ImmunoGen, Inc.

Protocol #: IMGC963-0901

A Phase 1, First-in-Human, Open-Label, Dose-Escalation Study of IMGC936 (Anti-ADAM9 Antibody Drug Conjugate) in Patients with Advanced Solid Tumors

Statistical Analysis Plan

Version 1.0
Nov 7, 2024

Prepared by:

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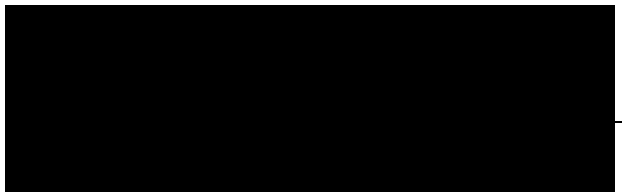
SIGNATURE PAGE

Declaration

The undersigned agree to the statistical analyses and procedures of this clinical study.



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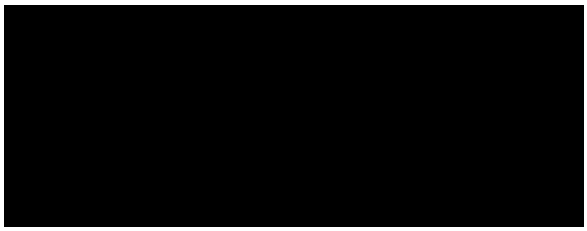

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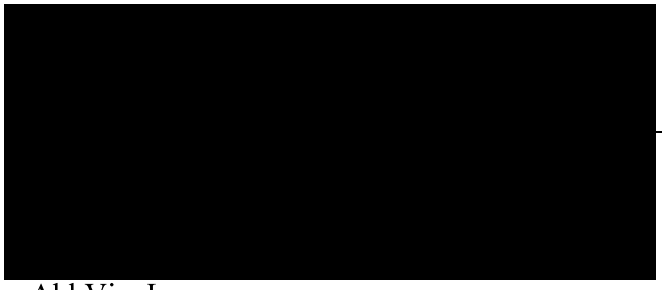

AbbVie, Inc.

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LIST OF ABBREVIATIONS

Abbreviation or Specialist Term	Explanation
AE	Adverse event
ALT	Alanine aminotransferase (SGPT)
AST	Aspartate aminotransferase (SGOT)
BP	Blood pressure
CR	Complete response
CRC	Cohort Review Committee
CRF	Case report form
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose-limiting toxicity
DoR	Duration of response
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
IV	Intravenous(ly)
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum tolerated dose
MUGA	Multigated acquisition
ORR	Objective response rate
PD	Progressive disease
PK	Pharmacokinetics
PR	Partial response
PT	Preferred term
QTc	Corrected QT interval
RP2D	Recommended Phase 2 dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease
SOC	System organ classes
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal

1. INTRODUCTION

1.1. Background

This document describes the statistical analysis plan (SAP) for the study IMGC936-0901, based on the Protocol Amendment #3, dated on 29-March-2022.

This SAP will govern the analysis of this study. Any deviations from the SAP will be documented as such in the study report.

2. STUDY OBJECTIVES

2.1. Dose Escalation Phase

2.1.1. Primary Objectives

- To assess safety, tolerability, and dose-limiting toxicities (DLTs), and determine a maximum tolerated dose (MTD), or maximum administered dose (MAD) (if no MTD is defined), and recommended Phase 2 dose (RP2D) for IMGC936 administered intravenously (IV)

2.1.2. Secondary Objectives

- To characterize pharmacokinetics (PK) and immunogenicity of IMGC936
- To describe objective response rate (ORR) and duration of response (DoR) for IMGC936 using Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1)

2.1.3. Exploratory objectives

- To explore progression-free survival (PFS)
- To explore potential biomarkers of clinical and/or immunologic response to IMGC936 in blood and tumor tissue
- To explore the relationship between baseline ADAM9 (a disintegrin and metalloprotease domain-containing protein 9) expression and antitumor activity

2.2. Dose Expansion Phase

2.2.1. Primary:

- To describe ORR for IMGC936 using RECIST v1.1

2.2.2. Secondary:

- To characterize safety and tolerability for IMGC936
- To characterize PK and immunogenicity of IMGC936
- To describe DoR and PFS

2.2.3. Exploratory:

- To explore potential biomarkers of clinical and/or immunologic response to IMGC936 in blood and tumor tissue
- To explore the relationship between baseline ADAM9 expression and antitumor activity
- To explore ocular primary prophylaxis regimens

3. STUDY DESIGN

3.1. Overall Study Design and Plan

This study is a Phase 1/2, first-in-human, open-label, dose-escalation study designed to characterize the safety, tolerability, PK, pharmacodynamics, immunogenicity, and preliminary antitumor activity of IMGC936 administered by IV infusion. Participants with unresectable, relapsed or refractory, locally advanced or metastatic non-squamous NSCLC, TNBC, CRC, gastroesophageal cancer, or pancreatic cancer will be enrolled globally in approximately 26 sites. Up to a maximum of 345 participants will be enrolled in the study if all expansion cohorts are fully enrolled.

