CLINICAL STUDY PROTOCOL

Study Title:	A Phase 1/2, First-in-Human, Open-Label, Dose-Escalation and Expansion Study of IMGC936 (Anti-ADAM9 Antibody Drug Conjugate) in Patients with Advanced Solid Tumors
Study Number:	IMGC936-0901
Study Phase:	1/2
Product Name:	IMGC936
IND Number:	141340
EudraCT Number:	2021-002264-41
Indication:	Advanced solid tumors including non-squamous non-small cell lung cancer, triple -negative breast cancer, gastroesophageal cancer, colorectal cancer, or pancreatic cancer
Sponsor:	ImmunoGen, Inc. 830 Winter Street Waltham, MA 02451 USA
Sponsor Contact:	[redacted] Email: [redacted]
Original Protocol Date (Version 1.0):	08 June 2020
Amendment No. and Date:	1 (05 August 2020)
Amendment No. and Date:	2 (22 April 2021)
Amendment No. and Date:	3 (29 March 2022)

Confidentiality Statement

SPONSOR SIGNATURE PAGE

[redacted]
ImmunoGen, Inc.

INVESTIGATOR'S AGREEMENT

I have read the IMGC936-0901 protocol and agree to conduct the study as outlined and in conformance with the International Conference on Harmonisation E6 Good Clinical Practice and applicable regulatory requirements. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

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Printed Name of Investigator

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Signature of Investigator

_____

Date

1. SYNOPSIS

Name of Sponsor/Company: ImmunoGen, Inc.		
Name of Investigational Product: IMGC936		
Name of Active Ingredient: IMGC936		
Protocol Number: IMGC936-0901	**Phase:** Phase 1/2	**Country:** United States
Title of Study: A Phase 1/2, First-in-Human, Open-Label, Dose-Escalation and Expansion Study of IMGC936 (Anti-ADAM9 Antibody Drug Conjugate) in Patients with Advanced Solid Tumors		
Study center(s): The study will be conducted globally at approximately 26 centers.		

Objectives:

Dose Escalation Phase

Primary:

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

Secondary:

- To characterize the 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 v1.1)

Exploratory:

- 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

Dose Expansion Phase

Primary:

- To describe ORR for IMGC936 using RECIST v1.1

Secondary:

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

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

Study Design:

This study is a Phase 1/2, first in human, open-label, dose-escalation and expansion study designed to characterize the safety, tolerability, PK, immunogenicity, and preliminary antitumor activity of IMGC936.

Participants with relapsed or refractory, unresectable locally advanced or metastatic solid tumors including non-squamous non-small cell lung cancer (NSCLC), triple-negative breast cancer (TNBC), colorectal cancer (CRC), gastroesophageal cancer, or pancreatic cancer will be enrolled.

Planned treatment for both the Dose Escalation Phase and the Dose Expansion Phase consists of IMGC936 administered via intravenous (IV) infusion on Day 1 of Cycle 1 and every subsequent 21-day cycle thereafter (Schedule A, Appendix 1) or IV infusion on Day 1, Day 8, and Day 15 of Cycle 1 and 2, followed by infusion on Day 1 and Day 8 in Cycle 3 and beyond of a 28-day cycle (Schedule B, Appendix 2). Participants may continue on study drug until disease progression, AE requiring discontinuation, withdrawal of consent, physician decision, or other discontinuation criteria are met (Section 5.4).

Dose Escalation Phase

The Dose Escalation Phase is designed to determine the MTD or MAD, if no MTD is defined, and select an RP2D. 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.

Up to 72 evaluable participants will be enrolled in Schedule A and Schedule B of the Dose Escalation Phase.

IMGC936 is administered via IV infusion at the assigned dose for each cohort. Infusion 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.

The DLT evaluation period is 21 days for Schedule A and 28 days for Schedule B.

During the Dose Escalation Phase, 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, antitumor activity, to facilitate selection of the RP2D. Intermediate dose levels, not exceeding the MTD, may also be explored.

Dose Expansion Phase

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.

Upon completion of the Dose Escalation Phase of the study, 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.

Up to 39 evaluable participants may be enrolled into each expansion cohort (up to 273 participants).

A futility assessment will be conducted on the first 13 participants (Section 14.1) 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 (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 specimens for determination of ADAM9 expression via immunohistochemical 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.

Dose Escalation and Dose Expansion Phases

During both the Dose Escalation and the Dose Expansion phases of the study, safety and tolerability will be closely followed. Further, PK, immunogenicity, antitumor activity, and survival assessments will occur (Appendix 1 and Appendix 4).

Safety Monitoring:

Dose Escalation Phase

For guiding dose-escalation decisions, DLTs will be defined based on treatment emergent adverse events (TEAEs) or abnormal laboratory values that occur up to study Day 21 of Cycle 1 (Schedule A) or study Day 28 of Cycle 1 (Schedule B). AE severity will be graded according to National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0.

Dose Expansion Phase

Safety will be evaluated continuously and in aggregate in the expansion cohorts (Section 4.3). Safety assessments will be based on all TEAEs and abnormal laboratory values.

Number of participants (planned):

Up to a maximum of 345 participants will be enrolled in the study if all expansion cohorts are fully enrolled.

Dose Escalation Phase

Up to 45 evaluable participants may be enrolled in Schedule A depending on results during the study and number of dose levels explored. If Schedule B is explored, up to 27 evaluable participants may be enrolled. This number does not account for replacement of non-evaluable participants or the possibility of expanding an individual dose escalation cohort to a maximum of 15 participants to allow for further evaluation of safety, PK, and antitumor activity at that dose level.

Dose Expansion Phase

Up to 39 evaluable participants may be enrolled in each of the 5-7 expansion cohorts.

Diagnosis and main criteria for inclusion:

The population to be enrolled consists of adults with relapsed or refractory, unresectable locally advanced or metastatic non-squamous NSCLC, TNBC, CRC, gastroesophageal cancer, or pancreatic cancer for whom no therapy with demonstrated clinical benefit is available.

Participants must have good performance status, adequate end organ function, and no serious concurrent illnesses that would increase the risk to the participant or confound study data.

Investigational product, dosage and mode of administration:

IMGC936 is an antibody-drug conjugate that consists of an ADAM9-targeting monoclonal antibody and a tubulin-targeting maytansinoid payload, conjugated. IMGC936 dose will be determined during

dose escalation (range 0.5 to 12 mg/kg) and is administered intravenously by following dosing Schedule A and Schedule B (Appendix 1 and Appendix 2).

Duration of treatment:

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

It is expected that enrollment for the Dose Escalation Phase of the study will occur over approximately 24 months. The enrollment for the Dose Expansion Phase will occur over approximately 18 months. The total time for conduct of the trial is expected to be approximately 48 months. These estimates of the timing for study conduct may vary from that observed in the actual conduct of the trial.

Criteria for evaluation:

Dose Escalation Phase and Dose Expansion Phase Assessments

Safety Assessments:

The safety assessment will be based on evaluation of AEs that occur from the time of initiation of administration of study drug through the end of treatment visit (EOTV) or 30 days following the last dose of study drug or until the start of subsequent anticancer therapy (whichever occurs first) and will be determined based on signs, symptoms, physical examination findings, and/or laboratory test results from enrolled participants as appropriate.

Ongoing AEs considered related to study drug will be followed until the event has resolved to baseline grade, the event is assessed by the investigator as stable, initiation of another anticancer therapy, withdrawal of consent, lost to follow-up (LTFU), or death.

Progression of the underlying tumor resulting in hospitalization or death (eg, participant hospitalized for or dies from progressive disease (PD) only, without any other serious adverse event [SAE]) will be documented as a PD outcome and not as an SAE.

Response Assessments:

Tumor assessments will be obtained using computed tomography and/or magnetic resonance imaging scans. Target and non-target lesions will be designated at screening and then evaluated after every other cycle, ie, every 6 weeks (± 7 days) on Schedule A and every 8 weeks (± 7 days) on Schedule B while on study drug.

At each tumor assessment time point, the overall response status will be determined based on assessment of target and non-target lesions as well as appearance of any new lesions. For RECIST v1.1, the overall responses will be categorized as complete response (CR), partial response (PR), stable disease, PD, or not evaluable.

If feasible, participants who discontinue study drug for reasons other than PD, (eg, toxicity, participant request) should continue to undergo tumor assessments every 12 weeks (± 21 days) until evidence of PD, initiation of another anticancer therapy, withdrawal of consent, LTFU, death, or end of study, whichever occurs first.

Pharmacokinetic Assessments:

Serum concentrations of conjugated antibody and total antibody following administration of IMGC936 will be monitored using quantitative validated bioanalytical methods. DM50/51 payload levels will be measured from plasma using a validated liquid chromatography-tandem mass spectrometry assay. Metabolites of IMGC936 may also be evaluated. Single and multiple-dose PK parameters will be derived from serum or plasma concentration versus time data as applicable.

Immunogenicity Assessments:

Antidrug antibodies against IMGC936 will be evaluated using a validated analytical method.

Biomarkers:

Exploratory biomarker assessments are described in the protocol.

Analysis Populations: Two populations will be used for this analysis: the Safety Population and the Response Evaluable Population as defined below.

Safety Population: All participants who received at least one dose of study drug. This population will be used for analyses of safety, PK, and immunogenicity. It will also be used for summary of baseline data and analyses of PFS.

Response Evaluable Population: 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 from 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.

Statistical methods:

A separate statistical analysis plan will further describe the details regarding statistical methods and will govern the analysis.

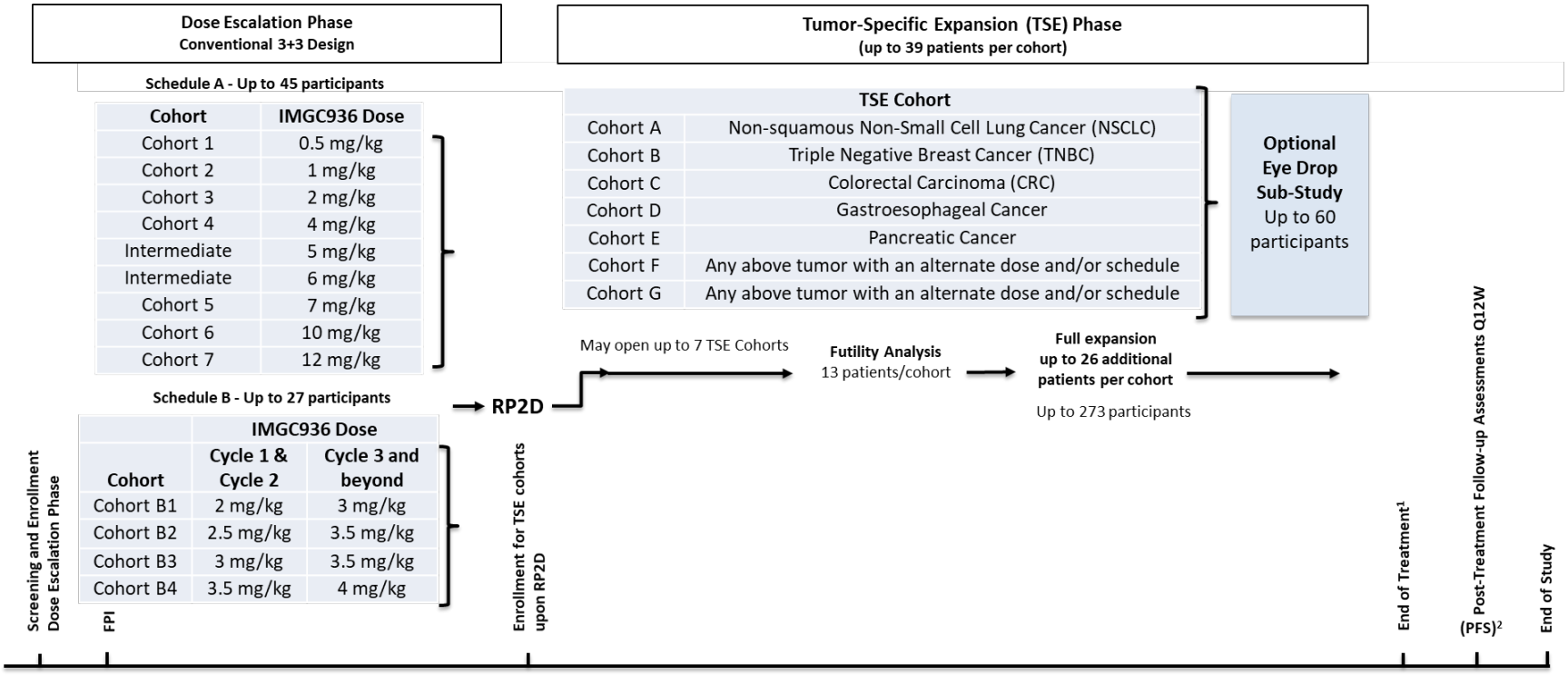
Sample Size: The study plans to treat up to approximately 45 participants in dose escalation on Schedule A and up to 27 participants on Schedule B. The sample size is based on a 3 + 3 design with 7 planned dose cohorts of IMGC936. Additional participants may be enrolled if a dose cohort is expanded,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

Safety: Treatment-emergent AEs will be summarized by system organ class and preferred term, by relationship to study drug~~s~~, and by highest severity. Summaries of laboratory values will display descriptive statistics for numerically quantified laboratory results.

Efficacy: Number and percent of participants with their best overall response will be summarized. Objective response rate will be calculated as the proportion of participants in the Response Evaluable Population achieving a best response of CR or PR. Response rates will be determined using RECIST v1.1. Two-sided 95% exact binomial confidence intervals (CIs) will be calculated around the response rates. Kaplan-Meier methods will be used to estimate duration of response and PFS.

1.1. Study Overview Schema



Abbreviations: FPI: first participant in; PFS: progression-free survival; QXW: every X weeks; RP2D: recommended Phase 2 dose.
Safety assessments occur from the time of initiation of administration of study drug through the End of Treatment Visit or 30 days following the last dose of study drug or until subsequent start of anticancer therapy.
Tumor assessments occur every 2 cycles during treatment (Q6W for Schedule A and Q8W for Schedule B) and Q12W if the participant has discontinued study treatment for reasons other than progressive disease.
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. The 3 + 3 dose escalation will apply to the alternate schedule. The starting dose for Schedule B will be equal to or less than the fractionated total dose of the maximum tolerated dose or maximum administered dose on the original every 3 weeks schedule.
[1] Pharmacokinetics and immunogenicity will be assessed throughout the study (Appendix 4 and Appendix 5).
[2] Participants who discontinue before progression of disease will be followed for PFS after end of study treatment.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Table 1: Abbreviations and Specialist Terms

Abbreviation	Definition
ADA	antidrug antibody
ADAM	a disintegrin and metalloproteinase
ADAM9	a disintegrin and metalloprotease domain-containing protein 9
ADC	antibody-drug conjugate
ADL	activities of daily living
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the curve
AUC_{0-t}	area under the curve from time zero to time t
AUC_{0-inf}	area under the curve from time zero to infinity
BOR	best overall response
CFR	Code of Federal Regulations
CL_{adc}	clearance of antibody-drug conjugate
C_{max}	maximum concentration
COVID-19	coronavirus disease 2019
CR	complete response
CRC	colorectal cancer
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
D5W	Dextrose 5% in Water
DLT	dose-limiting toxicity
DoR	duration of response
eCRF	electronic case report form
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture

Abbreviation	Definition
EOTV	end of treatment visit
Fc	fragment crystallizable
FcγR	Fc gamma receptor
FDA	Food and Drug Administration
FFPE	formalin-fixed paraffin-embedded
FOCBP	female of childbearing potential
G-CSF	granulocyte colony stimulating factor
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GM-CSF	granulocyte-macrophage colony stimulating factor
HNSTD	highest non-severely toxic dose
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IHC	immunohistochemistry
IRB	Institutional Review Board
IRR	infusion-related reaction
IV	intravenous(ly)
KD	binding affinity
LTFU	lost to follow-up
LVEF	left ventricular ejection fraction
mAb	monoclonal antibody
MAD	maximum administered dose
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MRSD	maximum recommended starting dose
MTD	maximum tolerated dose
NCI	National Cancer Institute
NE	not evaluable
NSCLC	non-small cell lung cancer
ORR	objective response rate

Abbreviation	Definition
OS	overall survival
PD	progressive disease
PFS	progression-free survival
PK	pharmacokinetic(s)
PO	orally
PQC	product quality complaint
PR	partial response
PT	preferred term
Q6W	every 6 weeks
Q8W	every 8 weeks
Q12W	every 12 weeks
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SD	stable disease
SOC	system organ class
SPR	surface plasmon resonance
TEAE	treatment-emergent adverse event
TNBC	triple-negative breast cancer
ULN	upper limit of normal
US	United States

2. BACKGROUND INFORMATION

2.1. Rationale for Study

Antibody-drug conjugates (ADCs) have emerged as a class of therapeutic agents for targeted treatment of cancer. ADCs combine the tumor target specificity of a monoclonal antibody (mAb) with highly potent cytotoxic "payloads" for selective delivery of cytotoxic agents to cancer cells. Targeted delivery of cytotoxic agents to cancer cells offers the potential for increased efficacy while minimizing exposure to normal tissues, thereby expanding the therapeutic window.

