer therapy start date, the following procedure will be employed for use in deriving efficacy variables such as PFS and BOR.

- The start date of subsequent anti-cancer therapy will be imputed by the earliest possible date that is not contradicting with any other available data in the database.

For records with a partial death date, the following procedure will be employed for use in deriving time to event variables (PFS, OS, DOR).

- The death date will be imputed by the earliest possible date that is not contradicting with any other available data in the database.

All other data will be reported as they are collected. No imputation methods will be used to replace missing data unless otherwise stated in this document.

3.4. Multiple Assessments for the Same Assessment Time Point

In the case of multiple observations at a specific visit, the first non-missing measurement will be used for analysis, unless multiple study assessments are expected (eg, pre-dose vs post-dose). When multiple study assessments are expected, the first non-missing measurement for the visit and assessment time point will be used for analysis.

3.5. Multiple Study Centers

No adjustment for study center is planned.

3.6. Covariate Adjustment in Primary Analysis

No covariate adjustment will be made.

3.7. Sample Size Reassessment

Not applicable.

3.8. Interim Analyses

No interim analysis is planned for this study.

3.9. Timing of Final Analysis

To allow for reasonable duration on treatment to achieve a confirmed response, the final analysis for ORR will be conducted after all efficacy evaluable patients (defined in Section 3.12.3) have:

- undergone at least 4 post-baseline tumor assessments, or
- experienced radiological disease progression, or
- died or had clinical progression within 105 days of first dose of MIRV, or
- withdrawn from study for other reasons

It is estimated that the final analysis will be conducted approximately 6 months after the last patient is enrolled.

3.10. Test Sizes

For the primary endpoint of ORR, the null hypothesis that ORR is 12% will be tested against 1-sided Type I error (α) of 0.025. This study will reject the null hypothesis if the lower bound of 95% (2-sided) confidence interval (CI) for ORR is greater than 12%.

3.11. Hypothesis Testing and Multiple Comparisons

3.11.1. Primary Endpoint

In this single-arm study, hypothesis testing for the primary endpoint of ORR is performed using a confidence interval approach. Instead of reporting a p-value, 95% CI will be reported. Multiple comparison is not applicable.

3.11.2. Secondary Endpoints

The secondary endpoints of DOR, GCIG CA-125 response rate, PFS, and OS will be evaluated to further characterize the efficacy of MIRV. No formal hypothesis testing will be performed on secondary endpoints.

3.12. Analysis Populations

Six (6) analysis populations will be defined for use with various analyses. Table 2 illustrates the relationship between each population and the analyses for which the data from the population will be used. Baseline and patient disposition analyses will be conducted on efficacy evaluable population only if there is at least 5% difference between safety population and efficacy evaluable population.

Table 2: Analysis Populations

Analysis Population	Analysis					
	Reason for Screen Failure	Baseline	Patient Disposition	Efficacy	Safety	PK Analysis
Screened	X					
Safety		X	X		X	
Efficacy Evaluable by Investigator				X		
Efficacy Evaluable by BICR				X		
CA-125 Evaluable				CA-125 only		
PK Analysis Population						X

3.12.1. Screened

The Screened population includes all patients entered into the clinical database who have signed an informed consent.

3.12.2. Safety Population

All patients who received at least 1 dose of MIRV will be included in the Safety population.

3.12.3. Efficacy Evaluable Population

The Efficacy Evaluable population is defined as all patients in the Safety population who have measurable disease at baseline.

- Efficacy evaluable population for efficacy measurements based on investigator's assessment (ORR, DOR, PFS per investigator): this population includes all patients in the safety population who have measurable disease at baseline per investigator.
- Efficacy evaluable population for efficacy measurements based on BICR assessment (ORR, DOR, PFS per BICR): this population includes all patients in the safety population who have measurable disease at baseline per BICR.

3.12.4. CA-125-Evaluable Population

The CA-125-Evaluable population is defined as all patients in the Safety population whose pretreatment sample is ≥ 2.0 times the upper limit of normal (ULN), within 2 weeks prior to first dose of MIRV, and who have at least 1 post-baseline CA-125 evaluation.