Each cycle is 21 days for Schedule A and 28 days for Schedule B. IMGC936 is administered via IV infusion at the assigned dose for each cohort. Infusion duration will vary depending on dose and participant tolerability. Participants may continue on study drug until disease progression, AE requiring discontinuation, withdrawal of consent, physician decision, or other discontinuation criteria are met.

Participants will be followed for safety throughout the study. Any participant who discontinues study drug should return to the study site for an end of treatment visit (EOTV). The visit should be performed within 30 days following last dose of study drug whenever possible.

3.2. Dose escalation

The goal is to characterize safety and tolerability of IMGC936 to define the single-agent maximum tolerated dose (MTD) and select a recommended Phase 2 dose (RP2D). If no MTD is defined after escalation to the maximum protocol-specified dose, then the highest dose level administered will be designated as the maximum administered dose (MAD).

Up to 72 evaluable participants will be enrolled in the Dose Escalation Phase of this study.

Dose escalation follows a conventional 3+3 design: successive cohorts of 3 to 6 participants each will be evaluated in sequential escalating doses of single-agent IMGC936 (Table 1).

Each cycle is 21 days for Schedule A. IMGC936 is administered via IV infusion on Day 1 of Cycle 1 and every subsequent 21-day cycle thereafter at the assigned dose for each cohort in Schedule A. Infution duration will vary depending on dose and participant tolerability. Sentinel dosing will be used for the first 2 dose levels. The first administration of IMGC936 (Cycle 1) in participants at the first 2 dose levels of Schedule A dose escalation will be staggered by at least 48 hours.

Upon agreement between investigators and the sponsor, intermediate dose levels may be evaluated based on review of cumulative safety and PK data. For example, participants have been enrolled in intermediate dose cohorts at doses of 5mg/kg and 6 mg/kg.

Table 1: IMGC936 Dose Levels: Dose Escalation

Cohort	IMGC936 Dose
Cohort 1	0.5 mg/kg
Cohort 2	1.0 mg/kg
Cohort 3	2.0 mg/kg
Cohort 4	4.0 mg/kg
Intermediate Dose	5.0 mg/kg
Intermediate Dose	6.0 mg/kg
Cohort 5	7.0 mg/kg
Cohort 6	10.0 mg/kg
Cohort 7	12.0 mg/kg

Dose escalation will follow standard 3 + 3 design until an MTD or MAD is established. To support the selection of the RP2D, upon agreement between investigators and the sponsor, any dose level not exceeding the MTD may be expanded to a maximum of 15 participants for further evaluation of safety, PK, antitumor activity, to facilitate selection of the RP2D. Intermediate dose levels, not exceeding the MTD, may also be explored.
Participants on Schedule A who are not able to complete the 21-day evaluation secondary to AEs considered unrelated to study drug or any other cause unrelated to study drug are considered unevaluable for safety and toxicity during the DLT evaluation period and may be replaced.

Participants may continue on study drug until disease progression, AE requiring discontinuation, withdrawal of consent, physician decision, or other discontinuation criteria are met.

If recommended by the Cohort Review Committee, in conjunction with the Sponsor, based on emerging safety, tolerability, PK, and preliminary antitumor activity of IMGC936, an alternate schedule (Schedule B) may be explored. Each cycle is 28 days in contrast to Schedule A, which is 21 days. Participants enrolled on Schedule B will receive study drug on Days 1, 8, and 15 of a 28-day cycle for the first 2 cycles. On all subsequent cycles (Cycle 3 and beyond), participants will receive study drug on Days 1 and 8 of a 28-day cycle (Table 3). To potentially reduce ocular or other safety events that may be driven by C_{max} (maximum drug concentration after infusion), PK modeling suggests a fractionated weekly schedule would allow reduction in C_{max} while maintaining AUC exposure. To reduce participant burden of an indefinite weekly schedule, starting from the third cycle, participants will only receive the study drug in the first 2 weeks in a 4-week cycle. The 3 + 3 dose escalation as described previously will apply to the alternate schedule. The recommended starting dose of 2 mg/kg/dose (Cycles 1 and 2) and 3 mg/kg/dose (Cycle 3 and beyond) for Schedule B in a 4-week cycle is less than the non-fractionated total dose of 7 mg/kg every 3 weeks, which was administered in Cohort 5 of Schedule A.