ADAMs (a disintegrin and metalloproteinase) are a family of transmembrane metalloproteinases that contribute to various cellular processes including growth factor and cytokine signaling, cell-cell interactions, adhesion, and extracellular matrix remodeling (Oria 2018). ADAMs also act as ligands for integrins by competing with matrix proteins. Furthermore, recent studies demonstrate that several ADAMs are highly expressed in cancer cells and cancer tissues. ADAM9 (a disintegrin and metalloprotease domain-containing protein 9) is a novel member of the ADAM family. Dysregulation of ADAM9 has been implicated in tumor progression and metastasis, as well as pathological neovascularization.

ADAM9 is an attractive target for tumor therapy because of its overexpression in many malignant tumors and limited expression in normal tissues. Many solid tumor types overexpress ADAM9 (Fritzsche 2008a, Fritzsche 2008b, Franzke 2009, Fan 2016, Hicks 2019), including, but not limited to non-squamous non-small cell lung cancer (NSCLC) (Chiu 2017, Kossmann 2017, Lin 2017, Hicks 2019), triple-negative breast cancer (TNBC) (Hicks 2019), colorectal cancer (CRC) (Li 2013), gastroesophageal cancer (Hicks 2019), and pancreatic cancer (Grutzmann 2004, Hicks 2019, Oria 2019). ADAM9 overexpression is associated with multiple adverse clinical and pathological features of disease, increased risk of cancer recurrence, and reduced survival (Izumi 1998, Karadag 2006, Genin 2015).

The sponsor will develop IMGC936 in advanced solid tumors including non-squamous NSCLC, TNBC, CRC, gastroesophageal cancer, and pancreatic cancer. Nonclinical development includes safety evaluation in several models, including Good Laboratory Practice (GLP) toxicology in cynomolgus monkeys.

2.2. Disease Background

This first-in-human clinical trial will evaluate the safety and initial antitumor activity of single-agent IMGC936 in participants with relapsed or refractory, locally advanced, unresectable or metastatic solid tumors known to express high levels of ADAM9 including non-squamous NSCLC, TNBC, CRC, gastroesophageal cancer, and pancreatic cancer. The rationale for selecting these distinct types of cancer without prescreening for ADAM9 expression is based on the relatively high level of ADAM9 expression observed in these cancers and the unmet medical need for patients with these advanced diseases.

Differential response to therapeutic mAbs correlates with specific polymorphisms of fragment crystallizable (Fc) gamma receptors (FcγRs), which are key mediators of antibody-dependent cellular cytotoxicity (Mellor 2013). Thus, an exploratory objective of the study is to investigate the relationship between FcγR genotype and antitumor activity of IMGC936.

2.2.1. Non-Squamous Non-Small Cell Lung Cancer

Lung cancer is the second most commonly diagnosed cancer worldwide. In 2020, an estimated 2.2 million new cases of lung cancer were diagnosed globally, accounting for approximately 11.4% of the global cancer burden (Sung 2021). In 2020, an estimated 228,820 adults (116,300 men and 112,520 women) in the United States (US) will be diagnosed with lung cancer (Siegel 2020). An immunohistochemistry (IHC) screen of non-squamous NSCLC specimens revealed that 86 of 86 total specimens (100%) exhibited ADAM9 expression at any level, while 60 of 86 (70%) had H-scores > 100 (ie, moderate or strong expression) (Hicks 2019).

In the first-line treatment setting, due to the introduction of new drugs and patient selection based on histological subtypes and driver mutations that influence the biology of these malignancies, median overall survival (OS) for patients with advanced non-squamous NSCLC receiving platinum-based chemotherapy in combination with agents targeting specific histologies and mutations has improved to 12 months or longer in controlled studies (Reck 2013). However, despite availability of multiple treatment options in the second-line setting, clinical outcomes remain poor. Response rates are, on average, less than 10%, and median OS is 7 to 9 months from start of second-line therapy (Zer and Leighl 2014).

ADAM9 is expressed on a high percentage of non-squamous NSCLC tumors and promotes an aggressive phenotype of adenocarcinoma xenografts in mice (Kossmann 2017). In addition, high expression of ADAM9 is linked to poor prognosis in lung adenocarcinoma patients (Lin 2017). These observations provide rationale for targeting ADAM9 with IMGC936 in patients with non-squamous NSCLC.

2.2.2. Triple Negative Breast Cancer

Globally, breast cancer in females is now the leading cause of cancer, with an estimated 2.3 million new cases in 2020. It is the fifth leading cause of cancer mortality worldwide with 685,000 deaths (Sung 2021). In the US, approximately 281,550 new cases of invasive breast cancer in women are predicted to occur in 2021, along with 2650 cases in men (Siegel 2021). Approximately 10% to 20% of breast cancers known as TNBC are negative for estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 (HER2) (Li 2019). TNBC is associated with a poorer prognosis than other types of breast cancer. An IHC screen of TNBC specimens, revealed that 20 of 20 total specimens (100%) exhibited ADAM9 expression at any level, while 13 of 20 (65%) had H scores > 100 (ie, moderate or strong expression) (Hicks 2019).

A recent study by Zhou et al. suggests a novel molecular mechanism in which proteolytic cleavage by ADAM9 releases stable homotrimers of tumor necrosis factor-α from the membrane. This in turn activates signaling leading to a metastatic TNBC phenotype (Zhou 2019).

Among available historical data, commonly used chemotherapies demonstrate limited durability of response, limited survival benefit, and challenging toxicity profiles, suggesting a considerable unmet medical need in metastatic TNBC (Li 2019). Therapeutic regimens that result in improved, sustainable clinical responses and longer survival, along with more manageable safety profiles, are still needed for patients with metastatic TNBC.

2.2.3. Colorectal Cancer

According to GLOBOCAN 2020, it is estimated that approximately 1,191,590 new cases of CRC were diagnosed worldwide (1,148,515 colon cancer, 732,210 rectal cancer, and 53,583 anus cancer). In 2020, there were approximately 935,173 new deaths from colorectal cancer (576,858 colon cancer, 339,022 rectal cancer, and 19,293 anus cancer). Together, CRCs are the third most commonly diagnosed form of cancer, comprising about 10% of all cancer diagnoses, and the second leading cause of cancer death worldwide is CRC (Bray 2018). Annually, approximately 147,950 new cases of large bowel cancer are diagnosed in the US, of which 104,610 are colon cancer, and the remainder are rectal cancer (Siegel 2020). An IHC screen of CRC specimens revealed that 12 of 15 total specimens (80%) exhibited ADAM9 expression at any level, while 6 of 15 (40%) had H scores ≥ 100 (ie, moderate or strong expression) (Hicks 2019).

Research by Li et al. suggest that ADAM9 contributes to cell invasion and progression in colon cancer (Li 2013). Chemotherapy for metastatic CRC has evolved significantly in the past decade with incorporation of biologics and targeted therapy, which has improved survival. In the US, 5 year survival rates for CRC, diagnosed during 2009 through 2015, were 64% for all disease stages but only 14% for those with distant metastases (Siegel 2020). Thus, despite advances in therapy, life expectancy remains limited in patients with advanced metastatic CRC. New therapeutic strategies are needed to improve the prognosis.

2.2.4. Gastroesophageal Cancer

Based on GLOBOCAN 2020 data, gastric cancer is the fourth leading cause of cancer death worldwide, and esophageal cancer ranks eighth in terms of incidence and sixth in mortality (Sung 2021). Gastric cancer has the fifth highest incidence among cancers, with 5.7% of all new cases attributable to the disease. Over a million new cases of gastric cancer are diagnosed worldwide each year (Sung 2021). In 2020, an estimated 27,600 (16,980 men and 10,620 women) in the US were diagnosed with gastric cancer, with an estimated 11,010 deaths (6,650 men and 4,360 women) (Siegel 2020). In 2020, 604,100 cases of esophageal cancers were diagnosed worldwide (Sung 2021). An estimated 18,440 new esophageal cancer cases will be diagnosed (14,350 in men and 4,090 in women), with about 16,170 deaths from esophageal cancer (13,100 in men and 3,070 in women) in the US.

Gastroesophageal cancer is associated with high mortality and poor prognosis, as it is often diagnosed at an advanced stage (Howlader 2020). In the US, the 5-year survival rate is 32% for gastric cancer and 20% for esophageal cancer. Average survival rates for gastroesophageal cancer reflect the fact that many cases are already metastatic at diagnosis. For those with distant metastases, 5-year survival is 5%.

An IHC screen of gastric cancer specimens revealed that 15 of 15 total specimens (100%) exhibited ADAM9 expression at any level, while 11 of 15 (73%) had H scores > 100 (ie, moderate or strong expression) (Hicks 2019). An IHC screen of esophageal cancer tissue microarray cores revealed that 18 of 19 total cores (95%) exhibited ADAM9 expression at any level, while 7 of 19 (37%) had H scores > 100 (unpublished data).

For patients with advanced-stage gastric cancer, treatment typically consists of fluoropyrimidine and platinum-based combination chemotherapy and is associated with a median OS of 7 to 10 months (Wagner 2006). Despite demonstrated efficacy of numerous chemotherapy options,

only 40% of patients who progressed to first-line chemotherapy are susceptible to a second-line chemotherapy on progression (Pellino 2019). Chemotherapy for metastatic esophageal cancer is considered to be a palliative approach, meant to alleviate symptoms like dysphagia. Treatment aims to improve symptom-free survival with limited if any at all, positive effect on OS. The most common cytotoxic approaches involve combination therapies with a platinum-based agent like carboplatin, cisplatin, or oxaliplatin, taxane or fluorouracil. In the US, median OS for metastatic esophageal cancer with cytotoxic and/or radiation therapy is only 8 to 10 months (Barsouk 2019). Consequently, there is an urgent, unmet need for targeted therapies in the treatment of metastatic esophageal cancer. Although newer therapies have improved survival for advanced cases of gastroesophageal junction and gastric cancer, there remains a significant medical need for additional treatment options.

2.2.5. Pancreatic Cancer

Globally, pancreatic cancer is the seventh leading cause of cancer death with an estimated 432,242 deaths and 458,918 new cases in 2018 (Bray 2018). Despite advancements in detection and management, the 5-year survival rate stands at 9% only (Siegel 2020). An estimated 57,600 new cases of pancreatic cancer will be diagnosed in the US, with an estimated 47,050 deaths in 2020. An IHC screen of pancreatic cancer specimens revealed that 20 of 20 total specimens (100%) exhibited ADAM9 expression at any level, while 17 of 20 (85%) had H-scores > 100 (ie, moderate or strong expression) (Hicks 2019).

Evaluation of second-line therapy in randomized trials indicates that 16 to 57% of patients with pancreatic cancer receive salvage chemotherapy after failure of first-line gemcitabine (Heinemann 2012). Median OS in gemcitabine-resistant patients receiving best supportive care was 2.3 months in a small randomized trial (Heinemann 2012).

Pancreatic ductal adenocarcinoma cells overexpress ADAM9, and increased ADAM9 expression correlates with poor tumor grading and the presence of vasculature invasion (Oria 2019). Similarly, Grutzmann et al. demonstrated that ADAM9 is overexpressed in pancreatic ductal adenocarcinomas and that cytoplasmic ADAM9 expression associates with poor survival in patients who underwent curative resection of these tumors (Grutzmann 2004). Thus, ADAM9 may be a potential target for treatment of pancreatic ductal adenocarcinoma.

2.3. IMGC936

IMGC936 is an ADC targeted against ADAM9. IMGC936 consists of the maytansinoid DM21-C conjugated to the MGA021 antibody via a cleavable peptide linker. Maytansinoids are anti-mitotic agents that inhibit tubulin polymerization and microtubule assembly. MGA021 is a humanized, IgG1/kappa mAb that recognizes human ADAM9 antigen and is cross-reactive with cynomolgus monkey ADAM9. MGA021 is composed of 2 IgG1 heavy chains of 452 amino acids and 2 kappa light chains of 218 amino acids and has a molecular weight of 147,425 Da. The triple mutation M252Y/S254T/T256E (YTE) is incorporated into the Fc portion of IMGC936 to improve the neonatal Fc receptor (FcRn) binding at acidic pH and therefore enhance pharmacokinetic properties. In IMGC936, each antibody molecule is conjugated to approximately 2.0 molecules of DM21-C (drug to antibody ratio of ~1.5-2.2) via site specific conjugation to engineered cysteine residues at position 442 of the IgG1 heavy chains. Owing to

payload conjugation via a cleavable linker, the active DM51 and DM50 maytansinoid catabolites are protease-released intracellularly, but can induce bystander killing of neighboring tumor cells, as they are membrane permeable. The bystander killing may occur irrespective of ADAM9 expression on neighboring cells in the tumor. Importantly, the bystander killing by the maytansinoid catabolites may contribute to the therapeutic benefit of IMGC936 toward tumor with heterogeneous expression of ADAM9.

2.4. IMGC936 Benefit/Risk in Humans

IMGC936 is an investigational drug with safety data available from nonclinical studies. No information is available about the adverse effects of IMGC936 in humans; therefore, as with any new product, administration of IMGC936 may involve risks that are currently unforeseen.

IMGC936 is an ADC that may lead to killing of the tumor cell. Based on the mechanism of action and the risks associated with similar drugs, infusion-related reactions, hematologic toxicity, ocular toxicity, and interstitial cystitis are potential risks of IMGC936 treatment.

2.5. Nonclinical Background on IMGC936

Nonclinical studies necessary to support clinical studies have been performed and are summarized below. Further information can be obtained in the Investigator's Brochure.

2.5.1. IMGC936 Nonclinical Experience

2.5.1.1. IMGC936 Pharmacology

The nonclinical pharmacology program was designed to characterize the binding affinity and biological activity of IMGC936 in vitro and in vivo and is briefly summarized below. Further details are in the IMGC936 Investigator's Brochure.