3.12.5. PK Analysis Population

The PK analysis population is defined as all patients who have at least one non-missing PK concentration data point.

3.13. Data Display Characteristics

Data displays produced for this study will include summary tables, data listings, and figures.

Data listings will report the data reported in the clinical database or derived for each patient. Data will be ordered by patient number, and date/time of assessment if applicable. When expedient, additional levels of ordering hierarchy may reflect subsets of assessments within patient. Data listings will not display patient initials.

Summary tables will display summary statistics calculated for the analysis population, unless described otherwise.

The summary statistics displayed will be a function of the type of data associated with the summarized assessment. Unless stated otherwise, continuous data will be summarized with the number of non-missing values, mean, standard deviation, minimum, median, and maximum. Categorical data will be summarized with the number of non-missing values and the numbers of values equal to each of the possible values. Percentages of patients with each of the possible values will be calculated from the number of patients in the corresponding analysis population, unless stated otherwise. Some continuous variables may also be grouped into categorical levels and evaluated in frequency tables.

4. PATIENT ACCOUNTABILITY

4.1. Patient Characteristics

Patient characteristics will be summarized and listed for the Safety population. These summaries will also be produced for the Efficacy Evaluable population if more than 5% of patients in the Safety population are excluded from the Efficacy Evaluable population.

4.1.1. Demography

Data collected about the following patient characteristics at the screening visit will be summarized as follows:

- Age is collected in the clinical database at the time of patient registration. As this is a global study, there are certain regions where local regulations prohibit the collection of a complete date of birth. Therefore, age will not be recalculated for analysis purposes. The collected age will be used for summarization.
- Sex
  - Childbearing potential (female only, yes/no)
- Ethnicity
- Race

All demography data, including informed consent date, will be listed.

4.1.2. Baseline Height, Weight, and AIBW

Baseline height, weight, and AIBW will be summarized and presented in a listing.

4.1.3. Medical History

Medical history will be coded using Medical Dictionary for Regulatory Affairs (MedDRA) (Version 24.0) and graded using Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0, associating lower-level terms with preferred terms (PTs) and system organ classes (SOCs) by the primary hierarchy. Medical histories will be summarized as the number and percentage of patients who reported at least 1 medical history event; and number and percentage of patients who reported at least 1 medical history event in each SOC. Within each SOC, tables will display the number and percentage of patients reporting at least 1 medical history event as designated by PT. All medical history information will also be listed.

4.1.4. Disease Characteristics, Prior Therapy, and Gene Mutations

Listings of all collected data related to disease characteristics and prior therapy will be provided. A summary of the following elements will also be provided:

- ECOG performance status (0/1)
- Primary diagnosis (epithelial ovarian cancer, fallopian tube cancer, primary peritoneal cancer, other)
- Histology

- Disease stage at initial diagnosis
- Histologic grade
- Prior radiotherapy (yes/no)
- Prior systemic therapy
  - The number of prior systemic therapies is defined as the number of distinct treatment regimens.
- Prior cancer related surgery (yes/no)
- Prior exposure to doxorubicin (yes/no), topotecan (yes/no), taxanes (yes/no)
- Prior exposure to PARP inhibitors (yes/no/uncertain)
  - If patient participated in a double-blind randomized trial comparing PARP inhibitor to placebo and the actual treatment was unknown, patient will be summarized under 'uncertain' category.
- Any *BRCA* mutations (yes [*BRCA1*, *BRCA2*]/no)
- Primary platinum-free interval (months, ≤12 months vs >12 months)
  - Defined as time from last dose of 1st line platinum therapy to the date of disease progression and/or relapse following 1st line therapy.
- Platinum-free interval (months, ≤3 months vs >3-6 months, vs >6 months)
  - Defined as time from last dose of latest line platinum therapy to the date of disease progression and/or relapse following that line of therapy.

4.2. Patient Disposition

4.2.1. Screened and Treated Patients

The number and percentage of patients who were screened, treated (Safety population), not treated (screen failure), and reason for screen failure will be summarized overall, and by geographic region, country, and site.