Table 3: IMGC936 Dose Levels: Dose Escalation (Schedule B)

Cohort	IMGC936 Dose on Days 1, 8, and 15 of Cycle 1 and Cycle 2	IMGC936 Dose on Days 1 and 8 of Cycle 3 and beyond
Cohort B1	2 mg/kg/dose	3 mg/kg/dose
Cohort B2	2.5 mg/kg/dose	3.5 mg/kg/dose
Cohort B3	3.0 mg/kg/dose	3.5 mg/kg/dose
Cohort B4	3.5 mg/kg/dose	4.0 mg/kg/dose

Upon agreement between investigators and the sponsor, intermediate dose levels may be evaluated based on review of cumulative safety and PK data.

Participants on Schedule B who are not able to complete the 28-day evaluation secondary to AEs considered unrelated to study drug or any other cause unrelated to study drug are considered unevaluable for safety and toxicity during the DLT evaluation period and may be replaced.

3.2.1. Dose escalation rule

Dose escalation will use a conventional 3 + 3 design. Participants who are not evaluable for safety for the full DLT evaluation period for reasons other than study drug-related toxicity may be replaced in the same dose-level cohort.

If 0 of the first 3 participants treated at a given dose level experience a DLT during the DLT evaluation period, the dose will be escalated, and 3 participants will be enrolled and treated at the next higher dose level.

If 1 of the first 3 participants treated at a given dose level experiences a DLT, then 3 additional participants will be enrolled at that dose level to further assess the safety of IMGC936.

- If ≥ 1 of these 3 additional participants (i.e., ≥ 2 of the 6 participants) experience a DLT, it will be concluded that the MTD has been exceeded, and 3 participants will be enrolled and treated at the next lower dose level.
- If 0 of the 3 additional participants (i.e., ≤ 1 of the 6 participants) experience a DLT, then the dose will be escalated, and 3 participants will be enrolled at the next higher dose level.

If ≥ 2 of the first 3 participants treated at a given dose level, or ≥ 2 of 6 participants treated at a given dose level, experience a DLT, then it will be concluded that the MTD for IMGC936 has been exceeded at that dose level, and all subsequent participants will be treated at the next lower dose level.

For participants being treated at a dose level subsequently determined to exceed the MTD for a given cohort of the study, the dose of IMGC936 will be reduced to the next lower dose level as summarized in Table 1. Following these rules for dose escalation, the MTD/MAD will be the highest dose administered at which the incidence of DLT is < 33%.

Dose escalation to the next dose level is permitted only after the participants enrolled in the current dose cohort have completed the DLT evaluation period and the safety data have been

reviewed by the sponsor medical monitor and the investigators participating in the study. Evaluation of safety data from each cohort will include an assessment of the proportion of participants who receive planned doses, and the percentage of participants that require dose reductions or dose discontinuations for toxicity. All available data from participants both during and beyond the DLT evaluation period will be considered when making dose escalation decisions and in determination of the RP2D.

At the discretion of the sponsor, dose escalation may be stopped before an MTD is reached. In this case, the MAD may be chosen based on an assessment of PK, pharmacodynamics, biomarker, safety, and response data. An MTD does not have to be reached to expand a dose cohort if the available data demonstrate that a lower dose level may provide antitumor activity while minimizing potential risk.

At the discretion of the sponsor, any dose escalation cohort at a dose level not exceeding the MTD may be expanded to a maximum of 15 participants for further evaluation of safety, PK, and antitumor activity. Following determination of the RP2D, tumor-specific expansion cohorts may be opened in tumor types selected from those enrolled in dose escalation. The sponsor will provide a substantial amendment to applicable regulatory authorities for review and approval before opening these tumor-specific expansion cohorts.

3.3. Expansion Cohorts

The Dose Expansion Phase is designed to explore efficacy of IMGC936 at the RP2D as a single-agent in study participants with relapsed or refractory, unresectable locally advanced or metastatic solid tumors.

RP2D will be selected by the investigators and sponsor. Following determination of the RP2D, and at the sponsor's discretion, up to 7 expansion cohorts may be opened in tumor types selected from those enrolled in dose escalation (Table 4). Participants in Cohorts A through G can be enrolled in either in Dosing Schedule A or Schedule B upon sponsor's discretion.