IMGC936 is an ADC targeted against ADAM9. IMGC936 consists of the maytansinoid DM21-C conjugated to MGA021a cleavable peptide linker. Maytansinoids are anti-mitotic agents that inhibit tubulin polymerization and microtubule assembly. MGA021 is a humanized, IgG1/kappa mAb that recognizes human ADAM9 antigen and is cross-reactive with cynomolgus monkey ADAM9. MGA021 is composed of 2 IgG1 heavy chains of 452 amino acids and 2 kappa light chains of 218 amino acids and has a molecular weight of 147,425 Daltons. The triple mutation M252Y/S254T/T256E (YTE) is incorporated into the Fc) portion of MGA021 to improve the neonatal Fc receptor (FcRn) binding profile and enhance pharmacokinetic (PK) properties. In IMGC936, each antibody molecule is conjugated to approximately 2.0 molecules of DM21-C (drug to antibody ratio of ~1.5–2.2) via site specific conjugation to engineered cysteine residues at position 442 of the heavy chains.

Binding of IMGC936 to its target antigen was characterized by surface plasmon resonance (SPR) using recombinant soluble human and cynomolgus ADAM9; IMGC936 binds with high affinity toward human (1.1 nM) and cynomolgus monkey (1.8 nM) ADAM9. Following binding to cell surface ADAM9 and internalization of IMGC936 through endocytosis, the peptide linker is cleaved by lysosomal proteases, such as cathepsin B, and release of intracellular DM21-C-Cys. The DM21-C-Cys catabolite undergoes further proteolysis to release the active maytansinoid catabolite DM51. DM51 may also undergo S methylation to the related active catabolite, DM50.

The active maytansinoid catabolites bind to tubulin at the vinca binding site, resulting in suppression of microtubule dynamics, leading to depolymerization of microtubules and cell cycle arrest in the G2/M phase of the cell cycle, resulting in cell death (Oroudjev 2010, Chen 2017). In addition, the active catabolites DM50 and DM51 are able to permeate the cell membrane, diffuse into the extracellular space, and kill nearby dividing cells (bystander effect). Consistent with SPR, flow cytometry demonstrated ADAM9-dependent binding toward cell lines expressing human and cynomolgus receptor with similar affinity.

Consistent with binding and internalization, IMGC936 demonstrated potent dose-dependent in vitro cytotoxicity against multiple human tumor cell lines with half maximal inhibitory concentration (IC_{50}) values ranging from 0.2 to 224.0 nM. IMGC936 mediated bystander killing of ADAM9-negative tumor cells in the presence of ADAM9-positive tumor cells in vitro. Importantly, the bystander killing property of IMGC936 may afford therapeutic benefit toward tumors with heterogeneous ADAM9 expression.

In vivo efficacy studies established proof-of-concept for targeting ADAM9-positive human tumor xenografts with IMGC936. In single-dose experiments, IMGC936 exhibited antitumor activity toward human tumor xenografts representing breast, lung, gastric, colorectal, and pancreatic cancer with a range of medium to medium-high ADAM9 expression (H-scores from 90 to 210). Antitumor activity was observed across a range of doses tested (1.25 to 10 mg/kg). IMGC936 was well tolerated in tumor-bearing mice at all doses and dosing regimens tested.

2.5.1.2. IMGC936 Pharmacokinetics and Toxicology

A summary of nonclinical PK and toxicology data are provided below. Please see the IMGC936 Investigator's Brochure for further details.

IMGC936 was administered to cynomolgus monkeys in toxicology studies that included single-dose (25 mg/kg) and repeat-dose (3 to 22.5 mg/kg/dose) studies at 2-week intervals for a total of either 2 or 3 doses. A single dose of 25 mg/kg was well tolerated; repeat-dose study results are described below.

Similar target expression was observed between a panel of human and cynomolgus monkey tissues examined in a tissue cross-reactivity study. The results showed that IMGC936 bound to epithelial cells in several tissues including urinary bladder. IMGC936-related microscopic bladder findings occurred in 3 animals in the repeat-dose toxicology studies. Two of these were animals that died on study; 10 mg/kg administered 3 times and 22.5 mg/kg/dose administered 2 times, both administered at a 2-week interval. Urinary bladder microscopic findings consisted of moderate degeneration/necrosis of the transitional epithelium associated with an infiltration of mixed inflammatory cells after 2 doses, and increased to moderate loss of the overlying epithelium in the urinary bladder noted with submucosal inflammation, mononuclear infiltrates, edema, and minimal fibrosis and the remaining epithelium was degenerative and disorganized after 3 doses. Both animals survived the dosing period and died either 11 or 19 days after the last dose. A third male that received 2 doses at 22.5 mg/kg/dose had mild epithelial single-cell necrosis in the urinary bladder associated with a mild infiltration of mixed inflammatory cells at the terminal necropsy.

Additional microscopic findings in the animal that received 3 doses included moderate myocardial fiber degeneration and necrosis observed predominately within the myocardium. The

cause of these are unknown and a relationship to IMGC936 cannot be ruled out; however, IMGC936 does not bind to myocardium and there were no findings noted in electrocardiograms (ECGs), heart rate, or respiration rate.

Maytansinoids are known to cause ocular toxicity when used as the payload in ADCs. IMGC936-related ophthalmic findings were observed in both repeat-dose nonclinical studies and included discharge, conjunctival swelling, congestion and/or cloudiness, pannus, cellular or keratic precipitates, and corneal pigmentation in one or both eyes and microscopic changes of minimal to moderate single cell necrosis and minimal to mild increased mitoses. All findings showed either complete or ongoing resolution at the end of the recovery period.

Across all GLP studies, there were no findings for changes in body weight, food consumption, ECGs (including jacketed external telemetry conducted in the GLP study on Day 15, 3 hours predose through at least 21 hours postdose), blood pressure, heart rate, or respiration rate. Non-adverse changes in clinical pathology parameters were observed after 3 biweekly repeat-doses and were transient, mild, and did not result in any microscopic correlates.

PK analysis showed accumulation of conjugated and total antibody as well as unconjugated DM51 when IMGC936 repeat doses were administered at 2-week intervals. The human cytochrome P450 enzyme CYP3A4/5 was implicated in the metabolism of DM51 and DM50.

Based on the GLP toxicology study, the highest non-severely toxic dose (HNSTD) for IMGC936 was 10 mg/kg/dose administered as a 10-minute intravenous (IV) infusion once every 2 weeks (total of 2 doses) at which level there were no life-threatening toxicities, mortality, and all findings were reversible.

2.6. IMGC936 Dose Selection

A dose of 0.5 mg/kg was estimated as the maximum recommended starting dose (MRSD) for the proposed Phase 1 trial using the lowest value of MRSD determined by two approaches: a traditional HNSTD-based approach ($MRSD_1$) and a PK-guided approach ($MRSD_2$).

In brief, using the HNSTD-based approach (CDER 2010), the starting dose was determined as follows. The HNSTD in the GLP toxicology study in cynomolgus monkeys was determined to be 10 mg/kg administered by 10-minute IV infusion every 2 weeks for 2 doses. $MRSD_1$ was defined as 1/6 the HNSTD ($10 \times 1/6 = 1.67$ mg/kg). The human equivalent of $MRSD_1$, based on a body surface area conversion factor (CDER 2014), was calculated as 0.53 mg/kg (ie, 1.67 mg/kg × 0.32). IMGC936 has similar binding affinity (KD) to human and cynomolgus monkey ADAM9 of 1.1 and 1.8 nM, respectively. This slight difference in KD can be attributed to within-assay variability and, therefore, considered to be similar. Consequently, no further adjustment for affinity differential was undertaken. Thus, 0.53 mg/kg dose was considered as the MRSD1.

The second approach for the determination of the starting dose was based on the PK guided approach (Krishnan and Andersen 1990, Mahmood 2009). The HNSTD in the GLP toxicology study in cynomolgus monkeys was determined to be 10 mg/kg and the corresponding predicted area under the curve from time zero to infinity ($AUC_{0\text{-}inf}$) after the administration of the first 10-minute IV infusion dose was 37,089 µg•h/mL. Using the mean predicted clearance of ADC (CL_{adc}) of 0.00010 L/h/kg in humans, the human equivalent dose producing the same area under

the curve (AUC) at the monkey HNSTD was estimated as 3.71 mg/kg (the product of the AUC in cynomolgus monkeys and the estimated CL_{adc} in humans). To this, a safety factor of 6 was applied as described above resulting in an estimated MRSD2 of 0.62 mg/kg.

The lower of the MRSD1 and MRSD2 values was 0.53 mg/kg. Therefore, 0.5 mg/kg was considered as the MRSD.

The proposed clinical doses for IMGC936 selected for the Phase 1 clinical trial are 0.5, 1.0, 2, 4, 7, 10, and 12 mg/kg administered every 3 weeks as an IV infusion. At the 12 mg/kg dose, the predicted first dose maximum concentration (C_{max}) and AUC for ADC in humans were approximately the same (1×) as the exposure at the HNSTD (10 mg/kg) in monkeys.

2.6.1. Multiples of Monkey Exposure

Allometric scaling, modeling, and simulations were used to estimate exposure data (C_{max} and AUC) in the human after the first dose of 0.5 to 12 mg/kg and compared to the mean cumulative exposure for the HNSTD in the cynomolgus monkey (10 mg/kg). In this estimation, predicted exposure parameters in a dosing interval of 3 weeks (504 hours) in humans after the first dose were compared to actual exposure parameters in a dosing interval of 2 weeks (336 hours) following administration of the second dose at the HNSTD (10 mg/kg). First-dose predicted exposure data suggested adequate multiples of monkey exposure for the proposed dose range (0.5 to 12 mg/kg) to be investigated in humans. Using exposure parameters for ADC, DM51, and total antibody (which includes conjugated and unconjugated antibody), the safety margins at the starting dose of 0.5 mg/kg in humans were 35-, 27- and 25-fold, respectively, based on C_{max} and 64-, 22-, and 67-fold, respectively, and based on cumulative AUC as calculated using human (predicted) and monkey (actual) exposure parameters. Multiples of monkey exposure at the proposed top dose of 12 mg/kg were in the range of 0.3- to 1.4-fold.

3. STUDY OBJECTIVES AND PURPOSE

3.1. Dose Escalation Phase

3.1.1. Primary Objective and Endpoints

- To assess safety and tolerability, including dose-limiting toxicities (DLTs), maximum tolerated dose (MTD), or maximum administered dose (MAD; if no MTD is defined), and recommended Phase 2 dose (RP2D) for IMGC936
    - Incidence of adverse events (AEs), serious adverse events (SAEs), and DLTs

3.1.2. Secondary Objectives and Endpoints

- To characterize PK and immunogenicity of IMGC936
    - Study drug concentration
    - Summary PK parameters
    - Incidence of antidrug antibodies (ADA)
- To describe objective response rate (ORR) and duration of response (DoR) for IMGC936 using Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1)
    - ORR
    - DoR

3.1.3. Exploratory Objectives and Endpoints

- To explore progression-free survival (PFS)
    - PFS
- To explore potential biomarkers of clinical and/or immunologic response to IMGC936 in blood and tumor tissue
    - Change in soluble ADAM9 levels over time
    - Correlation of potential biomarkers (FcγR genotype, soluble ADAM9, cell-free tumor DNA) and response
- To explore the relationship between baseline ADAM9 expression and antitumor activity
    - Correlation of ADAM9 expression and response

3.2. Dose Expansion Phase

3.2.1. Primary Objective and Endpoint

- To describe ORR for IMGC936 using RECIST v1.1
    - ORR

3.2.2. Secondary Objectives and Endpoints

- To assess safety and tolerability for IMGC936
    - Incidence of AEs, SAEs, and study drug–related treatment-emergent adverse events (TEAEs) that lead to discontinuation
- To characterize PK and immunogenicity of IMGC936
    - Study drug concentration
    - Summary PK Parameters
    - Incidence ADA
- To describe DoR and PFS
    - DoR
    - PFS

3.2.3. Exploratory Objectives and Endpoints

- To explore potential biomarkers of clinical and/or immunologic response to IMGC936 in blood and tumor tissue
    - Change in soluble ADAM9 levels over time
    - Correlation of potential biomarkers (FcγR genotype, soluble ADAM9, cell-free tumor DNA) and response
- To explore the relationship between baseline ADAM9 expression and antitumor activity
    - Correlation of ADAM9 expression and response
- To explore ocular primary prophylaxis regimens
    - Frequency and severity of ocular events

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan

This study is a Phase 1/2, first-in-human, open-label, dose-escalation and expansion study designed to characterize the safety, tolerability, PK, immunogenicity, and preliminary antitumor activity of IMGC936.

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 centers.

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 (Section 5.4).

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.

4.1.1. Dose Escalation

The primary objective of the Dose Escalation Phase of the study is to characterize safety and tolerability of IMGC936 to define the single-agent MTD and select a 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 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 2).

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. Infusion 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 5 mg/kg and 6 mg/kg.

Table 2: 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 (Section 5.4).

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 (Appendix 2 - Time and Events Schedule (Schedule B - 28 day Cycle). 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 Day 1 and Day 8 dose 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 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.

4.1.2. 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	Tumor Type
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

Abbreviations: CRC: colorectal cancer; TNBC: triple-negative breast cancer; NSCLC: non-small cell lung cancer.

Participants may continue on study drug until disease progression, AE requiring discontinuation, withdrawal of consent, physician decision, or other discontinuation criteria are met (Section 5.4).

A futility assessment will be conducted on the first 13 participants (Section 14.1) 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.

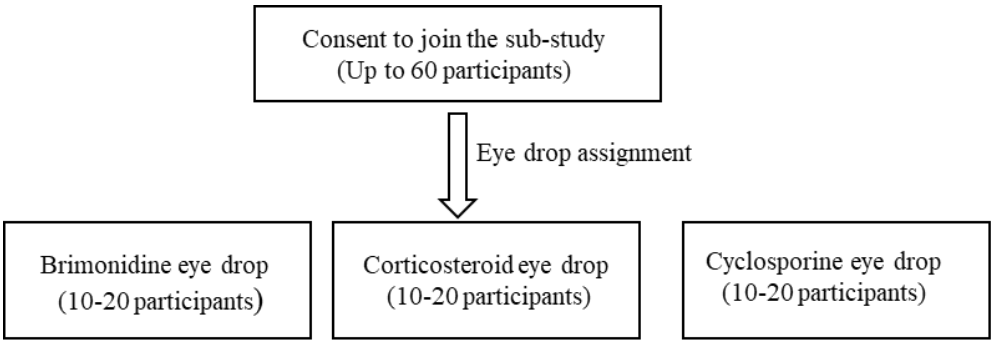
The expansion cohorts may test more than 1 dose and/or schedule, not exceeding the MTD.

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 (see Section 10.3.1). ADAM9 testing results are not required for enrollment.

4.1.3. Eye Drop Sub-Study

4.1.3.1. Sub-Study Schema



4.1.3.2. Sub-Study Design

Up to 60 participants from Cohorts A to G may voluntarily consent to join a sub-study to evaluate the effect of different prophylactic eye drops, beyond standard lubricating eye drops. Consenting participants will be assigned to cohorts of 10 to 20 participants who will receive additional eye drops as primary prophylaxis to mitigate ocular symptoms and signs. Participants in this sub-study will be monitored for the frequency and severity of ocular events and will have an ocular examination after 2 cycles of therapy regardless of whether they have ocular symptoms and signs, as required of all participants in this trial. Major differences in ocular AEs (eg, 50% reduction in participants with ≥ Grade 2 keratopathy, or 50% reduction in ocular AEs leading to dose reduction/discontinuation) will be used to determine whether different eye drop regimens provide benefit in comparison to others and to participants on trial that only receive prophylactic lubricating drops. Knowledge gained from this sub-study may be applied to the remainder of the study participants. Details of the eye drop options are described in Section 7.2.1.