4.2.2. Patient Disposition

A summary of patient disposition will summarize, for the Safety population, the number of patients treated and the reason for treatment and study discontinuation. This summary will also be produced for the Efficacy Evaluable population by Investigator if more than 5% of patients in the Safety population are excluded from the Efficacy Evaluable population.

Percentage of patients who withdrew for each reason on the End-of-Treatment and End-of-Study forms will be calculated using all members of the relevant population for the denominator.

The number and percentage of Safety population included in each analysis population defined in Section 3.12 will be presented. This table will be produced for all patients at all sites, pooled.

4.2.3. Protocol Deviations and Population Inclusions

Protocol deviations will be captured in a protocol deviation log. A summary of the number of patients with any protocol deviation will be provided for the Safety population.

Major protocol deviations will also be summarized in these categories:

- Patients entered the study even though they did not satisfy the entry criteria.
- Patients received incorrect dose.
- Major deviations that affect safety and/or efficacy endpoints assessments.
- Major deviations due to Covid-19 pandemic.
- Deviations that impact the principles of ICH GCP regarding patient rights, safety, and well-being.
- Other important deviations not otherwise described that may significantly affect a subject's rights, safety, or well-being.

5. EFFICACY ANALYSES

The main efficacy analyses will use data from the Efficacy Evaluable population based on investigator's assessment. Sensitivity analyses will be performed with BICR assessment.

5.1. Efficacy Outcomes

5.1.1. Best Overall Response

Best overall response (BOR) for a patient is the best response designation as assessed by the Investigator recorded between the date of first dose of MIRV and the date of objectively documented PD per RECIST Version 1.1, the date of the start of new anti-cancer therapy, or the date of study discontinuation, whichever occurs first. When an analysis cutoff date is implemented, only radiological assessments occurring on or prior to the cutoff date will be used for analysis. Patients with an overall response of CR or PR must have a repeat tumor assessment performed no less than 4 weeks (28 days) after the criteria for response are first met. When stable disease is the best overall response, it must meet the minimum duration of 35 days (6 weeks – 1-week window = 35 days from the date of first dose of MIRV). The confirmatory scan is valid following treatment discontinuation if the patient has not started a new anti-cancer therapy.

5.1.1.1. ORR

The ORR will be calculated as the number of patients with a confirmed BOR of CR or PR divided by the number of patients in the Efficacy Evaluable population. Patients without at least 1 post-baseline RECIST assessment will be treated as non-responders (ie, these patients will contribute to the denominator, but not the numerator).

5.1.1.2. DOR

DOR is defined as the time from the date of the first response (CR or PR), whichever occurs first, to the date of PD or death from any cause, whichever occurs first. DOR is only defined for patients who have a confirmed BOR of CR or PR.

Per the BOR definition, patients with an overall response of CR or PR must have a repeat tumor assessment performed no less than 4 weeks after the criteria for response are first met. The first

date at which a CR or PR response was noted will be used to calculate DOR, not the date of the confirmatory tumor assessment.

Patients who started a new anti-cancer therapy prior to documented PD or death will be censored at the last radiological assessment prior to initiation of new anti-cancer therapy. Patients who did not have PD or death will be censored at the date of their last radiological assessment. Patients who had PD or death after missing 2 or more consecutive radiological assessments (PD or death date - last radiological assessment date +1 ≥ 105 days) will be censored at the date of their last radiological assessment before the missing radiological assessment. When an analysis cutoff date is implemented, only data (deaths or radiological assessments) occurring on or before the cutoff date will be used for analysis.

5.1.1.3. Time to Response

Time to response (TTR) is defined as the time from the date of first dose of MIRV until the date of the first observed CR or PR. TTR is only defined for patients who have a confirmed BOR of CR or PR.

5.1.2. PFS

PFS is defined as the time from the date of first dose of MIRV until the date of PD or death from any cause, whichever occurs first. PFS is defined based on radiological assessments and determined by the Investigator. Clinical progression is not considered a progression endpoint.

Table 3 summarizes the rules to be used for PFS. When an analysis cutoff date is implemented, only data (deaths and radiological assessments) occurring on or prior to the cutoff date will be used for analysis.