Table 4: Expansion Cohorts

Cohort	IMGC936 Dose
Cohort A	Non-squamous NSCLC
Cohort B	TNBC
Cohort C	CRC
Cohort D	Gastroesophageal cancer
Cohort E	Pancreatic cancer
Cohort F	Any one above-mentioned tumor with an alternate dose and/or schedule
Cohort G	Any one above-mentioned tumor with an alternate dose and/or schedule

Participants may continue on study drug until disease progression, AE requiring discontinuation, withdrawal of consent, physician decision, or other discontinuation criteria are met.

A futility assessment will be conducted on the first 13 participants in each expansion cohort. If there are at least 2 responders out of 13 response-evaluable participants at the first stage, an additional 26 participants may be recruited to that cohort (full expansion) (for a total of 39 participants) to further evaluate safety, tolerability, PK, immunogenicity, biomarkers, antitumor activity, and survival of participants who received IMGC936.

The expansion cohorts may test more than 1 dose and/or schedule, not exceeding the MTD. Tumor types examined in Cohorts A to E may be further explored at a second dose and/or schedule in Cohorts F and G.

Tumor specimens for determination of ADAM9 expression via IHC staining will be collected from all participants and will be assayed at a central laboratory designated by the sponsor. ADAM9 testing results are not required for enrollment.

3.4. Study Population

Eligible patients will be ≥ 18 years of age and will have unresectable, relapsed or refractory, locally advanced or metastatic non-squamous NSCLC, TNBC, CRC, gastroesophageal cancer, or pancreatic cancer.

Patients who have consented to the study and who have received at least one dose of study drug will be considered enrolled. Patients who are issued a patient number but who do not successfully complete the screening process, and/or qualify but who do not receive a dose of study drug, will be considered screen failures. Patient numbers for patients who screen fail will not be reissued.

3.4.1. Sample Size

The study plans to treat up to approximately 45 participants in dose escalation on Schedule A and up to 27 participants on Schedule B. The sample size is based on a 3 + 3 design with 7 planned dose cohorts of IMGC936. Additional participants may be enrolled if a dose cohort is expanded, participants are replaced, or intermediate dose levels are evaluated.

Each expansion cohort may be expanded independently following an optimal Simon's 2-stage design. If there are at least 2 responders out of 13 response-evaluable participants at the first stage, each may enroll an additional 26 participants to that cohort (a total of 39 participants).

3.4.2. Assessment Schedule

See the protocol synopsis for study schedules of assessments.

3.5. Interventions

IMGC936 is administered by IV infusion. The drug product is diluted in a solution of sterile Dextrose 5% in Water (D5W), United States Pharmacopeia (USP) in an IV bag for administration with an infusion pump.

IMGC936 is administered on Day 1 of each 21-day cycle. It is expected that Day 1 of subsequent cycles will be no more than 3 days after the previous cycle. IMGC936 is administered as an IV

infusion at the assigned dose for each cohort. Infusion duration will vary depending on dose and participant tolerability.

4. GENERAL ANALYTICAL CONSIDERATIONS

4.1. Data Sources

Data including local laboratory data are recorded on eCRFs. The protocol provides additional details regarding data recording and handling.

4.2. Definition of Baseline

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

4.3. Missing Data

Partial dates are allowed on the eCRF for prior anti-cancer systemic therapy start and stop dates, 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 eCRF system for each of these dates. Only the month and day may be entered as unknown. Dates from these forms will be reported in listings as collected. Every effort will be made to query missing dates.

4.3.1. Missing AE Onset Date

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.

4.3.2. Missing Medication Date

For records with a missing medication (including prior systemic therapy) 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).

4.3.3. Missing Procedure Date

For records with a missing procedure (including prior radiotherapy) 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.

4.3.4. Missing Death Date

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

- 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.

4.4. Multiple Assessments for the Same Assessment Time Point

In general, no by-visit analyses is planned for this study, unless otherwise indicated for a specific parameter.

4.5. Multiple Study Centers

Patients from all study centers will be pooled for analyses. No adjustment for study center will be made.

4.6. Covariate Adjustment in Primary Analysis

As the sample size is relatively small, no covariate adjustment will be made.

4.7. Sample Size Reassessment

Not applicable.

4.8. Interim Analyses

Not applicable.

4.9. Test Sizes

No statistical hypothesis test will be performed.

4.10. Hypothesis Testing and Multiple Comparisons

No statistical hypothesis test will be performed, and there will be no multiple comparisons.