4.1.4. Study Assessments

Safety and tolerability will be closely monitored throughout both phases of the study (Section 12).

Additionally, PK and immunogenicity and biomarker assessments will occur as described in Section 10, Appendix 1, and Appendix 4.

Further, antitumor activity is described in Section 11.

4.2. Dose-Limiting Toxicity

For guiding dose-escalation decisions, DLTs will be defined based on TEAEs or abnormal laboratory values that meet DLT criteria that occur up to Day 21 of Cycle 1 for Schedule A and Day 28 of Cycle 1 for Schedule B. AE severity will be graded according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v5.0). DLTs will be defined separately for hematologic, non-hematologic, and hepatic events.

In addition to conventional Cycle 1 DLTs to guide escalation, cumulative toxicity and tolerability for all cohorts will be considered and may be utilized to inform dose escalation.

4.2.1. Hematologic Dose-Limiting Toxicity

Hematologic DLT is defined as follows:

- Grade 4 neutropenia lasting > 7 days
- ≥ Grade 3 febrile neutropenia Grade 4 thrombocytopenia, irrespective of duration
- Grade 3 thrombocytopenia associated with clinically significant bleeding
    - ≥ Grade 3 hemolysis

The following events will be specifically **excluded** from the definition of hematologic DLT:

- ≥ Grade 3 lymphopenia
- Grade 3 anemia that is not associated with other clinically significant complications

4.2.2. Non-hematologic Dose-Limiting Toxicity

Non-hematologic DLT is defined as any ≥ Grade 3 non-hematologic event, including Grade 3 ocular symptoms and signs.

The following events will be specifically excluded from the definition of non-hematologic DLT:

- Grade 3 electrolyte abnormality that lasts < 72 hours, is not otherwise associated with clinical complications, and responds to medical intervention
- Grade 3 fever that lasts < 72 hours and is not associated with hemodynamic compromise
- Grade 3 nausea or vomiting that lasts < 72 hours and responds to medical intervention
- Grade 3 or greater amylase and/or lipase elevation that is not associated with clinical or radiographic evidence of pancreatitis requiring hospitalization
- Grade 3 gastrointestinal AEs of diarrhea, constipation, abdominal pain, cramping, dyspepsia, or dysphagia that resolves to ≤ Grade 1 or baseline within 72 hours with maximal supportive care
- Grade 3 fatigue that lasts < 72 hours

Note: The following Grade 2 non-hematologic AEs may also be considered as DLTs:

- Grade 2 AEs that are prolonged inordinately, based upon the medical judgment of the investigator, and/or lead to permanent discontinuation of study drugs due to participant intolerance
- Hepatic laboratory abnormalities meeting Hy's law criteria (described within Section 4.2.3)
- Eye pain or reduction in visual acuity that does not respond to topical ophthalmic therapy and does not improve to Grade 1 within 14 days of initiation of topical ophthalmic therapy, or that requires systemic treatment

4.2.3. Hepatic Dose-Limiting Toxicity

Hepatic DLTs will be defined as follows:

- Any elevation of one or more transaminases > 8 × the institutional reference laboratory upper limit of normal (ULN) irrespective of duration
- Any Grade 3 elevation of one or more transaminases > 5.0–8.0 × ULN that does not resolve to Grade 2 (ie, > 3.0–5.0 × ULN) within 7 days and Grade 1 (ie, > ULN– 3.0 × ULN) within 14 days.
- Grade 3 elevation of total bilirubin that is > 5 × the ULN irrespective of duration
- Any Grade 3 elevation of total bilirubin > 3.0–5.0 × ULN that does not resolve to Grade 2 (ie, > 1.5–3.0 × ULN) within 7 days and Grade 1 (ie, > ULN–1.5 × ULN) within 14 days.
- Any event meeting criteria for Hy's law as follows (all 3 features):
  - Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) > 3 × ULN
  - Concurrent elevation of total bilirubin > 2 × ULN without initial evidence of cholestasis
  - No alternative etiology can be identified

4.3. Expansion Phase Safety Monitoring

Safety will be evaluated continuously and in aggregate in the expansion cohorts. Safety assessments will be based on all TEAEs and abnormal laboratory values. If at any time ≥ 33% of at least 3 participants who received study drug in an expansion cohort experience a study drug–related TEAE leading to discontinuation, enrollment will be paused within that cohort and may also be paused in ongoing cohorts at the discretion of the sponsor. If it is determined that the clinical investigation should be halted due to an unacceptable participant risk, the study must be terminated after appropriate consultation between the sponsor and investigators.

4.4. Dose Escalation Rules

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 (ie, ≥ 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 (ie, ≤ 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 2. 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, 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, antitumor activity, to facilitate selection of the RP2D. Intermediate dose levels, not exceeding the MTD, may also be explored. Following determination of the RP2D, tumor-specific expansion cohorts may be opened in tumor types selected from those enrolled in dose escalation.

4.5. Guidelines for Dose Modification

Dose modifications are allowed for toxicity according to the guidelines in Section 7.

Dose reductions of study drug are allowed for participants experiencing significant toxicity, or an underlying condition that may warrant dose reduction, but are considered to be receiving clinical benefit by the investigator. The investigator should contact the sponsor to discuss the appropriate dose of study drug based on the safety profile and evidence of antitumor activity. A dose reduction by 1 dose level may be allowed, if considered appropriate, rather than study drug discontinuation. The participant must be discontinued from study drug if more than 2 dose reductions are required. Sponsor approval must be obtained in advance of dose reduction of study drug.

4.5.1. Dose Delays

Participants who experience toxicity should have study drug held pending assessment, management, and resolution of the toxicity. If the toxicity is assessed as unrelated to study drug or does not meet DLT criteria, study drug may be restarted at the previous dose and schedule, after consultation with the medical monitor. The toxicity should have resolved prior to reinstitution of study drug per guidelines outlined in Section 7. Reinstitution of study drug shall be conducted as follows:

- Dose delays of up to 21 days are allowed for participants who experience toxicity. This may include 1 missed dose of IMGC936 on Schedule A and 2 missed doses on Schedule B. The procedures at the originally scheduled missed visit should be performed as soon as possible with study drug reinstituted as if no delay had occurred, picking up at the day where the interruption occurred per the schedule in Appendix 1 and Appendix 2. Participants who have a dose delay of > 21 days may restart study drug with discussion and approval of the sponsor.

4.5.1.1. COVID-19/SARS-CoV-2 Infection

The following guidelines apply to participants with confirmed (positive by regulatory authority approved test) or presumed (test pending/clinical suspicion) coronavirus disease 2019 (COVID-19)/severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection:

- For participants with active SARS-CoV-2 infection, study drug should be delayed for at least 14 days from the first positive COVID-19 test or start of symptoms whichever is later.
- Prior to restarting study drug, participants should be afebrile for 72 hours and SARS-CoV-2–related symptoms should have recovered to ≤ Grade 1 for a minimum of 72 hours. The sponsor should be informed when resuming study drug.

The sponsor must be informed of a participant with COVID-19/ SARS-CoV-2 infection.

4.6. Study Duration

It is expected that enrollment for the Dose Escalation Phase of the study will occur over approximately 24 months. Enrollment for study expansion will occur over approximately

18 months. The total time for conduct of the trial is expected to be approximately 48 months. These time estimates may vary from that observed in the actual conduct of the trial.

4.6.1. Participant Accrual

During dose escalation, the number of participants could be up to 45 depending on results during the study and the number of dose levels explored. If Schedule B is explored, up to 27 evaluable participants may be enrolled. This number does not consider replacement of non-evaluable participants or the possibility of expanding an individual escalation cohort up to 15 participants to allow for further evaluation of safety, PK, and antitumor activity at that dose level.

For study expansion, based on futility assessments at 13 participants per cohort for the 5 to 7 expansion cohorts, and at the sponsor's discretion, an additional 26 participants may be enrolled in each selected expansion cohort (for a total of up to 39 participants per cohort if fully expanded). The number of participants may vary depending on results of futility assessments. Up to 273 participants will be enrolled in the dose expansion cohort.

4.6.2. Definition of End of Study

The end of study will occur after the Safety Follow-up Visit for the last participant remaining on treatment or 1 year from the last accrued participant's first visit, or at the sponsor's discretion.

End of study for each participant is defined as follows: Participant is lost to follow-up (LTFU) (Section 9.15.3) or discontinues from the study due to any reason listed in Section 6.5. Each participant's end of study status will be recorded in the end of study electronic case report form (eCRF) page.

5. SELECTION AND WITHDRAWAL OF PARTICIPANTS

To be eligible for the study, participants must meet all the inclusion criteria. Participants will be excluded from the study if they meet any exclusion criteria. No exceptions to these criteria will be granted by the sponsor.

5.1. Inclusion Criteria

1. Ability to provide informed consent and documentation of informed consent prior to any study-related tests or procedures that are not part of standard of care for the participant's disease. Participants must be willing and able to comply with study procedures.
2. Participants with histologically proven, relapsed or refractory, unresectable locally advanced or metastatic non-squamous NSCLC, TNBC, CRC, gastroesophageal cancer, or pancreatic cancer for whom no therapy with demonstrated clinical benefit is available. Participants in expansion cohorts must have received all appropriate approved therapy and fit within the prior lines of therapy restrictions listed below.

   Note: Neoadjuvant/adjuvant systemic treatment are included as 1 line in prior lines of therapy, except for TNBC where they are excluded.

   Note: Maintenance therapies are considered part of the prior line of therapy and will not be counted as a separate line of therapy.

   a. Non-squamous NSCLC: Participants in dose expansion phase may have been treated with up to 3 prior lines of systemic chemotherapy, with no limit on prior targeted therapy containing lines, eg, for targetable mutations.
   b. TNBC: Participants in dose expansion phase may have been treated with up to 4 prior lines of systemic therapy for metastatic disease, excluding checkpoint inhibitors and neoadjuvant/adjuvant therapies.
   c. CRC: Participants in dose expansion phase may have been treated with up to 4 prior lines of systemic therapy.
   d. Gastroesophageal cancer: Participants in dose expansion phase may have been treated with up to 4 prior lines of systemic therapy.
   e. Pancreatic cancer: Participants in dose expansion phase must have been treated with 1 to 3 prior lines of systemic therapy, with no more than 2 chemotherapy-containing lines.
3. Either non-measurable or measurable disease per RECIST v1.1 and documented by computed tomography (CT) and/or magnetic resonance imaging (MRI) obtained within 28 days of Cycle 1 Day 1.

   a. Dose Escalation Phase: Participants may have non-measurable or measurable disease per RECIST v1.1.
   b. Dose Expansion Phase: Participants must have measurable disease per RECIST v1.1.
4. Age ≥ 18 years old.
5. Tumor tissue must be submitted. If archival tissue (formalin-fixed paraffin-embedded [FFPE] block or slides) is not available, participants may undergo a low-risk, medically routine procedure, if appropriate.

a. For all participants, tumor specimens for retrospective determination of ADAM9 expression via IHC staining will be collected and assayed at a central laboratory designated by the sponsor.

6. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.

   Note: If ECOG performance status is an inappropriate performance measurement for participant enrollment (eg, chronically non-ambulatory), then Karnofsky performance status must be ≥ 70.

7. Life expectancy ≥ 12 weeks.
8. Acceptable laboratory parameters as follows:
   - Platelet count ≥ 75 × 10^3/μL without platelet transfusion within 28 days prior to initiation of study drug.
   - Absolute neutrophil count ≥ 1.5 × 10^3/μL in the absence of any growth factor support within 21 days prior to initiation of study drug.
   - ALT/AST ≤ 3.0 × ULN; for participants with hepatic metastases, ALT and AST ≤ 5 × ULN.
   - Total bilirubin ≤ 1.5 × ULN, except participants with Gilbert's syndrome, who may enroll if the conjugated bilirubin is within normal limits.
   - Estimated glomerular filtration rate (eGFR) > 30 mL/min/1.73 m^2 or an estimated creatinine clearance of > 30 mL/min.
   - Urinalysis protein and occult blood cells within normal limits or 1+.
   - Negative serum pregnancy test for females of childbearing potential (FOCBP).
9. FOCBP, defined as not surgically sterilized (hysterectomy, bilateral salpingectomy, and bilateral oophorectomy) and between menarche and 1-year post menopause, must have a negative serum pregnancy test performed within 72 hours prior to initiation of study drug administration. Female participants must abstain from egg donation during the study.
10. FOCBP and male participants with partners of FOCBP must agree to use highly effective methods of contraception, according to Section 8.1.3, from the time of consent through 28 weeks after discontinuation of study drug administration. Male participants must abstain from sperm donation during the study.
11. FOCBP is not pregnant or breastfeeding, or a male participant is not expecting to father children within the projected duration of the study, starting with screening visit through 28 weeks after the last dose of study drug.

5.2. Exclusion Criteria

Participants who meet any of the following criteria will be excluded from the study.

1. Participants with active central nervous system disease within the last 6 months.

2. Active or chronic corneal disorders, history of corneal transplantation, or active ocular conditions requiring ongoing treatment/monitoring, such as uncontrolled glaucoma, wet age-related macular degeneration requiring intravitreal injections, active diabetic retinopathy with macular edema, macular degeneration, presence of papilledema, and/or monocular vision.
3. Participants who had prior therapies within the specified times below:
    - Systemic antineoplastic therapy within at least 5 half-lives or 4 weeks (whichever is shorter) prior to initiation of study drug.
    - Mediastinal or pelvic radiation therapy within 6 weeks prior to initiation of study drug administration. Palliative, limited field radiation for symptom control to soft tissues, or bone lesions within 2 weeks prior to initiation of study drug.
        - Note: Previously irradiated lesions are not considered measurable disease unless they have demonstrated progression per RECIST v1.1.
4. Participants must have stabilized or recovered (Grade 1 or baseline) from all prior therapy-related toxicities (except alopecia).
5. Clinically significant cardiovascular disease including but not limited to:
    - Myocardial infarction or unstable angina within 6 months prior to initiation of study drug.
    - Stroke or transient ischemic attack within 6 months prior to initiation of study drug.
    - Current clinically significant cardiac arrhythmias, eg, atrial fibrillation that are not well controlled with optimal medical intervention.
    - Current uncontrolled hypertension: systolic blood pressure > 160 mmHg, diastolic blood pressure > 100 mmHg.
    - Current congestive heart failure (New York Heart Association class III-IV).
    - Current pericarditis or clinically significant pericardial effusion.
    - Current myocarditis.
    - Left ventricular ejection fraction (LVEF) of < 50% by scan.
    - QTc interval > 480 msec.
6. Clinically significant pulmonary compromise, including pneumonia, pneumonitis, or a requirement for supplemental oxygen (excluding for sleep apnea) or history of ≥ Grade 3 drug-induced or radiation pneumonitis.
7. Participants with serious concurrent illness or clinically relevant active infection, including, but not limited to the following:
    - Active hepatitis B or C infection (whether or not on active antiviral therapy).
    - Human immunodeficiency virus infection.
    - Cytomegalovirus infection.