Table 3: PFS Definitions

Situation	Date of PFS[a] Event or Censoring	Outcome
No post-baseline radiological assessments, and patient did not die within 105 days of first dose	Date of first dose	Censored
No post-baseline radiological assessments, and patient died within 105 days of first dose	Date of death	Death
Death	Date of death	Death
Radiological Progression	Date of first radiological assessment indicating progression (ie, OR = PD).	Progression
New anti-cancer therapy prior to PD or death (including palliative radiotherapy during study treatment)	Date of last radiological assessment prior to the start of the new anticancer therapy	Censored
No death or PD	Date of last radiological assessment	Censored
PD or death after missing 2 or more consecutive radiological assessments (PD or death date - last radiological assessment date +1 ≥ 105 days)	Date of last adequate radiological assessment showing no PD	Censored

Abbreviations: OR = overall response; PD = disease progression; PFS = progression-free survival.
[a] Includes radiographic progression only.

5.1.3. OS

OS is defined as the time from the date of first dose until the date of death from any cause.

Patients who are alive or lost to follow-up at the analysis are censored at the last known date at which they were known to be alive. When an analysis cutoff date is implemented, only deaths occurring on or before the cutoff date are counted as OS events. Patients whose date of death or the last date at which the patient was known to be alive (eg, after the data cutoff date) will be censored at the analysis cutoff date.

5.1.4. GCIG CA-125 Response

A GCIG CA-125 response is defined as a ≥ 50% reduction in CA-125 levels from baseline. The response must be confirmed and maintained for at least 28 days. The CA-125 response will be conducted using the CA-125-Evaluable population. The date of response corresponds to the date when the CA-125 level is first reduced by 50%. The summary table for CA-125 will include the number (percentage) of patients in the CA-125-Evaluable population, and that number will then be used as the denominator for CA-125 response rate.

5.2. Primary Efficacy Outcome Analysis

The primary endpoint of ORR will be calculated based on the Efficacy Evaluable population and its 95% exact CI will be estimated using the Clopper-Pearson method.

5.3. Secondary Efficacy Analyses

5.3.1. Key Secondary Efficacy Analysis

The key secondary endpoint of DOR will be summarized in patients with a confirmed BOR of CR or PR only.

The distribution of DOR will be summarized using the Kaplan-Meier method. DOR rates will be reported at 3-month intervals (eg, 3 months, 6 months, etc.). Median DOR will be estimated from the 50^{th} percentile of the corresponding Kaplan-Meier estimates. 95% CIs for the 3-month intervals and median DOR will also be provided.

5.3.2. Additional Secondary Efficacy Analyses

The following additional efficacy endpoints will be summarized.

- PFS
- OS
- TTR
- GCIG CA-125 response

PFS and OS will be summarized using the Efficacy Evaluable population. Their distribution will be estimated using the Kaplan-Meier method. PFS and OS rates will be reported at 3-month intervals (eg, 3 months, 6 months, etc.). Median PFS and OS will be estimated the 50^{th} percentile of the corresponding Kaplan-Meier estimates. The 95% CI for the 3-month intervals and median

times will also be provided. Additionally, the restricted mean survival time (RMST) will also be reported at 3-month intervals (eg, 3 months, 6 months, etc.).

The median follow-up time and its 95% CI will be estimated using reverse Kaplan-Meier method on OS.

GCIG CA-125 response rate will be calculated using the CA-125 Response-Evaluable population and its 95% exact CI will be estimated using the Clopper-Pearson method.

TTR will be summarized in patients with a confirmed BOR of CR or PR only with the simple summary statistics.

5.4. Efficacy Analysis on Subgroups of Patients

Efficacy endpoints (ORR, DOR, PFS, OS, and GCIG CA-125 response rate) will be analyzed with the following subgroups of patients:

- Number of prior lines of therapy (1 vs 2 vs 3)
- Prior exposure to PARPi (yes vs no vs uncertain)
  - If patient participated in a double-blind randomized trial comparing PARP inhibitor to placebo and the actual treatment was unknown, patient will be summarized under 'uncertain' category.
- ADA status

The summaries for ORR and GCIG CA-125 response include the response rate and its 95% exact CI.