4.11. Analysis Populations

4.11.1. Safety Population

Safety population consists of all participants who received at least one dose of study drug. This population will be used for analyses of safety, PK, pharmacodynamics, and immunogenicity. It will also be used for summary of baseline data and analyses of progression-free survival (PFS).

4.11.2. Response Evaluable Population

Response evaluable population consists of all participants who received at least one dose of study drug, had baseline measurable or non-measurable disease, and had at least one post-baseline radiographic tumor assessment or discontinued study drug due to clinical progression or death if no post-baseline tumor assessment. This population will be used for summary of tumor assessment data and analyses of response rates.

4.12. Data Display Characteristics

Data displays produced for this study will include summary tables, data listings, and figures. Data listings will be produced for all recorded data as described in Section 5, Section 6, and Section 7. Summary tables will be produced as specified in Section 5, Section 6, and Section 7. Additional data listings will be produced for outcome measures that involve extensive procedures to derive the analyzed outcomes. Figures will be produced when specified in Section 5, Section 6, and Section 7.

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

The summary statistics displayed will be a function of the type of data associated with the summarized assessment. Unless stated otherwise in relevant sections, Section 5, Section 6, and Section 7, 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.

5. PATIENT ACCOUNTABILITY

Patient accountability will be summarized for the Safety population.

5.1. Patient Characteristics

Patient characteristics will be summarized and listed.

5.1.1. Demography

The following patient characteristics collected at the screening visit will be summarized:

- Age
- Sex
- Ethnicity
- Race

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

5.1.2. Height, Baseline Weight, and BMI

Height and baseline weight as well as BMI will be summarized and presented.

5.1.3. Medical History

Medical history will be coded using Medical Dictionary for Regulatory Affairs (MedDRA), 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.

5.1.4. Disease Characteristics and Prior Therapy

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:

- Baseline ECOG performance status
- Baseline left ventricular ejection fraction (LVEF) results
- Primary tumor type

a) Non-Squamous non-small cell lung cancer (NSCLC)
b) Triple Negative Breast Cancer (TNBC)
c) Colorectal Cancer (CRC)
d) Gastroesophageal Cancer
e) Pancreatic Cancer

- Disease status (Locally Advanced Disease, Metastatic Disease, both)
- Disease stage at diagnosis (I, II, III, IV, Unknown)
- Time since initial diagnosis (months)
- Prior cancer surgery (yes/no)
- Prior radiotherapy (yes/no)
- Prior systemic therapy

5.2. Patient Disposition

5.2.1. Disposition

A summary of patient disposition will present the number of patients enrolled and the reason for treatment and study discontinuation.

The number and percentage of patients who withdrew for each reason on the End-of-Treatment and End-of-Study eCRF forms will be provided.

5.2.2. Protocol Deviations and Population Inclusions

Protocol deviations will be captured in a protocol deviation log. A listing of major and minor protocol deviations will be provided.

6. EFFICACY ANALYSES

The efficacy analyses will be performed on the Response Evaluable Population.

6.1. Efficacy Outcomes

The response outcomes such as best overall response and overall response rates will be determined based on the response data recorded on the Response and Response Follow-up eCRFs between the date of the first dose of study drug and the date of study discontinuation.

6.1.1. Progression-free survival (PFS)

Progression-free survival will be defined as the time from the first dose date of study drug to the date of first documented progression or death from any cause, whichever occurs first. The documented progression is determined by objective assessment of disease per RECIST v1.1. For participants who are not known to be dead or progressed at the time of data cut-off for PFS

analysis, the PFS will be censored at the date of the last tumor assessment. Specifically, the following censoring rules (Table 2) will be applied to the PFS analysis.

Table 2: Censoring rules for PFS

Situation	Date	Outcome
No baseline tumor assessments	First dose date	Censored
Death prior to first scheduled tumor assessment	Date of death	Event
No post-baseline tumor assessments in absence of death prior to first scheduled tumor assessment	First dose date	Censored
Documented progression	Date of progression	Event
Initiation of alternative anti-cancer treatments in absence of documented progression	Date of last tumor assessment on or prior to initiation of such treatment	Censored
Death or documented progression immediately after missing 2 or more consecutive scheduled tumor assessments (i.e, documented progression or death date - last radiological assessment date +1 ≥ 105 days)	Date of last tumor assessment prior to missed assessments	Censored

6.1.2. Best Overall Response

Best overall response (BOR) is the best response designation recorded for a patient. In determining the best overall response, the overall responses for a patient should be ordered according to descending best response as CR > PR > SD > PD. For example, if a patient had an SD, PR, CR, CR, PD at Cycle 1, 2, 3, 4, and 5 respectively, the best overall response for this patient is CR. Patients who have no post-baseline response assessment data will be considered as non-responders with response category of not evaluated (NE).