- Active COVID-19/SARS-CoV-2 infection. While SARS-CoV-2 testing is not mandatory for study entry, testing should follow local clinical practice guidelines/standards.
- Any other concurrent infectious disease requiring IV antibiotics within 2 weeks prior to initiation of study drug.

Note: Testing at screening is not required for the above infections unless clinically indicated.

8. History of prior bone marrow, stem cell, or solid organ transplantation.
9. Second primary invasive malignancy that has not been in remission for greater than 2 years, except nonmelanoma skin cancer; cervical carcinoma in situ on biopsy; or squamous intraepithelial lesion on Pap smear; localized prostate cancer (Gleason score < 6); or resected melanoma in situ or similar.
10. Major trauma or major surgery within 4 weeks prior to initiation of study drug.
11. Any serious underlying medical or psychiatric condition that would impair the ability of the participant to receive or tolerate the planned treatment at the study site.
12. Prior life-threatening hypersensitivity reactions to antibodies or any excipient contained in the drug formulation (Section 6.5).
13. Vaccination with replication-competent live virus vaccine within 4 weeks prior to initiation of study drug. Not all vaccine adverse effects have resolved to Grade 1. Inactivated annual influenza non-live vaccination is allowed (Section 8.1.1).

5.3. Withdrawal of Participant from the Study

Participants who withdraw before Cycle 1 Day 21 (Schedule A) or Cycle 1 Day 28 (Schedule B) for a reason unrelated to drug toxicity may be considered to have inadequate data to support dose escalation. These participants will be followed for safety assessments (see Section 12.2) and replacement participants may be enrolled in the same dose level.

5.4. Guidelines for Study Drug Discontinuation

Participants who tolerate study drug may continue to receive the study drug, as specified in the protocol, until any one of the following conditions are met:

- Progressive disease (PD) – Objective progression per RECIST v1.1 or clinical progression as determined by investigator
  - Participants who experience PD by RECIST v1.1 should discontinue study drug. However, participants who have experienced clinical benefit may continue the treatment if agreed upon between the sponsor and the investigator
- AE requiring study drug discontinuation including, but not limited to, the following events:
  - Study drug-related ≥ Grade 3 cardiac event

  - Study drug-related Grade 4 non hematologic event
- DLT during dose-escalation window (DLT period)
- Pregnancy
- Death
- Investigator decision
- LTFU
- Major protocol deviation requiring study drug discontinuation
- Participant declining further treatment
- Participant decision to withdraw consent for study
- The sponsor, investigator, or regulatory agency terminate the study

If the investigator decides that the participant should be withdrawn from the study or from dosing for any reason other than disease progression, the sponsor or its designee must be alerted in a timely manner by completing the appropriate eCRFs.

6. STUDY DRUG ADMINISTRATION

6.1. Description of Study Drug Administration

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

For Schedule A, IMGC936 is administered on Day 1 of each 21-day cycle.

For Schedule B, IMGC936 is administered on Day 1, Day 8, and Day 15 of a 28-day cycle for Cycles 1 and 2. For each subsequent 28-day cycle (Cycle 3 and beyond), IMGC936 is administered on Day 1 and Day 8. Subsequent cycles may be delayed up to 3 days after the previous cycle for scheduling purposes. IMGC936 is administered as an IV infusion at the assigned dose for each cohort, over approximately 2 to 3 hours.

6.2. Method of Assigning Participants to Study Drug

Participants will be assigned sequentially to dose-escalation cohorts as specified in Section 4.1.1.

6.3. Blinding

This is an open-label study.

6.4. Emergency Unblinding

Not applicable. This is an open-label study.

6.5. Guidelines for Discontinuation of Participant from Study

Participants who are no longer on study drug but are still followed on the study can be terminated from the study for the following reasons:

- Completion of protocol-defined follow-up period
- Uncontrolled intercurrent illness unrelated to cancer that prevents continuing study follow-up
- Noncompliance with protocol-required evaluations
- The participant requests to be discontinued from the study, ie, withdrawal of consent
- The sponsor, investigator, or regulatory agency terminates the study
- Death

6.6. Study Drug and Supplies

6.6.1. IMGC936

IMGC936 drug product is a sterile and preservative-free solution. The drug product yields a solution that is clear to slightly opalescent, colorless to pale yellow, and essentially free from foreign visible particles. It is supplied at a nominal protein concentration of 7 mg/mL in a single-dose glass vial containing 100 mg/14.3 mL IMGC936. The drug product is formulated in a

solution of 1.18 mg/mL succinic acid, 0.35 mg/mL sodium hydroxide, 90 mg/mL sucrose, and 0.1 mg/mL polysorbate 20, pH 4.7. The concentration and function of each component in IMGC936 drug product are summarized in Table 5.

Table 5: IMGC936 Drug Product Composition

Name of Ingredient	Concentration (mg/mL)	Amount per Vial (mg)[a]	Function[b]
IMGC936	7	100	Active ingredient
Succinic acid	1.18	16.90	Buffer component
Sodium hydroxide	0.35	5.00	Buffer component
Sucrose	90	128.70	Stabilizer
Polysorbate 20	0.10	1.40	Surfactant

[a] Amount per vial based on 14.3 mL nominal fill volume.
[b] Excipients are added to Water for Injection (United States Pharmacopeia).

6.7. Study Drug Infusion Preparation

6.7.1. General Guidelines and Precautions

Under no circumstances is the investigator allowed to release clinical study supplies for use by another physician not named on Form FDA (Food and Drug Administration) 1572 (or equivalent form) or to administer study drug to patients not enrolled in this study. Study drug must be dispensed at an institution specified on Form FDA 1572 (or equivalent form).

6.7.1.1. IMGC936 Dosage

The calculated dose of IMGC936 will be administered based on the participant's body weight at Cycle 1, Day 1. Body weight will be measured at screening and Day 1 of each cycle. Significant (≥ 10%) change in body weight from baseline should prompt recalculation of dose. Refer to the pharmacy manual for further instructions on allowable parameters for dose rounding.

IMGC936 should not be administered as an IV push or bolus. All doses of IMGC936 will be diluted in D5W and administered as an IV infusion with a commercially available infusion pump. All infusion pumps must be calibrated in accordance with the institutional standards, policies, and procedures to ensure consistent, accurate delivery of IMGC936.

Infusion or allergic reactions may occur with the infusion of mAb and other protein-based therapeutics. Precautions for anaphylaxis should be observed during administration. Refer to Section 7.1 for specific guidelines regarding the management of infusion reactions. Supportive care measures consistent with optimal care will be provided throughout the study according to institutional standards.

6.7.2. Study Drug Preparation and Administration

Visually inspect parenteral drug products for particulate matter and discoloration prior to administration. Return the vial if the solution is cloudy, there is pronounced discoloration (solution may have pale-yellow color), or there is foreign particulate matter.

Instructions on study drug preparation for IV infusion are detailed in the pharmacy manual.

Do not mix the study drug with, or administer as an infusion with, other medicinal products or IV fluids other than D5W.

IMGC936 is administered as an IV infusion following preparation instructions as outlined in the pharmacy manual. Details on required compatible infusion materials and IV infusion instructions are included in the IV infusion instructions manual.

All doses of IMGC936 must be diluted in sterile D5W prior to dose administration. IMGC936 diluted in D5W must be within the concentration range of 0.4 mg/mL to 6.0 mg/mL for IV administration. See the pharmacy manual for instruction on dilutional volumes for each dose level. Administer the prepared diluted IMGC936 through an IV line with a commercially available infusion pump. A sterile, non-pyrogenic, low protein binding polyethersufone (PES) 0.2 or 0.22 µm in-line IV filter must be used for IV administration of IMGC936. Do not administer as an IV push or bolus.

IMGC936 should be administered at a flat infusion rate of 80 mL/hr at any treatment cycle. Recommended adjustments in infusion rate are outlined in the IV infusion instructions manual should an infusion reaction occur, or a dose change be required. After infusion, the IV line will be flushed with D5W to ensure delivery of the full dose. Additional directions in the pharmacy manual and IV infusion instructions should be used should there be any subsequent changes to the preparation of IMGC936 or its IV administration.

Because there is no preservative in the study drug vial, study drug administration should begin immediately after the study drug is prepared, but no later than 4 hours when the diluted IMGC936 IV bag is stored at room temperature after preparation. Although, the diluted IMGC936 in the IV bag may be stored for up to 24 hours at 2°C to 8°C, it may not be used if the refrigerated storage time and expected administration time exceeds 24 hours. If the dose solution is stored at 2 to 8°C, it should be removed from the refrigerator at least 30 to 60 minutes prior to administration, to allow solution to reach room temperature.

Participants will be carefully observed during each infusion and vital signs are taken as outlined in Appendix 1. Participants will remain in the clinic under observation for 4 hours after the first infusion, and for at least 1 hour after each subsequent infusion. While in the treatment area, participants are closely monitored for AEs.

6.8. Study Drug Compliance

The study drug will be administered by healthcare professionals under the supervision of the investigator or designee. Records of dose calculation, administration, and dosing regimen will be accurately maintained by site staff. The sponsor or its designee will monitor and review dose calculation, administration, and regimen as well as medication accountability per the study monitoring plan.

6.9. Packaging and Labeling

IMGC936 drug product is filled into Type I, 20 mL clear glass vials. Each vial is stoppered with a 20 mm diameter butyl rubber stopper that has an ethylene tetrafluoroethylene (ETFE) fluoropolymer coating on the product contact surface and on the top of the stopper. The

stoppered vial is sealed with non-embossed 20 mm overseal with a plastic overseal and an aluminum collar.

IMGC936 is labeled according to local regulatory health authority requirements. Please see the pharmacy manual for detailed information about the packaging of the study drug. All study drug will be labelled with a minimum of the protocol number, directions for use, and storage conditions; the statements "For clinical trial use only," and/or "CAUTION: New Drug – Limited by Federal (United States) Law for Investigational Use"; and the sponsor's name and address.

6.10. Study Drug Accountability

The investigator or their designee is required to maintain accurate drug accountability records. Instructions and the required accountability documentation will be provided to the investigator or their designee. When the study is completed, copies of study drug accountability records must be sent to the sponsor. The original drug accountability records must be maintained with the rest of the documentation in accordance with Section 15.1 of the protocol.

Accurate accounting of all study medication must be maintained. The investigator agrees to keep an inventory of study drugs using the institution's drug accountability logs or logs provided by the sponsor. Drug disposition records must be kept in compliance with applicable guidelines and regulations.

A pharmacy manual will be provided to the investigator or designee. Additional details regarding storage, handling, and accountability can be found in the pharmacy manual.

6.10.1. IMGC936

Vials containing study drug should be stored upright under refrigeration at 2°C to 8°C (36°F to 46°F) in an appropriate, locked room accessible only to pharmacy personnel, the investigator, or duly designated personnel. To ensure compliance with storage conditions, temperature logs should be maintained. Vials should be protected from light during storage by storing the vial in the original carton. Vials should not be shaken or frozen. Standard laboratory practices should be used for avoidance of contact with IMGC936.

6.11. Investigational Product Disposition at End of Study

Upon completion or termination of the study, all unopened vials of study drug will either be disposed of at the study site according to the study site's standard operating procedure or returned to the sponsor, as determined by the study site. The sponsor must evaluate and approve the study site's standard operating procedure for drug disposal prior to initiation of drug destruction by the site. If the study site chooses to destroy study drug, the investigator must ensure arrangements are made for proper disposal and that appropriate records of disposal are documented and maintained, and copies provided to the sponsor. All drug returns to the sponsor or its representative must be accompanied by the appropriate documentation.

7. POTENTIAL ADVERSE EVENTS AND SUPPORTIVE CARE MEASURES

7.1. Infusion Related Reactions

Infusion-related reactions (IRRs) (non-serious and serious) are adverse events of special interest (AESI) and must be reported using an SAE form per Section 12.2.2.

The IRRs associated with administration of mAb-based therapeutics should be managed according to the standard practice of medicine. General guidelines for management of such reactions are provided in this section. However, severe reactions may require more intensive interventions (eg, steroids).

Participants should be monitored closely for development of IRRs during infusions. Medications and supportive measures for treatment of severe hypersensitivity reactions should be available for immediate use for an infusion reaction during study drug administration and may include, but are not limited to, subcutaneous epinephrine (0.3 to 0.5 mL of a 1:1000 solution), antihistamines (eg, diphenhydramine 25 to 50 mg IV [or orally (PO) if IV not available]), corticosteroids (eg, hydrocortisone 20 to 40 mg IV push or equivalent), IV fluids, vasopressors, oxygen, bronchodilators, and antipyretics. Resuscitation equipment and other supplies for the emergency management of an allergic/toxic reaction must be available. The participant should be treated according to the best available local practices and procedures. All supportive measures consistent with optimal care will be provided throughout the study according to institutional standards.

Should symptoms of fever, rigors, or chills develop, it may be difficult to distinguish among potential causes of the symptoms including emerging infection or infusion reaction. Participants should be evaluated carefully for the presence of infection (including COVID-19), with the acquisition of cultures and/or implementation of empiric antibiotic therapy as appropriate based on the assessment of the investigator. Refer to Section 7.1.3 for guidance on the management of IRRs.

Participants who experience a Grade 2 or greater IRR following administration of IMGC936 will have blood drawn to further study the IRR, including determination of drug concentration and antibodies to IMGC936. Samples should be obtained within 3 hours of the onset of the reaction and again 1 week later.

7.1.1. Grading and Management of Infusion Reactions

Infusion reactions are graded per the criteria in Table 6.

Table 6: Grading of Infusion Related Reactions (CTCAE v5.0)

System Organ Class	**Injury, Poisoning and Procedural Complications**	**Immune System Disorders**
Preferred Term	**Infusion Related Reaction**	**Allergic Reaction**
Grade 1	Mild transient reaction; infusion interruption not indicated; intervention not indicated	Systemic intervention not indicated
Grade 2	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, non-steroidal anti-inflammatory drugs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hours	Oral intervention indicated
Grade 3	Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae	Bronchospasm; hospitalization indicated for clinical sequelae; IV intervention indicated
Grade 4	Life-threatening consequences; urgent intervention indicated	
Grade 5	Death due to AE	

Abbreviations: AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; IV: intravenous.

7.1.2. Premedication and Prophylaxis

Premedication is required to mitigate the occurrence of infusion reactions. Equivalent medications may be substituted based on institutional standard of care and availability. Oral premedication should be given at least 30 minutes prior to infusion of study drug include:

- Acetaminophen 650 to 1000 mg PO, or ibuprofen 400 mg PO
- Diphenhydramine 25 to 50 mg IV (or PO if IV is not available) or equivalent H1 antagonist

No prophylactic pre-infusion steroid administration is required.

For subsequent study drug administration in a participant who had an IRR that was not adequately or only moderately controlled with acetaminophen and diphenhydramine, IV corticosteroids should be considered as part of the premedication regimen, (eg, 10 mg dexamethasone or equivalent. Nonsteroidal premedications may be administered prior to the subsequent infusion, if warranted.

7.1.3. Management of Observed Infusion Reactions

All changes in the study drug infusion, including interruption of the infusion and its duration as well as reductions in infusion rate and duration, must be recorded. The following are treatment guidelines (which may be modified as needed by the investigator according to the best practices of medicine) for IRR. Note that for participants who have an infusion reaction requiring corticosteroid administration, corticosteroid administration should be used as prophylaxis on subsequent infusions.