The summaries for time to event variables (DOR, PFS, and OS) include the number and percentage of events, median and its 95% CI.

5.5. Additional Sensitivity Analyses

Analysis of ORR, DOR, and PFS as assessed by BICR will be performed as sensitivity analysis using the same methods described in the previous sections.

5.6. Other Efficacy-related Summaries

Listings of efficacy-related data for will include the following:

- All lesion assessments (target lesion, non-target lesion, new lesion)
- New anti-cancer therapy
- Investigator's RECIST assessments
- CA-125 results
- Derived parameters for CA-125 response, BOR, PFS, DOR, and OS
- Censoring for time-to-event variables

6. SAFETY ANALYSES

The main safety summary tables will use data from the Safety population. Listings will be provided for patients in the Safety population.

6.1. Exposure

Summary tables will be provided with the following information.

Exposure to MIRV will be summarized with descriptive statistics for the number of doses received, the number of cycles received, duration of dosing (weeks), total cumulative dose (mg), absolute dose intensity (mg/kg/dose, calculated as total cumulative dose [mg])/number of valid drug administration records /AIBW [kg]).

The number of infusions with dose decreased, and dose delayed will also be summarized.

A listing will be provided with the information from all MIRV administration case report forms (CRFs) over the treatment period.

6.2. AEs

AEs will be documented on the AE CRF and monitored continuously throughout the study from the time of informed consent until 30 days after the patient's last MIRV or until the event has resolved, stabilized, or returned to baseline. AEs attributed to study procedures, including those events that occur prior to the first dose, should also be documented on the AE CRF.

AE data are available to ImmunoGen from 2 sources, the clinical database and the serious adverse event (SAE) forms. While reconciliation will be performed, the production of data summaries and listings will be based on the data collected on the clinical database.

Pre-treatment AEs are defined as AEs with an onset date prior to the first dose of MIRV. TEAEs are defined as AEs with an onset date on or after the first dose of MIRV, and within 30 days of the last dose of MIRV or prior to the start of a new anti-cancer treatment, whichever occurs first. Medical history conditions that exist before the initiation of MIRV but worsen in severity during the study will also be recorded on the AE CRF as an AE and will be included as treatment-emergent in the summary tables and listings.

The adverse events will be coded using MedDRA (Version 24.0), associating lower-level terms with PT and SOC by the primary hierarchy. The tables will display the counts and percentages of patients who reported at least 1 TEAE in each SOC represented in the AE data. Within each SOC, the tables will display the counts and percentages of patients reporting at least 1 TEAE as designated by the PT.

AEs are graded using CTCAE Version 5.0. AE summaries may include summaries for all AEs and by the maximum CTCAE grade for the item being summarized (ie, SOC or PT). In these cases, the outputs will include a row for All Grades as well as rows for the 5 potential CTCAE grades, Grade 1 (Mild), Grade 2 (Moderate), Grade 3 (Severe), Grade 4 (Life threatening or disabling), or Grade 5 (Death). AEs missing a severity grade will not be included in the Grade 1-5 rows of the tables. An AE reported by a patient more than once will be represented in the most severe category. TEAEs will be categorized as MIRV-related if "Possibly Related", "Probably

Related", or "Definitely Related" is selected by investigator. AEs missing relationship to MIRV will be included in the Related TEAE tables and listings.

The following summary tables will be produced:

- An overall summary of safety will summarize the numbers of patients with TEAEs of each grade and the number of patients who died during the study or within 30 days of last dose.
- All TEAEs.
- Serious TEAEs.
- Non-Serious TEAEs (ie, TEAEs excluding SAEs).
- Grade 3 or higher TEAEs.
- TEAEs leading to drug withdrawal. This subset includes TEAEs with an action taken of drug permanently discontinued.
- Related TEAEs leading to drug withdrawal. This subset includes TEAEs related to MIRV with an action taken of drug permanently discontinued.
- TEAEs related to MIRV.
- Serious, related TEAEs.
- TEAEs leading to dose modifications (dose reduction or dose delay).
  - TEAEs leading to dose reduction.
  - TEAEs leading to dose delay.
  - TEAEs leading to dose reduction or dose delay.
- Related TEAEs leading to dose modification (dose reduction or dose delay).
  - Related TEAEs leading to dose reduction.
  - Related TEAEs leading to dose delay.
  - Related TEAEs leading to dose reduction or dose delay.
- Deaths on study treatment or within 30 days of the last dose. This table includes all deaths during study treatment or within 30 days of the last dose, regardless of cause of death.
- TEAEs leading to death. This table includes all TEAEs with CTCAE Grade 5.
- Related TEAEs leading to death. This table includes all TEAEs related to MIRV with CTCAE Grade 5.