To be qualified as BOR, CR and PR require a confirmation at least 4 weeks after initial observation of such response, and SD requires to be observed at least once after 6 weeks (-3 days) from the first dose of study drug.

6.1.3. Objective Response Rate (ORR)

The ORR will be calculated as the number of patients with a BOR of CR or PR divided by the number of patients in the corresponding analysis population. Patients without at least 1 post-baseline efficacy assessment will be treated as non-responders and their BORs will be set to NE (not evaluated).

6.1.4. Duration of Response (DoR)

DoR is defined only for patients who achieve a response (CR/PR) and will be measured from the

date of initial response to progressive disease or death, whichever occurs first.

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.

DoR is only defined for responders (ie, patients who have a BOR of CR or PR). The censoring rule for DOR is same as that for PFS. Specifically, the last 3 situations described in Table 2 will be applied. DoR analyses will be performed only if there are enough responders to render the analyses meaningful.

6.2. Efficacy Outcome Analysis

The protocol specifies the following as exploratory analyses:

- To describe antitumor activity of IMGC936 using Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1)
- To explore progression-free survival (PFS)

The number and percent of participants with their BOR will be presented. The objective response rate (ORR) will be presented together with BOR. Two-sided 95% exact binomial confidence intervals (CIs) of the response rates will be calculated using the method of Clopper–Pearson.

Percent change of tumor size from baseline over time will be summarized and presented by spider plot. The tumor size is defined as the sum of diameters of the target lesions. The best percent change of tumor size from baseline will be presented by waterfall plot.

The Kaplan-Meier method will be applied to estimate PFS and DoR curves; their median times, and PFS rates at 3 and 6 months, respectively. The method of Brookmeyer and Crowley will be used to construct 95% CIs for median time. The 95% CIs for PFS rates at each time point of interest will be calculated by normal approximation after log(-log) transformation.

6.3. Other Exploratory Efficacy Analyses

The exploratory analyses on the relationship of immunogenicity, biomarker and PK with antitumor activity will be covered by a separate, independent analysis plan.

6.4. Efficacy Analysis on Subgroups of Patients

No subgroup efficacy analysis will be planned.

6.5. Additional Sensitivity Analyses

Not applicable.

6.6. Other Efficacy-related Summaries

A listing of new anti-cancer therapies will be provided.

7. SAFETY ANALYSES

The safety analyses will be performed on the Safety population. The assessments/events up to 30 days (inclusive) of the last dose of study drug or prior to the start of a new anti-cancer treatment, whichever occurs first, will be analyzed, unless otherwise stated. Baseline is defined as the last non-missing observed measurement prior to the first dose of study drug.

Unless otherwise stated, summaries of safety data will be presented for each dose level of IMGC936, combined RP2P dose (6mg/kg) as well as for overall of all patients in the Safety population.

7.1. Exposure

Study treatment attributes to be used in analyses will include the following. Summary tables will be provided for each dose level of IMGC936.

- Number of treatment doses (or cycles) is defined as the number of infusions of IMGC936.
- Treatment duration (weeks) = [(last infusion date - first infusion date) + length of cycle] / 7
- Total cumulative dose (mg) = sum of actual dose administered in all cycles while the patient is on study drug
- Actual dose intensity (mg/kg/dose) = total cumulative dose (mg) / baseline weight (kg)/(total treatment duration (weeks) / number of weeks in each cycle)
- Relative dose intensity (%) = actual dose intensity/planned dose intensity*100%

A listing will be provided with the information from all study drug administration eCRFs over the treatment period.

7.2. Adverse Events (AEs)

AEs will be documented on the AE eCRF and monitored continuously throughout the study from the time of informed consent until 30 days after the patient's last study drug 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 eCRF.

AE data are available to ImmunoGen from 2 sources, the eCRFs 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 eCRF.

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

The adverse events will be coded using MedDRA, 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 Common Terminology Criteria for Adverse Events (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.

Ocular AEs including blurred vision events and grouped keratopathy events will be analyzed for outcome, resolution, time to onset and time to resolution. Patients at 6mg/kg who administered different prophylactic eye drops will be further analyzed.

The criteria for eye drop subgroups are defined as follows.