Grade 1:

- Slow the infusion rate by 50%.
- Monitor the participant for worsening of condition.
- Continue rate at 50% reduction and increase dose rate to the original rate by doubling the infusion rate after 30 minutes, as tolerated to the initial rate. Consideration can be given to beginning subsequent infusions at 50% rate and increasing as tolerated.
- If a participant has an infusion reaction, prophylactic pre-infusion medications should be given prior to all subsequent infusions. The following prophylactic pre- infusion medications are recommended prior to future study drug infusions for participants who experience Grade 1 infusion reactions: diphenhydramine 25 to 50 mg (or equivalent) IV (or PO if IV not available) and acetaminophen 650 mg PO and/or ibuprofen 400 mg PO, with or without famotidine 40 mg PO or 20 mg IV (or equivalent H2 antagonist) at least 30 minutes before additional study drug administrations.
- Report the event as an AESI.

Grade 2:

- Stop the infusion.
- Administer diphenhydramine hydrochloride 25 to 50 mg IV (or PO if IV not available).
- Acetaminophen 650 mg PO or ibuprofen 400 mg PO for fever.
- Oxygen and bronchodilators for mild bronchospasm.
- Resume the infusion at 50% of the prior rate once the infusion reaction has resolved or decreased to Grade 1. The rate may then be escalated to the original rate after 30 minutes, as tolerated. Consideration can be given to beginning all subsequent infusions at 50% rate and increasing as tolerated.
- Monitor for worsening condition. If symptoms recur, discontinue the infusion; no further study drug will be administered at that visit.
- Prophylactic pre-infusion medications should be given prior to subsequent study drug infusions. Participants who experience a Grade 2 infusion reaction, for subsequent doses of study drug, pre medicate with diphenhydramine hydrochloride 25 to 50 mg IV (or PO if IV is not available), acetaminophen 650 mg PO and/or ibuprofen 400 mg

PO, with or without famotidine 40 mg PO or 20 mg IV (or equivalent H2 antagonist) at least 30 minutes before additional study drug administrations. For these participants, corticosteroids (dexamethasone 10 mg IV or hydrocortisone 25 to 100 mg IV or higher) also should be added to the premedication regimen for subsequent dosing of study drug.

- Report the event as an AESI.

Grade 3:

- Stop the infusion and disconnect the infusion tubing from the participant.
- To avoid exacerbation of infusion reaction: do not flush the tubing – aspirate residual drug from the vascular access device.
- Administer diphenhydramine hydrochloride 25 to 50 mg IV (or PO if IV is not available), dexamethasone 20 mg IV (or equivalent), and other medications/treatment as medically indicated. Higher doses of corticosteroids (eg, methylprednisolone 2 to 4 mg/kg IV or the equivalent) may also be considered for acute management.
- IV fluids, supplemental oxygen, and bronchodilators should be considered, as appropriate.
- If the Grade 3 infusion reaction occurs with study drug administration, it will be discontinued for that day. If symptoms have resolved to baseline within 12 hours, study drug may be infused the next day. In addition, participants should be pre medicated for this re-challenge and for any subsequent doses of study drug with the following: diphenhydramine hydrochloride 25 to 50 mg IV (or PO if IV is not available), acetaminophen 650 mg PO and/or ibuprofen 400 mg PO, with or without famotidine 40 mg PO or 20 mg IV (or equivalent H2 antagonist). Corticosteroids (dexamethasone 10 to 20 mg IV or hydrocortisone 50 to 100 mg IV or higher) should be considered as well.
- Participants who have a Grade 3 infusion reaction that does not resolve within 12 hours despite medical management should not receive further study drug. Participants who experience a second Grade 3 infusion reaction at the time of study drug re-challenge will permanently discontinue study drug.
- Report the event as an AESI and as an SAE, if appropriate.

Grade 4:

- Stop the infusion and disconnect the infusion tubing from the participant.
- To avoid exacerbation of infusion reaction: do not flush the tubing – aspirate residual drug from the vascular access device.
- Administer diphenhydramine hydrochloride 50 mg IV (or PO if IV is not available), dexamethasone 20 mg IV (or more as considered appropriate), and other medications/treatment as medically indicated.
- Give epinephrine or bronchodilators as indicated.

- Support ventilation and blood pressure as indicated.
- Report the event as an AESI and an SAE.
- Participants who have a Grade 4 infusion reaction will not receive further study drug.

Grade 5:

- Report the event as an AESI and an SAE.

7.2. Ocular Toxicity

Maytansinoids are known to cause ocular toxicity when used as the payload in ADCs. IMGC936-related ophthalmic findings were observed in repeat-dose nonclinical studies. These findings included reversible ocular events, eg, discharge, conjunctival swelling, congestion and/or cloudiness, pannus, cellular or keratic precipitates, and corneal pigmentation in one or both eyes and microscopic changes of minimal to moderate single cell necrosis and minimal to mild increased mitoses.

Ocular events have been observed in patients receiving IMGC936 in clinical trials. As such, participants should be monitored for symptoms with each cycle and action taken as noted below both to monitor for and manage ocular toxicity should it arise. Ocular symptoms and signs to be closely monitored are included but not limited to those defined in the IMGC936 Investigator's Brochure, Section 6.6.2.

For participants in dose escalation cohorts in Schedule A, ocular symptom assessment should occur weekly during the first 3 cycles and subsequently on Day 1 of each cycle. For participants in dose escalation cohorts in Schedule B, ocular symptom assessment should occur weekly in Cycle 1 and 2, and occur on Day 1 and Day 8 in each subsequent cycle. Participants' ocular symptoms and signs are also evaluated on Cycle 3 Day 15.

During the Dose Expansion Phase (at the RP2D), if ocular toxicity is limited (eg, does not lead to dose reductions or discontinuations in > 10% of participants) at the RP2D during escalation, ocular symptom assessment will occur on Day 1 of each cycle or more frequently if ocular symptoms or signs are observed. Phone-based ocular symptoms assessments are acceptable if no clinic visit is scheduled. If a participant develops ocular symptoms or signs of any grade (eg, blurred vision, dry eye, eye pain), the participant is required to have a complete ophthalmic examination by an ophthalmologist. If a participant develops ≥ Grade 2 ocular symptoms or signs, the study drug must be interrupted. Study drug may resume if ocular symptoms or signs improve to Grade 1 or baseline within 14 days (see Table 7 for details). Subsequent ophthalmic examinations will be scheduled to occur in every other cycle going forward, from the time that the AE was initially reported until resolution to Grade 1 or less, stabilization, or return to baseline, even after study drug discontinuation, if needed.

Note: To monitor for asymptomatic ocular effects, all participants will be required to have an ophthalmic examination at screening, the end of Cycle 2, and then approximately every 3 cycles (ie, Cycle 5, 8, 11, etc.) regardless of whether they reported any ocular symptoms or signs. Participants with Grade 2 or greater ocular AE which have not resolved to Grade 1 or baseline must have an ophthalmic examination at EOTV.

All participants should use a prophylactic regimen of lubricating artificial tears to mitigate ocular symptoms and signs. In certain circumstances, additional prophylactic eye drops may also be given, including the outlined options below.

7.2.1. Eye Drop Options

During this study, different eye drops will be tested to mitigate ocular events. Investigators and participants will be informed of which eye drop regimen(s) they should use before the start of study treatment. Participants are required to receive prophylactic lubricating artificial tears and may receive additional eye drop(s) as prophylaxis as recommended by the investigators and Sponsor.

A formal voluntary ocular sub-study may be used to assign participants to different eye drop regimens to compare the frequency and severity of ocular AEs (Section 4.1.3).

Lubricating Artificial Tears

All participants should be instructed to use lubricating artificial tears for the treatment and prophylaxis of ocular symptoms and signs, as directed by the product label or the treating physician. Participants should start their regimen of lubricating artificial tears prior to each dose of IMGC936 and after dosing continue application at least 4 times per day. Lubricating artificial tears are to be continued indefinitely throughout study treatment, at the ophthalmologist or treating physician's discretion.

Vasoconstricting Eye Drops

If instructed to do so, participants should also use refrigerated, topical vasoconstricting eye drops (ie, prescription strength brimonidine 0.1-0.2% twice daily, or potent adrenergic receptor agonist) unless the risks outweigh the benefits as determined by the treating physician or ophthalmologist (see product label warnings and drug interactions). Vasoconstricting eye drops should be applied within 1 hour prior to dosing of IMGC936 and continued for at least 3 days or throughout study treatment at a frequency as directed by the product label, and at the local ophthalmologist or treating physician discretion. If ocular symptoms occur that may be caused by vasoconstricting eye drops (eg, conjunctivitis, redness, itching, burning, visual disturbance), they may be interrupted or discontinued at the discretion of the local ophthalmologist or treating physician.

Corticosteroid Eye Drops

If instructed to do so, participants should also use prophylactic corticosteroid eye drops and should be instructed to self-administer 1% prednisolone (Pred Forte or equivalent). For Schedule A participants, steroid should be self-administered 6 times daily on the day of dosing through Day 4, and 4 times daily on Day 5 to Day 8 of each cycle during the study. For Schedule B participants, steroid should be self-administered 6 times daily on the day of dosing through 4 days after each dose.

Participants receiving multiple drops should be advised to administer the drops at different times if feasible. Participants are suggested to wait at least 15 to 30 minutes between the administration of different eye drops.

In addition, local ophthalmologists or treating physicians may choose to begin therapeutic corticosteroid eye drops when ocular symptoms or signs occur. These may be used in addition to the prophylactic regimen used.

Cyclosporine Eye Drops

If instructed to do so, participants should also use refrigerated, topical cyclosporine (0.025% - 0.2%) eye drops unless the risks outweigh the benefits as determined by the treating physician or ophthalmologist. Cyclosporine eye drops should be applied within 1 hour prior to dosing of IMGC936 and continued for at least 3 days or throughout study treatment at a frequency as directed by the product label, and at the local ophthalmologist or treating physician discretion unless contraindicated. If ocular symptoms occur that may be caused by cyclosporine eye drops (eg, itching, burning, swelling), they may be interrupted or discontinued at the discretion of the local ophthalmologist or treating physician.

7.2.2. Management of Ocular Symptoms and Signs

Table 7: Management of Ocular Symptoms and Signs

Grade (CTCAE v5.0)	Management	Guidelines for Dose Modification[a]
Grade 1	Complete eye examination. Participants should have weekly symptomatic ocular assessments to monitor for worsening symptoms and signs and repeat eye examinations as needed.	Continue study drug dosing.
Grade 2	Complete eye examination. Participants should have weekly symptomatic ocular assessments and repeat eye examinations at least every 6 weeks until resolved to Grade 1 or less, stabilized, or returned to baseline, even after treatment discontinuation, if needed.	Hold study drug dosing until AE has resolved to ≤ Grade 1. Participants whose ocular symptoms and signs resolve to ≤ Grade 1 in ≤ 14 days may be allowed to resume study drug at the same dose level. Participants whose ocular symptoms and signs resolve to ≤ Grade 1 in > 14 and ≤ 28 days may resume study drug at 1 lower dose level with sponsor approval.
Grade 3	Complete eye examination. Participants should have weekly symptomatic ocular assessments and repeat eye examinations at least every 6 weeks until resolved to Grade 1 or less, stabilized, or returned to baseline, even after treatment discontinuation, if needed.	Hold study drug dosing. Participants whose ocular symptoms and signs resolve to ≤ Grade 1 in ≤ 28 days may resume study drug at 1 lower dose level with sponsor approval.

Grade (CTCAE v5.0)	Management	Guidelines for Dose Modification[a]
Grade 4	Complete eye examination. Participants should have weekly symptomatic ocular assessments and repeat eye examinations at least every 6 weeks until resolved to Grade 1 or less, stabilized, or returned to baseline, even after treatment discontinuation, if needed.	Permanently discontinue study drug.

Abbreviations: AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events.

Note: All participants are recommended to have an EOTV ophthalmic examination, regardless of whether they reported any ocular symptoms or signs. Participants with ongoing Grade 2 or greater ocular symptoms or signs must continue to have ophthalmic examinations at EOTV and during the follow-up period.

7.3. Diarrhea

Participants should be monitored closely for evidence of diarrhea or other change in bowel habits. Participants with diarrhea should be treated accordingly per institutional standard practice. Guidelines for dose modification are provided in Table 8.

Table 8: Dose Modification for Diarrhea

Grade (CTCAE v5.0)	Guidelines for Dose Modification[a]
Grade 1	Closely monitor until resolution. No dose reduction required.
Grade 2	Hold study drug until resolved to baseline or ≤ Grade 1. No dose reduction required
Grade 3 (despite use of optimal anti-diarrheal treatment)	Hold study drug until resolved to ≤ Grade 1, then resume at 1 lower dose level
Grade 4	Permanently discontinue study drug

Abbreviations: CTCAE: Common Terminology Criteria for Adverse Events.

[a] Failure to meet guidelines for dose modification after the missed dose due to insufficient recovery from a treatment-related toxicity will result in treatment discontinuation unless otherwise specified in the specific management guidance for a particular toxicity (see Section 4.5.1 for details). Specification of the efficacy parameters.

7.4. Hepatic Toxicity

7.4.1. Elevations in Transaminases

Management guidelines for participants experiencing hepatic toxicity are as follows:

- Grade 1 elevations – No specific therapy required. Monitor and evaluate liver function tests.

- Grade 2 elevations – For elevations in transaminases 3 to 5 × ULN, rule out viral and other etiologies. Consider imaging studies such as ultrasound or CT scan and liver biopsy to ascertain etiology of liver dysfunction. Monitor and evaluate liver function tests.
  - Resume study drug at the next scheduled dose if no more than one dose of study drug was missed.
- Grade 3 elevations – Hold study drug.
  - For elevations in transaminases > 8 × ULN, permanently discontinue study drug. Rule out viral and other etiologies. Consider imaging studies such as ultrasound or CT scan and liver biopsy to ascertain etiology of liver dysfunction.
    - Monitor liver function tests at least twice weekly (or more frequently as clinically appropriate in the judgment of the investigator) until transaminases have returned to Grade 1 or baseline.
  - For elevations in transaminases > 5 but ≤ 8 × ULN:
    - Monitor liver function tests at least twice weekly (or more frequently as clinically appropriate in the judgment of the investigator) until transaminases have returned to Grade 1 or baseline.
    - If the elevation does not improve to Grade 2 within 7 days and to Grade 1 within 14 days, discontinue study drug.
  - Resume study drug administration if following conditions are met:
    - Laboratory elevations improved to ≤ Grade 2 within 7 days and improve to ≤ Grade 1 or baseline within 14 days.
    - On resuming study drug, AST, ALT, and total and direct bilirubin laboratory test values will be evaluated at least once per week for 3 consecutive weeks.
  - Permanently discontinue study drug in the case of a second increase of AST or ALT to ≥ Grade 3.
- Grade 4 elevation – Discontinue study drug and treat as for Grade 3 elevation.

7.5. Pneumonitis

The risk of noninfectious pneumonitis due to IMGC936 is unknown. Noninfectious pneumonitis may result in fatigue, shortness of breath, cough, or respiratory distress. Drug induced pneumonitis may be immediately life threatening. If a participant presents with signs or symptoms consistent with pneumonitis and/or other clinically meaningful signs or symptoms of pulmonary toxicity, the participant should be evaluated immediately (evaluation for infection including COVID-19 should be performed). Participants are advised to notify their treating physician immediately if they experience new or worsening shortness of breath, cough, or respiratory distress. Participants who are asymptomatic may continue dosing of IMGC936 with close monitoring.

The management and treatment guidelines outlined in Table 9 should be followed.