The following listings will be produced:

- All pre-treatment AEs will be listed.
- All AEs, sorted chronologically by patient. This listing includes SOC, PT, onset and end dates, and other relevant information.

- Serious TEAEs, sorted chronologically within patient.
- TEAEs leading to drug withdrawal. This subset includes TEAEs with an action taken of drug permanently discontinued.
- TEAEs leading to dose reduction or dose delay.
- TEAEs related to MIRV.
- Serious TEAEs related to MIRV.
- TEAEs resulting in death. This listing includes TEAEs with a CTCAE grade of Grade 5 (death).
- All deaths, with an indication of whether the death occurred on study or within 30 days of the last dose.

The following groupings of TEAEs will be generated as part of the focused analysis of safety:

- Ocular TEAEs.
  - A list of PTs for ocular AEs will be provided and finalized by the Sponsor before the final database lock.
- Peripheral neuropathy TEAEs.
  - A list of PTs for peripheral neuropathy AEs will be provided and finalized by the Sponsor before the final database lock.
- Pneumonitis.

For each of the focused safety analysis groups, the following summary tables will be produced:

- TEAEs by SOC, PT, and maximum CTCAE grade.
- Related TEAEs by SOC, PT, and maximum CTCAE grade.
- Serious TEAEs by SOC, PT, and maximum CTCAE grade.
- Related serious TEAEs by SOC, PT, and maximum CTCAE grade.
- TEAEs leading to discontinuation.
- TEAEs leading to dose reduction or dose delay.
- TEAEs leading to dose reduction.
- TEAEs leading to dose delay.
- Related TEAEs leading to discontinuation.
- Related TEAEs leading to dose reduction or dose delay.
- Related TEAEs leading to dose reduction.
- Related TEAEs leading to dose delay.

Additionally, a table will be produced which contains the following for each of the focused safety analysis groups:

- The number of patients with at least 1 TEAE in each group, presented by treatment arm.
- Time to first onset of each group of TEAEs.
- Action taken with MIRV with respect to each group of TEAEs.

For the focused safety analysis, the following listings will be produced:

- Ocular TEAEs.
- Peripheral neuropathy TEAEs.
- Pneumonitis TEAEs.

6.2.1. Fresh Biopsy Patient AE

Summary of adverse events, not necessarily TEAEs, experienced within 7 days of fresh biopsy will be generated by SOC, PT, and CTCAE grade. A listing of AEs experienced within 7 days of biopsy will also be generated for patients who have undergone fresh biopsy.

6.2.2. Infusion-related Reactions

Both broad and narrow standard MedDRA query (SMQ) for hypersensitivity will be performed. A summary table of all TEAEs matching broad or narrow SMQ will be generated by SOC, PT, and CTCAE grade. A listing will also be generated.

6.3. Clinical Laboratory Results

Laboratory test results (including hematology, coagulation, serum chemistry, and urinalysis) and abnormal laboratory values will be presented in data listings.

CTCAE Version 5.0 laboratory grades will also be presented. CTCAE grades will be derived based on laboratory results and will not factor in clinical evaluations.

Shift tables summarizing the changes from baseline in severity of laboratory grades will be provided for laboratory parameters graded according to CTCAE Version 5.0. Grade 3 or higher laboratory values will be summarized based on the worst grade observed during MIRV treatment or within 30 days of last dose.