Brimonidine + lubricating eye drop group: patient who started brimonidine prior to or on C1D1 reported in concomitant medicine or cycle 1 eye drop compliance form.

Steroid + lubricating eye drop group: patient who started steroid prior to or on C1D1 reported in concomitant medicine or cycle 1 eye drop compliance form.

Lubricating only eye drop group: all other patients at 6 mg/kg who are not included in above two groups.

The following AE summary tables will be produced:

- An overall summary: present the numbers (and percentages) of patients with any TEAEs, TEAEs ≥ Grade 3, study drug related AEs, AEs leading to permanent discontinuation of study drug, TEAEs leading to death, and any death during the study treatment or within 30 days of last dose.
- All TEAEs
- TEAEs with CTCAE severity Grade ≥ 3
- Study drug related TEAEs (ie, TEAEs with a drug relationship of possibly related, probably related, or definitely related; TEAEs with missing drug relationships will be also included).
- Study drug related TEAEs with CTCAE severity Grade ≥ 3
- Serious TEAEs
- Non-Serious TEAEs (ie, TEAEs excluding SAEs)

- Study drug related SAEs
- TEAEs leading to discontinuation of study drug (ie, TEAEs with an action taken of study drug discontinued permanently)
- TEAEs leading to interruption of study drug (ie, TEAEs with an action taken of study drug with dose interrupted)
- Study drug related TEAEs leading to discontinuation of study drug
- Study drug related TEAEs leading to interruption of study drug
- TEAEs leading to death (ie, TEAEs with CTCAE Grade 5)
- 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.
- Ocular TEAE resolution (blurred vision and keratopathy)
- Time to onset of first ocular TEAE (blurred and keratopathy)

Time to resolution of ocular TEAE (blurred vision and keratopathy)The following listings will be produced:

- All pre-treatment AEs
- All TEAEs, sorted chronologically within patient. This listing includes SOC, PT, onset and end dates, and other relevant information.
- Serious TEAEs, sorted chronologically within patient
- TEAEs leading to discontinuation of study drug
- TEAEs leading to interruption of study drug
- Study drug related TEAEs
- Study drug related SAEs
- Dose-limiting toxicities (DLTs)
- TEAEs leading to death

The following PTs will be grouped for the analyses:

AEPT3	**PTs**
Keratopathy	“Corneal cyst”, “Corneal disorder”, “Corneal epithelial microcysts”, “Keratitis”, “Keratopathy”, “Corneal opacity”, “Corneal erosion”, “Corneal pigmentation”, “Corneal deposits”, “Keratitis interstitial”, “Punctate keratitis”, “Corneal epithelium defect”, “Corneal epithelial microcysts”, “Limbal stem cell deficiency”
Blurred vision event	“Vision blurred”, “Visual impairment”, “Vitreous floaters”, “Visual acuity reduced”, “Diplopia”, “Presbyopia”, “Accommodation disorder”, “Refraction disorder”, “Hypermetropia”
Dry eye	“Lacrimation decreased”, “Dry eye”

AEPT3	PTs
Cataract	"Cataract", "Cataract nuclear", "Cataract cortical"
Eye pain	"Eye pain"
Ocular discomfort	"Eye pruritus", "Eye irritation", "Ocular discomfort", "Foreign body sensation in eyes"
Peripheral neuropathy	"Neuropathy peripheral", "Peripheral sensory neuropathy", "Peripheral motor neuropathy", "Paraesthesia", "Hypoaesthesia", "Neurotoxicity", "Polyneuropathy", "Peripheral sensorimotor neuropathy"
Pneumonitis	"Pneumonitis", "Interstitial lung disease", "Pulmonary fibrosis", "Organizing pneumonia", "Organising pneumonia"
Abdominal pain	"Abdominal pain", "Abdominal pain upper", "Abdominal pain lower", "Abdominal discomfort"
Fatigue	"Fatigue", "Asthenia"
Dyspnea	"Dyspnea", "Exertional dyspnea"
Hypertension	"Hypertension", "Increased blood pressure", "High blood pressure"
Hypokalaemia	"Hypokalaemia", "Blood potassium decreased"
Hyponatraemia	"Hyponatraemia", "Blood sodium decreased"
Hypomagnesaemia	"Hypomagnesaemia", "Blood magnesium decreased"
Thrombocytopenia	"Thrombocytopenia", "Platelet count decreased"

7.3. 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 to worst post-baseline values (high or low, as applicable) in severity of laboratory grades will be summarized by CTCAE grade.