Table 9: Management of Noninfectious Pneumonitis

Grade (CTCAE v5.0)	Definition (CTCAE v5.0)	Medical Management of Pneumonitis	Guidelines for Dose Modification[a]
Grade 1	Asymptomatic; clinical or diagnostic observations only; intervention not indicated.	Radiologic assessments (CT scan and/or chest x-ray) should be performed as clinically indicated. Monitor for pulmonary symptoms.	Continue dosing in asymptomatic participants and monitor closely.
Grade 2	Symptomatic; medical intervention indicated; limiting instrumental ADL	Radiologic assessments (CT scan and/or chest x-ray) should be performed as clinically indicated. Participant must be evaluated by a pulmonary specialist. Treatment with corticosteroids may be indicated as recommended by a pulmonary specialist and/or institutional guidelines.	Hold dosing until symptoms resolve to ≤ Grade 1. Study drug may be resumed at same dose level or 1 dose level lower after discussion with the sponsor.
Grade 3	Severe symptoms; limiting self-care ADL; oxygen indicated	Radiologic assessments (CT scan and/or chest x-ray) should be performed as clinically indicated. Participant must be evaluated by a pulmonary specialist. Treatment with corticosteroids until resolution of symptoms may be indicated as recommended by a pulmonary specialist and/or institutional guidelines. Bronchoscopy with lavage and/or biopsy when clinically feasible should be performed. The pneumonitis event must be followed until resolution.	Permanently discontinue study drug.
Grade 4	Life-threatening respiratory compromise: urgent intervention indicated (eg, tracheotomy or intubation)	Manage as Grade 3 event. Hospitalize and initiate maximal supportive care. Urgent intervention may be indicated.	Permanently discontinue study drug.

Abbreviations: ADL: activities of daily living; CT: computed tomography; CTCAE: Common Terminology Criteria for Adverse Events.

[a] Failure to meet guidelines for dose modification after the missed dose due to insufficient recovery from a treatment-related toxicity will result in treatment discontinuation unless otherwise specified in the specific management guidance for a particular toxicity (see Section 4.5.1 for details).

7.6. Interstitial Cystitis

Participants should be monitored closely for evidence of interstitial cystitis. Investigators should contact the medical monitor for management of interstitial cystitis.

- Grade 1 interstitial cystitis – No specific therapy required; close monitoring of renal function and urinalysis. Consider oral H1-antihistamine or tricyclic antidepressant for symptom management. Recommend participant maintain hydration with oral intake of fluids.
- Grade 2 interstitial cystitis – Hold study drug.
  - Administer intravenous fluids for hydration
  - Begin corticosteroids: 1 to 2 mg/kg of oral prednisone or equivalent per day divided twice daily. Taper over 4 weeks as clinically indicated.
  - Resume study drug administration at next scheduled dose if:
    - Interstitial cystitis resolves to ≤ Grade 1 within 14 days.
- Grade 3 and 4 interstitial cystitis – Permanently discontinue study drug.
  - Consider hospitalization, urology consultation, and biopsy to confirm interstitial cystitis.
  - Begin corticosteroids: 2 to 4 mg/kg of oral or IV methylprednisolone or equivalent per day divided twice daily. Taper over 4 weeks as clinically indicated.

7.7. Hematologic Toxicity

No specific treatment or study drug holds are required for lymphopenia, regardless of CTCAE grade.

7.7.1. Neutropenia

- Grade 1 or Grade 2 – No specific therapy required.
- Grade 3
  - Hold study drug until recovery to ≤ Grade 1.
  - Monitor neutrophil counts weekly until recovery to ≤ Grade 1.
  - Discontinue study drug if not recovered to ≤ Grade 1, within 21 days.
  - Restart study drug at the same dose level if recovered to ≤ Grade 1 within 21 days.
  - Consider secondary prophylaxis with granulocyte colony-stimulating factor (G-CSF) for subsequent cycles.
- Grade 4
  - Hold study drug until recovery to ≤ Grade 1.

- Monitor neutrophil counts weekly until recovery to ≤ Grade 1.
- Discontinue study drug if not recovered to ≤ Grade 1 within 21 days.
- Restart study drug with one level dose reduction if recovered to ≤ Grade 1.
- Consider secondary prophylaxis with G-CSF for subsequent cycles.

7.7.2. Thrombocytopenia

- Grade 1 or Grade 2 – No specific therapy required.
- Grade 3
  - Hold study drug until recovery to ≤ Grade 1.
  - Monitor platelet counts weekly until recovery to ≤ Grade 1.
  - Discontinue study drug if not recovered to ≤ Grade 1 within 42 days.
- Grade 4
  - Hold study drug until recovery to ≤ Grade 1.
  - Monitor platelet counts weekly until recovery to ≤ Grade 1.
  - Discontinue study drug if not recovered to ≤ Grade 1 within 21 days.
  - Restart study drug with one level dose reduction if recovered to ≤ Grade 1.

8. CONCOMITANT THERAPY AND RESTRICTIONS

8.1. Concomitant Therapy

All concomitant medications, including prophylactic pre-infusion medications (ocular prophylaxis regimens detailed in Section 7.2.1), and blood products administered during the participant's participation in the study until the EOTV must be recorded in the source document and eCRF. All changes in infusions, including interruptions and their duration as well as reductions in rate and duration, must be recorded.

Please consult the treating physician for any questions related to concomitant medications including known drug interactions and side effects.

8.1.1. Prohibited Therapy

CYP3A4/5 is implicated in the metabolism of DM50 and DM51. Therefore, strong CYP3A inhibitors and inducers, if clinically feasible, should be avoided as concomitant medications for at least 14 days prior to start of treatment and throughout the study or used with caution if critical to the participant's ongoing care. See Appendix 7 for a list of strong CYP3A inhibitors and inducers.

The following rules concerning concurrent treatment(s) apply in this study:

- Any other anti-neoplastic therapies including but not limited to, chemotherapy or other small molecules, biologics, or radiotherapy are not allowed.
  - Anticancer vaccines are considered concomitant cancer therapy and are prohibited from use during the study.
  - Palliative radiation may be allowed for participants who have local symptoms but overall clinical benefit with sponsor approval. Participant needs to pause study drug during the radiation and may resume the treatment after radiation related adverse events return to baseline. The restart of treatment requires the approval from sponsor.
- Participants may not receive other investigational drugs during the period of study participation.
- Use of corticosteroids should be limited to the extent possible (except as specified in this protocol).
- Primary prophylactic use of G-CSF, granulocyte-macrophage colony stimulating factor (GM-CSF), or other growth factors is prohibited during the first cycle of study drug. Use of growth factors with successive cycles of study drug may be considered on a case by case basis in consultation with the sponsor.
- Inactivated annual influenza vaccination and COVID-19 vaccination are allowed and the sponsor recommends they be administered no less than 5 days before or after the dose of study drug, when feasible, to avoid overlapping AEs.

8.1.2. Permitted Therapies

Participants may receive the following concurrent therapy:

- Antiemetics, antidiarrheals, anticholinergics, antispasmodics, antipyretics, antihistamines, analgesics, antibiotics and other antimicrobials, histamine receptor antagonists or proton pump inhibitors, and other medications intended to treat tumor-related signs or symptoms.
- Transfusions such as red blood cells and platelets are permitted to treat symptoms or signs of anemia or thrombocytopenia.
- Use of bisphosphonates or receptor activator of nuclear factor kappa-B ligand (RANK L) inhibitors is allowed.
- Secondary prophylactic use of G-CSF, GM-CSF, or other growth factors for observed Grade 3 or Grade 4 neutropenia.

8.1.3. Contraception

Male and female participants are required to use highly effective contraceptive measures as specified below from the time of consent through 28 weeks after discontinuation of study drug administration. Male participants are required to use a condom regardless of his FOCBP partner's method of contraception and must abstain from sperm donation during the study.

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Intravaginal
  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Injectable
  - Implantable
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomized partner is a highly effective birth control method provided that the vasectomized partner is the sole sexual partner of the FOCBP trial participant and that the vasectomized partner has received medical assessment of the surgical success.
- Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with study treatment. The reliability of sexual abstinence needs to be evaluated in

relation to the duration of the clinical trial and the preferred and usual lifestyle of the participant.

8.2. Restrictions

8.2.1. Fluid and Food Intake

There are no requirements for fasting and no restrictions for fluid or food intake by participants during the study, although it is recommended that, to the extent possible, participants have a fluid intake of ≥ 2 liters on days associated with PK sampling.

8.2.2. Participant Activity Restrictions

There are no study-related restrictions on participant activities and no requirement for participant confinement during the study. However, participants are advised to limit direct sun exposure and to use broad-spectrum sunscreen when outdoors. Participants are advised to avoid using contact lenses while on IMGC936.

9. STUDY PROCEDURES

This section provides a general description of the procedures and assessments associated with this study. The timing of study procedures is presented in Appendix 1 and Appendix 2.

During the COVID-19 pandemic, alternative methods for conducting study assessments should be considered when compliance, feasibility, and safety can be assured. These methods may include:

- Telemedicine visits, eg, via telephone/video (using compliant video-conference tools as permitted by health authority regulations)
- Use of primary care centers and local laboratories for blood draws and imaging/radiographs

If alternative methods are used, local laboratory reference ranges will be documented and submitted to the sponsor. Local laboratory test results, laboratory accreditation, and reports of tumor assessments should be retrieved and documented in the participant's study records.

9.1. Informed Consent

The investigator is responsible for ensuring that the participant provides informed consent prior to performing any study-related assessments, evaluations, or procedures that are not part of standard-of-care for the participant's disease. Informed consent for this study must be provided by signing an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved informed consent document. A copy of the relevant signed informed consent document must be provided to the participant and the original maintained according to institutional procedures and current Good Clinical Practice (GCP). The participant's medical records will include documentation of the informed consent process. Remote informed consent via telemedicine technology may be considered if approved by the IRB/IEC.

Participants will provide consent to join the ocular sub-study.

9.2. Screening Period

Participants may receive the first dose up to 28 days from providing signed informed consent. This period is defined as the screening period. The date when participant was consented is considered as Day 1 of screening and participant needs to be dosed no later than Day 28. At the screening visit, participants will enter the study upon signing the informed consent document. No screening activities outside of usual standard-of-care should be performed prior to obtaining informed consent from the participant.

9.2.1. Screen Failures

Participants who provide informed consent but fail to meet inclusion and/or exclusion criteria within 28 days of signing informed consent or are not able to complete the screening period are defined as screen failures. An eCRF with a minimum of the following information must be completed for participants who fail screening: demographics, reason for screen failure, adverse events, and SAEs if applicable.

Participants who fail the screening the first time can be re-screened once if approved by the investigator. A new participant number will be assigned and used in the electronic data capture (EDC).

9.3. Enrollment

Once the participant has been determined to be eligible for enrollment into the study, the following information will be collected for enrollment:

- Age
- Tumor type
- Date of signed informed consent

9.4. Medical History

A complete medical history should be obtained during the screening visit. All concurrent medical conditions in the last 60 days and any significant past medical conditions (eg, hospitalizations, surgeries, chronic conditions, prior cancer history) should be collected. Any untoward event that occurs prior to the first dose of study drug should be recorded as medical history and not as an AE, unless it is due to a protocol related procedure.

9.5. Prior and Concomitant Medications

All concomitant medications and blood products administered for 30 days prior to study drug administration through the EOTV must be recorded in the source document and on the eCRF.

Prior courses of systemic cancer therapy (eg, chemotherapy, immunotherapy) will be documented in the medical records and on the eCRF.

9.6. Physical Examination

The investigator will perform physical examination of all participants per the schedule in Appendix 1 and Appendix 2. A full physical examination includes height (screening only), weight, and examination of head, eyes, ears, nose, throat, lymph nodes, heart, chest, lungs, abdomen, extremities, neurologic system, and skin examination.

Directed physical examination will be conducted per Appendix 1 and Appendix 2. The examination will be based on review of participant symptoms, medical history, and as clinically indicated. Each examination will include a total body skin examination to detect mucocutaneous AEs. Participants on Schedule A in dose escalation cohorts will have weekly directed physical examination through treatment Cycle 3. Beginning on Cycle 4, physical examination will occur on Day 1 of each cycle (Schedule A). Participants on Schedule B in dose escalation cohorts will have weekly directed physical examination in Cycle 1 and 2, and directed physical examination on Cycle 3 Day 1, Day 8, and Day 15. Beginning on Cycle 4, physical examination will occur on each dosing visit of each cycle (Schedule B).

Participants in the dose expansion cohorts will have physical examination recorded on Day 1 of each treatment cycle (Schedule A) or each dosing visit (Schedule B).

9.6.1. Vital Signs

Vital signs include temperature, pulse, blood pressure, and respiratory rate and are obtained on days with physical examinations per Appendix 1 and Appendix 2. It is recommended vital signs are obtained in a seated, semi recumbent, or supine position after an appropriate rest. Vital signs should be measured prior to any blood draws or other procedures whenever possible.

Participants in dose escalation cohorts must have vital signs recorded on both dosing and non-dosing days through treatment Cycle 3. Beginning on Cycle 4, vital signs must be recorded on Day 1 of each treatment cycle for Schedule A, and on Day 1 and Day 8 of each cycle for Schedule B.

Participants in expansion cohorts must have vital signs recorded on Day 1 of each treatment cycle for Schedule A, and on Day 1 and Day 8 of each cycle for Schedule B.

9.7. Performance Status

9.7.1. ECOG Performance Status

ECOG performance status should be measured per the schedule in Appendix 1 and Appendix 2. A description of the scale is in Appendix 8.

- Note: ECOG performance status should be the primary performance measure for participant enrollment. If ECOG performance status is an inappropriate performance measurement for participant enrollment (eg, chronically nonambulatory), then Karnofsky performance status may be used. A description of the scale is in Appendix 8.

9.8. Clinical Laboratory Tests

Blood and urine samples will be collected per the schedule in Appendix 1 and Appendix 2. Hematology, chemistry, pregnancy, urinalysis, coagulation time, and endocrine evaluation tests will be performed locally. Test results for pregnancy, chemistry, and hematology must be reviewed before study drug administration. For days when only clinical laboratory tests are required (no PK, ADA, or biomarker), participants may have clinical laboratory tests collected at local (non-study site) labs approved by investigator. Laboratory assessment results must be entered into the clinical database.

Clinical laboratory tests to be performed are presented in Appendix 3.

9.8.1. Central Laboratory Assays

Laboratory tests for PK, immunogenicity, and biomarkers (Appendix 4 and Appendix 5) will be performed at sponsor-specified central laboratories. Details on collection, processing, storage, and shipping of central laboratory samples are provided in the laboratory manual.

9.8.1.1. Pharmacokinetics/Immunogenicity

Blood samples for conjugated antibody, total antibody, and DM50/51 PK will be collected per the schedule in Appendix 4 and Appendix 5. Blood samples should be collected from the arm contralateral to the site of IV infusion. If an indwelling catheter is used, the fluid in the catheter will be removed and discarded prior to collection of blood samples for PK assessment.

Antidrug antibodies (ADAs) will be evaluated per Appendix 4 and Appendix 5 from an aliquot of the PK blood draw and do not require a separate blood draw. See the laboratory manual for details.

9.8.1.2. Biomarkers

Procedures for the acquisition, handling, and processing of biomarker specimens are provided in the laboratory manual. Samples for biomarker tests will be collected according to Appendix 4 and Appendix 5.

9.8.1.3. Sample Collection, Storage, and Shipping

Details on central laboratory specimen processing, storage, and shipping will be provided in the laboratory manual.