Clinically significant values in liver function tests (LFTs) will be summarized by the following categories, using the maximum value while on MIRV. The denominator for the summaries will be the number of patients who had at least 1 non-missing value during treatment. The categories for each test are not mutually exclusive:

- Aspartate aminotransferase (AST)
  - $> 3 \times$ ULN
  - $> 5 \times$ ULN
  - $> 10 \times$ ULN
  - $> 20 \times$ ULN

- Alanine Aminotransferase (ALT)
  - > 3 × ULN
  - > 5 × ULN
  - > 10 × ULN
  - > 20 × ULN
- AST or ALT
  - > 3 × ULN
  - > 5 × ULN
  - > 10 × ULN
  - > 20 × ULN
- Total bilirubin (TBILI)
  - > ULN
  - > 2 × ULN
- Alkaline phosphatase (ALP)
  - > 1.5 × ULN
- (AST or ALT) and TBILI (concurrent)
  - AST or ALT > 3 × ULN and TBILI > 1.5 × ULN
  - AST or ALT > 3 × ULN and TBILI > 2 × ULN
- (AST or ALT) and ALP and TBILI (concurrent)
  - AST or ALT > 3 × ULN and ALP < 2 × ULN and TBILI > 2 × ULN

Here, concurrent means that all the associated LFTs must be from the same visit. In addition, worst postbaseline grade for LFTs will be summarized. Because baseline values of LFTs are already taken into account in CTCAE V5.0, shift table from baseline to worst postbaseline grade will not be generated for LFTs.

Results from pregnancy tests will be provided in listings.

6.4. Vital Signs

Vital signs (including temperature, pulse rate, systolic blood pressure, diastolic blood pressure, and respiratory rate) will be collected throughout the study. Pulse rate and respiratory rate are optional.

Vital signs results will be classified into 4 or 5 categories (low, borderline low, normal, borderline high, or high) according to Table 4 below. Shift tables based on this classification will be summarized from baseline to the last post-baseline visit value.

Table 4: Classification of Vital Signs

Vital Sign	Low	Borderline Low	Normal	Borderline High	High
Heart Rate (beats per minute)	< 50	50-59	60-90	91-99	≥ 100
Systolic BP (mmHg)	< 80	-	80-120	121-139	≥ 140
Diastolic BP (mmHg)	< 60	-	60-80	81-89	≥ 90
Respiratory Rate (breaths per minute)	< 12	-	12-20	21-24	≥ 25
Temperature (°C)	< 35.0	35.0-36.4	36.5-37.2	37.3-37.9	≥ 38.0

6.5. ECGs

ECGs are collected at screening visit only. All ECG results will be presented in data listings. If a different correction for QT is captured in the CRF, that QTc will be reported in the listing for that patient with QTcF.

6.6. Concomitant Medications

All medications and supportive therapy taken within 4 weeks prior to Cycle 1 Day 1 and through 30 days after last study treatment must be recorded on the appropriate CRF. The identity of all medications, dosage, route of administration, frequency, duration of administration, and indication for use will be recorded in the appropriate sections of the CRF.

Prior medications are defined as medications with a stop date prior to the first dose of MIRV.

Concomitant medications are defined as medications which are taken during the course of study treatment and within 30 days of the last dose of MIRV, as follows:

- Medications started before the first dose of MIRV, but with a stop date after the first dose of MIRV and within 30 days of the last dose of MIRV will be considered concomitant medications.
- Medications started before the first dose of MIRV that are ongoing will be considered concomitant medications.
- Medications started after the first dose of MIRV and within 30 days of the last dose of MIRV or before the start of a new anti-cancer treatment, whichever occurs first, are considered concomitant medications.
- Medications started before the first dose of MIRV, but with a stop date after the first dose of MIRV and within 30 days of the last dose of MIRV or prior to the start of a new anti-cancer treatment, whichever occurs first, will be considered concomitant medications.

Prior and concomitant medications will be coded using the March 2021 version of World Health Organization drug dictionary (WHO Drug). Summary tables will be provided for prior and concomitant medications.

Summary tables will be organized to display the anatomical main class of each coded medication (ATC Level 1 term) and, within that, the pharmacological subgroup (ATC Level 3 term) of the coded medication. The summary table will display number and percentage of patients who reported using at least 1 medication in each represented pharmacological subgroup. If a patient has more than 1 medication in the subgroup, the patient will be counted only once.