Clinically significant values in liver function tests (LFTs) will be summarized by the following categories, using the maximum lab value among visits. The denominator for the summaries will be the number of patients who had at least 1 non-missing post-baseline value within 30 days of the last dose of study drug or prior to the start of a new anti-cancer treatment, whichever occurs first. 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 (TBL)
  - > ULN
  - > 2 × ULN
- Alkaline phosphatase (ALP)
  - > 1.5 × ULN
- (AST or ALT) and TBL (concurrent)
  - AST or ALT > 3 × ULN and TBL > 1.5 × ULN
  - AST or ALT > 3 × ULN and TBL > 2 × ULN
- (AST or ALT) and ALP and TBL (concurrent)
  - AST or ALT > 3 × ULN and ALP < 2 × ULN and TBL > 2 × ULN

Here, concurrent means that all the associated LFTs must be from the same visit.

Results from pregnancy tests will be provided in listings.

7.4. Vital Signs

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

Vital signs results will be classified into 4 or 5 categories (low, borderline low, normal, borderline high, or high) according to Table 3 below. Shift tables based on this classification will be summarized from baseline to the last post-baseline visit value.

Table 3: 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

Vital Sign	Low	Borderline Low	Normal	Borderline High	High
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

7.5. ECGs

ECGs will be performed in triplicate for some visits and assessment time points. The average of these multiple non-missing measurements for these visits and assessment time points will be used for analysis.

QTcF (QT correction according to Fridericia's formula) will be calculated as follows based on the QT interval and the RR interval (= 60/HR(heart rate)):

$$QTcF = \frac{QT}{\sqrt[3]{RR}}.$$

Number and percentage of patients in the following categories will be summarized by visit for QTcF:

- >450 msec
- >480 msec
- >500 msec
- change from baseline >30 msec
- change from baseline >60 msec

The categories above are not mutually exclusive.

By-patient listings of ECG data will be provided.

7.6. Concomitant Medications

All medications and supportive therapy taken within 14 days prior to Cycle 1 Day 1 and through 30 days after last study treatment must be recorded on the appropriate eCRF. 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 eCRF.

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

Concomitant medications are defined as medications which are taken during the course of study treatment and within 30 days of the last dose of study drug or before the start of a new anti-cancer treatment, whichever occurs first:

- Medications started before the first dose of study drug, but with a stop date after the first dose of study drug will be considered concomitant medications.

- Medications started before the first dose of study drug that are ongoing will be considered concomitant medications.
- Medications started after the first dose of study drug and within 30 days of the last dose of study drug or before the start of a new anti-cancer treatment, whichever occurs first, are considered concomitant medications.

Prior and concomitant medications will be coded using the September 2019 or later 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 eCRF and the WHO Drug anatomical main class (ATC Level 1 term) and pharmacological subgroup (ATC Level 3 term).

7.7. Concomitant Procedures

All procedures within 14 days before the Cycle 1 Day 1 through 30 days after last study treatment must be recorded on the appropriate eCRF. Prior procedures are defined as occurring before the first dose of study drug (by procedure date). Concomitant procedures are defined as procedures with a procedure date on or after the first dose of study drug, and within 30 days of the last dose of study drug or prior to the start of a new anti-cancer treatment, whichever occurs first.

Prior and concomitant procedures will be coded using MedDRA, 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 eCRF 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 eCRF and the SOC and PT.

7.8. Physical Examination

Physical examination results will be presented in data listings.

7.9. ECOG PS

ECOG PS results will be presented in data listings. Baseline ECOG PS will be summarized in disease characteristics table (Section 5.1.4).

7.10. ECHO/MUGA

Left ventricular ejection fraction (LVEF) results at screening and End of Treatment visit are collected via eCRF. The screening results will be summarized in disease characteristics table (Section 5.1.4). Change in LVEF from baseline to End of Treatment visit will be summarized. All results will be presented in data listings.

7.11. Ophthalmic exam and ocular symptom assessment

Baseline and post treatment ophthalmic exam and ocular symptom assessment results are collected via eCRF. Findings during these assessments are reported as adverse events and summarized in TEAE and ocular TEAE tables. Best correct visual acuity (BCVA) changes are summarized in the table of BCVA shift from baseline to the worse post baseline.

8. QUALITY OF LIFE (QOL)

Not applicable.

9. IMMUNOGENICITY

The immunogenicity analyses will be covered by a separate, independent analysis plan.

10. BIOMARKERS

The biomarker analyses will be covered by a separate, independent analysis plan.

11. PHARMACOKINETICS (PK)

The PK analyses will be covered by a separate, independent analysis plan.

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