A complete listing of medications will be generated by patient. The listing will indicate which medications are prior and which are concomitant. The listing will display entries from the concomitant medications form, ordered within patient by start date. The listing will display the recorded term from the CRF and the WHO Drug anatomical main class (ATC Level 1 term) and pharmacological subgroup (ATC Level 3 term).

6.7. Concomitant Procedures

All procedures within 4 weeks of Cycle 1 Day 1 and through 30 days after last study treatment must be recorded on the appropriate CRF.

Prior procedures are defined as occurring before the first dose of MIRV (by procedure date).

Concomitant procedures are defined as procedures with a procedure date on or after the first dose of MIRV, and within 30 days of the last dose of MIRV, as follows:

- Procedures are defined as concomitant procedures with a procedure date on or after the first dose of MIRV, and within 30 days of the last dose of MIRV or prior to the start of a new anti-cancer treatment, whichever occurs first.

Prior and concomitant procedures will be coded using MedDRA (Version 24.0), associating lower-level terms with PT and SOC by the primary hierarchy. Summary tables will be provided for prior and concomitant procedures. The tables will display number and percentage of patients who reported at least 1 procedure in each SOC represented in the CRF data. Within each SOC, the tables will display number and percentage of patients reporting at least 1 concomitant procedure as designated by PT.

A complete listing of procedures will be generated. The listing will indicate which procedures are prior and which are concomitant. The listing will display entries from the concomitant procedures form, ordered within patient by date of procedure. The listing will display the recorded term from the CRF and the SOC and PT.

6.8. Ophthalmic Examinations

Ophthalmic Examinations are collected at the Screening, End-of-Treatment, and 30-Day Follow-up Visits. Results of the ophthalmic examinations will be presented in data listings.

Worst decline in both eye best corrected visual acuity (BCVA) grade will be summarized. Shift of both eye BCVA from baseline to worst post baseline will be summarized using the following categories: ≥20/40, <20/40 to ≥20/200, and <20/200.

Shift of intraocular pressure (mmHg) from baseline to highest post baseline value will be summarized using the following categories: ≤22 and >22.

Cataract shift from baseline to maximum on treatment CTCAE grade will be summarized based on data collected on the ocular symptom assessments CRF.

6.9. Ocular Symptom Assessments

Results of the ocular assessments will be presented in data listings.

6.10. Corticosteroid and Lubricating Eye Drop Compliance

All compliance information collected on the CRF will be presented in data listings.

6.11. Transfusions

All transfusions recorded on the CRF will be presented in data listings.

6.12. Physical Examination

Physical examination results will be presented in data listings.

6.13. ECOG PS

ECOG PS results will be presented in data listings. Baseline ECOG PS will be summarized in disease characteristics table (Section 4.1.4).

7. IMMUNOGENICITY

[redacted] Patients will be grouped into five categories based on ADA status before and post the first dose of MIRV:

- Treatment-emergent ADAs: Patients who had a baseline-negative ADA result who developed ADAs at any time after initial administration of drug.
- Treatment-enhanced ADAs: Patients who had a baseline positive ADA result in whom the assay signal was enhanced (greater than baseline titer by ≥ 4 folds) at any time after initial drug administration.
- Treatment-unaffected ADA: Patients who had a baseline-positive ADA result in whom the assay signal was not enhanced (negative or not greater than baseline titer by ≥ 4 folds) at any time after initial drug administration.
- Seronegative: a patient who tests negative at all visits.

If a titer is below LLQ, it will be imputed as half of LLQ.

Efficacy endpoints ORR and DOR will be analyzed by the above ADA status group.

TEAE by SOC and PT will be summarized for the above ADA status group.

8. BIOMARKERS

The exploratory biomarker analyses for this study will be covered by a separate, independent analysis plan.

9. PHARMACOKINETICS

Plasma concentration data collected in this study will be listed and summarized for the PK analysis population. Mean and 95% CI, standard deviation, geometric mean, coefficient of variation (CV, expressed as percentage), median, Q1, Q3, min, and max will be reported by visit. Data points that are below the lower limit of quantitation will be excluded from the analyses.

10. REFERENCES

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