9.9. Radiographic, CT, or MRI Assessments

Tumor assessments are performed according to the schedule in Appendix 1 and Appendix 2. Baseline tumor imaging consists of a CT/MRI scan with contrast, unless medically contraindicated, to document tumor burden. Subsequent tumor assessments on study should use the same imaging modality as that for the baseline assessment.

Tumor assessments are performed every 6 weeks (Q6W; ± 7 days) on Schedule A and every 8 weeks (Q8W; ± 7 days) on Schedule B while on study drug then every 12 weeks (Q12W; ± 21 days). Tumor assessments continue until discontinuation criteria are met. Tumor assessments are performed at EOTV except if prior assessment was ≤ 30 days of EOTV and results are available for RECIST v1.1 assessment.

CT or MRI scan of the brain will be performed when clinically indicated (eg, history or suspicion of brain metastases) and repeat brain scans will be performed only if the screening brain scan was positive, or as clinically indicated.

If feasible, participants who discontinue study drug for reasons other than PD (eg, toxicity) should continue to undergo tumor assessments Q12W until evidence of PD, initiation of another anticancer therapy, withdrawal of consent, LTFU, death, or end of study whichever occurs first.

9.10. Electrocardiography

Twelve-lead ECGs will be obtained according to the schedule in Appendix 1 and Appendix 2 to evaluate potential cardiac effects including QTc interval prolongation. ECGs will be collected at screening, on selected days where PK sampling is conducted in the first three cycles, and at EOTV.

To account for intrinsic variability, all ECGs should be obtained in triplicate (3 ECGs per time point at approximately 1-minute intervals). The actual time of the first of three ECGs per timepoint will be recorded as the actual time of the ECG.

QTc > 480 milliseconds calculated from the average of 3 repeat ECGs will be obtained at approximately 1-minute intervals. QTcF or QTcB, whichever is most appropriate for the participant, should be calculated.

ECGs will be performed and stored at sponsor-specified central facilities.

9.11. Echocardiography

An echocardiogram will be performed to evaluate LVEF at Screening and according to the schedule in Appendix 1 and Appendix 2. Echocardiogram may be performed at the investigator's discretion as clinically indicated.

The Investigator can choose another appropriate modality (eg, multigated acquisition scan [MUGA]) to assess LVEF.

9.12. Ophthalmic Examination

Ophthalmic examinations and ocular symptoms and signs assessments are performed according to the schedule in Appendix 1 and Appendix 2.

Baseline ophthalmic examinations will be performed for all participants during screening by an ophthalmologist and include the following: visual acuity (with/without corrective lens; whichever best reflects the participant's usual functioning), slit-lamp examination, intraocular pressure measurement, and indirect fundoscopy. All participants will have a complete ophthalmic examination when ocular symptoms and signs develop, repeated as indicated in Table 7. Participants without ocular symptoms or signs will have ophthalmic examinations at the end of Cycle 2 and then approximately every 3 cycles (ie, Cycle 5, 8, 11, etc.) in both escalation and expansion phases. Participants with Grade 2 or greater ocular AEs that have not resolved to Grade 1 or baseline must have an ophthalmic examination at EOTV. All other participants are recommended to have ophthalmic examination at EOTV to document any subclinical findings.

Ocular symptoms and signs assessment will be performed by the treating physician or other qualified individual. For participants reporting > Grade 1 ocular symptoms and signs, treatment will be held until the participant is evaluated by an ophthalmologist for a complete examination (Section 7.2).

Participants in the ocular sub-study will be monitored for the frequency and severity of ocular events as usual. Participants without ocular symptoms or signs should have an ophthalmic examination at the end of Cycle 2 and followed with ophthalmic examinations every three cycles until the end of treatment. Participants with ocular AEs must have ophthalmological examinations per Table 7, but will be required to have an early ocular examination after 2 cycles of therapy (instead of after 3 cycles) regardless of whether they have ocular symptoms and signs.

9.13. Archival Tumor Tissue

Participants must submit archival tumor tissue (FFPE block, or unstained slides) for analysis of ADAM9 expression. If a participant does not have archival material available for analysis, the participant may alternatively undergo a low-risk, medically routine procedure to obtain a tissue sample, if appropriate. The decision to biopsy will be made once participant eligibility has been determined and on the basis of tumor accessibility and participant safety. This will typically require that the tumor lesions are superficially accessible or that the lesions can be biopsied under CT or ultrasound guidance without traversing major blood vessels or other vital structures. The specimens will be analyzed retrospectively and will not be used to determine participant

eligibility. Instructions regarding processing and shipment of archival tissues and biopsy samples are detailed in the Laboratory Manual.

9.14. End of Treatment Visit

A list of evaluations at the EOTV is provided in Appendix 1 and Appendix 2. The EOTV should be performed after the participant has met study drug discontinuation criteria (Section 5.4). The visit should be performed within 30 days following last dose of study drug whenever possible. Tumor assessments are performed at EOTV except if prior assessment was ≤ 30 days of EOTV and results are available for RECIST v1.1 assessment.

9.15. Follow-up Assessments

Post-treatment follow-up is performed until the end of study for each participant. The post-treatment follow-up period includes the following assessments:

9.15.1. Safety

Ongoing TEAEs will be followed until the event has resolved to baseline grade, the event is assessed by the investigator as stable, initiation of another anticancer therapy, withdrawal of consent, LTFU, or death. The investigator should follow and provide updates for all AEs until clinical recovery is complete, laboratory values return to normal, the participant stabilizes, or death occurs to ensure the safety of the participants.

9.15.2. Response Assessments

Tumor assessments (eg, CT scans) will occur after participant has discontinued study drug Q12W (± 21 days) until evidence of progressive disease, initiation of another anticancer therapy, withdrawal of consent, LTFU, death, or end of study, whichever occurs first (Appendix 1 and Appendix 2).

- For RECIST v1.1, the overall responses will be categorized as complete response (CR), partial response (PR), stable disease (SD), PD, or not evaluable (NE) (Appendix 6).

9.15.3. Lost to Follow-up

A participant may be determined to be LTFU after there have been at least 3 documented telephone contact attempts. If this fails, a certified letter should be sent to the participant. Only after these attempts have failed can a participant be determined to be LTFU.

10. ASSESSMENT OF PHARMACOKINETICS AND BIOMARKERS

10.1. Pharmacokinetics Assessments

Serum concentrations of conjugated antibody and total antibody following administration of IMGC936 will be monitored using quantitative validated bioanalytical methods. Plasma concentrations of DM50/51 following administration of IMGC936 will be monitored using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay. Metabolites of IMGC936 may also be evaluated. Single- and multiple-dose PK parameters will be derived from serum or plasma concentration versus time data as applicable (Section 14.6.1). The collection schedules are in Appendix 4 and Appendix 5.

10.2. Immunogenicity Assessments

Blood samples for immunogenicity assessments will be collected per the schedules in Appendix 4 and Appendix 5. ADAs against IMGC936 will be detected using a validated analytical method.

10.3. Biomarker Assessments

Blood and tissue samples will be collected per the schedules in Appendix 1, Appendix 2, Appendix 4, and Appendix 5. Studies to evaluate potential biomarkers of clinical and/or immunologic response to IMGC936 may include the following analyses:

- Correlation of ADAM9 expression and clinical response to IMGC936.
  - Retrospective analysis of ADAM9 expression in tumor tissues for all participants.
- Baseline and on-treatment analysis of circulating soluble biomarkers (eg, cell-free tumor DNA and soluble ADAM9).
- Retrospective analysis of other potential predictive and/or prognostic biomarkers including analysis of protein levels as well as gene expression and genomic analyses of DNA and RNA isolated from tumor samples.
- FcγR genotype will be determined retrospectively from peripheral blood mononuclear cells to evaluate the association of FcγR genotype and clinical response.

10.3.1. ADAM9 Expression in Tumor Tissue

ADAM9 expression can vary across and within solid tumor indications, but is highly expressed in non-squamous NSCLC, TNBC, CRC, gastroesophageal cancer, and pancreatic cancer (Hicks 2019), (Ab 2021). During the study, ADAM9 expression in participant tumor tissue will be analyzed at a central laboratory and correlated with response to IMGC936.

11. ASSESSMENT OF EFFICACY

11.1. Efficacy Assessments

11.1.1. Disease Response Assessments

Tumor assessments will be obtained using CT and/or MRI scans. Target and non-target lesions will be designated at screening and then evaluated after every other cycle, ie, Q6W (± 7 days) on Schedule A and every 8 weeks (Q8W; ± 7 days) on Schedule B while on study drug (Appendix 1 and Appendix 2). At each tumor assessment time point, the overall response status will be determined based on assessment of target and non target lesions as well as appearance of any new lesions.

If feasible, participants who discontinue study drug for reasons other than PD (eg, toxicity, participant request) should continue to undergo tumor assessments Q12W (± 21 days) until evidence of PD, initiation of another anticancer therapy, withdrawal of study consent, LTFU, death, or end of study, whichever occurs first.

- For RECIST v1.1 (Appendix 6), the overall responses will be categorized as CR, PR, SD, PD, or NE. For participants who experience an objective response of CR or PR, responses will be considered unconfirmed until the response has been documented by a subsequent confirmatory scan obtained no less than 4 weeks after the initial scan demonstrating an objective response.

12. ADVERSE EVENT REPORTING AND ASSESSMENT OF SAFETY

Safety assessment will be based on evaluation of AEs that occur from the time of initiation of study drug administration through the EOTV or 30 days following the last dose of study drug or until the start of subsequent anticancer therapy (whichever occurs first) and will be determined based on signs, symptoms, physical examination findings, and/or laboratory test results from enrolled participants, as appropriate. The investigator should follow and provide updates for all AEs until clinical recovery is complete, laboratory values return to normal, the participant stabilizes, or death occurs to ensure the safety of the participants. This may mean that observations continue beyond the last planned visit per protocol and that additional investigations may be requested by the sponsor.

Protocol-related AEs and SAEs will be collected from the time the participant has consented to study participation. AEs and SAEs reported between the time participant consent is obtained and administration of the first dose of study drug will be captured as medical history unless the events are attributed to protocol-specified procedures that are not part of standard of care that occur during this time period, in which case the events will be collected on the AE CRFs.

SAEs will continue to be followed by ImmunoGen Pharmacovigilance until resolution, stabilization or return to baseline. Beyond the defined reporting period, any unsolicited SAE assessed as related to the study drug by the investigator and reported to ImmunoGen will be collected and processed. Additional information obtained after database lock will reside solely in the safety database.

Progression of the underlying neoplasm resulting in hospitalization or death (eg, participant hospitalized for or dies from PD only, without any other SAE) will be documented as a PD outcome and not as an SAE. If an SAE occurs and it is unclear whether the event is related to disease progression, the SAE should be reported.

12.1. Definitions

12.1.1. Adverse Event

AE means any untoward medical occurrence in a patient or clinical trial participant associated with the use of a drug in humans, whether or not considered drug related. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

12.1.2. Adverse Drug Reaction

An adverse drug reaction is a noxious and unintended response to the medicinal product related to any dose. As used herein, the phrase “response to a medicinal product” means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility.

12.1.3. Adverse Event of Special Interest

An adverse event of special interest (AESI) is an event of scientific and medical interest or concern to the sponsor's product or program, for which ongoing monitoring and rapid communication to the sponsor could be appropriate. It may be a serious or non-serious AE, which may require further investigation in order to characterize and understand it; refer to Section 12.2.3 for full details.

12.1.4. Attribution/Assessment of Causality

Attribution/assessment of causality is a determination that describes the relationship or association of the study product with an AE.

This assessment of causality or relationship of AEs to the study drug is provided by the investigator and is determined by 1) temporal relationship of the event to the administration of study drug; 2) whether an alternative etiology has been identified, and 3) biological plausibility. Causality must be assessed separately for each study drug.

The causality assessment categories that will be used for this study are described below.

Causality assessments that are considered not related to study drug:

None: The event is related to an etiology other than the study drug (the alternative etiology should be documented in the medical record).

Unlikely: The event is unlikely to be related to the study drug and likely to be related to factors other than study drug. An alternative explanation is more likely (eg, concomitant drugs, concomitant disease), or the relationship in time suggests that a causal relationship is unlikely.

If an SAE is considered "unlikely" or "unrelated" to study drug, the investigator should offer their clinical opinion as to what factor(s), agent(s), or process(es) were the likely causative mechanism for the event.

Causality assessments that are considered related to study drug:

Possible: There is an association between the event and the administration of the study drug and there is a plausible mechanism for the event to be related to study drug; but there may also be alternative etiology, such as characteristics of the participant's clinical status or underlying disease.

Probable: There is an association between the event and the administration of study drug; there is a plausible mechanism for the event to be related to the study drug and the event could not be reasonably explained by known characteristics of the participant's clinical status or an alternative etiology is not apparent.

Definite: There is an association between the event and the administration of study drug; there is a plausible mechanism for the event to be related to the study drug, causes other than the study drug is ruled out, and/or the event re-appeared on re-exposure to the study drug.

12.1.5. Serious Adverse Event

An SAE is any AE that results in any of the following outcomes:

- Death
- Is life-threatening
- Requires inpatient hospitalization (excludes 23-hour hold for observation, admission to hospice or nursing home, respite care, outpatient surgery, social admission, or admission for elective/preplanned surgery)
- Requires prolongation of existing hospitalization
- A persistent or significant disability or incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly or birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, or blood dyscrasias or convulsions that do not result in inpatient hospitalization.

12.1.6. Severity Criteria

An assessment of severity grade will be made using NCI CTCAE v5.0. The CTCAE are published standardized definitions for AEs to describe the severity of laboratory and organ toxicity for patients receiving cancer therapy. The investigator should use clinical judgment in assessing the severity of events not directly experienced by the participant (eg, laboratory abnormalities).

For events not contained in CTCAE, the investigator may assign intensity according to the following generic CTCAE grading scale:

- Grade 1 = Mild; asymptomatic or mild symptoms, clinical or diagnostic observations only; intervention not indicated.
- Grade 2 = Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL).
- Grade 3 = Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL.
- Grade 4 = Life-threatening consequences; urgent intervention indicated.
- Grade 5 = Death related to AE.

12.2. Adverse Event Collection and Documentation

12.2.1. All Adverse Events

All participants who receive at least one dose of study drug will be considered evaluable for safety. AEs will be determined based on signs, symptoms, physical examination findings, and/or laboratory test results from enrolled participants as appropriate.

All AEs, whether serious or non-serious, will be reported from the time participant consent is obtained through the EOTV or 30 days following the last dose of study drug or until the start of subsequent anticancer therapy (whichever occurs first). The investigator should follow and provide updates for all AEs until clinical recovery is complete, laboratory values return to normal, the participant stabilizes, or death occurs to ensure the safety of the participants.

Both protocol-related AEs and SAEs will be collected from the time the participant has consented to study participation. AEs and SAEs reported between the time participant consent is obtained and administration of the first dose of study drug will be captured as concurrent medical history unless the events are attributed to protocol-specified procedures. Events attributed to protocol-specified procedures will be collected on the AE eCRFs and SAE report form as appropriate.

All AEs, regardless of seriousness, severity, or presumed relationship to study drug, must be recorded using medical terminology in the source document and the eCRF. All records will need to capture:

- Duration, severity, and seriousness of each AE
- Action taken with respect to the study drug
- Investigator's attribution/causality assessment
- Event outcome

Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). All treatment measures that are required for AE management must be recorded in the source document. The intensity (severity) of AEs will be assessed using NCI CTCAE v5.0 and serious events will be determined by the definition provided in Section 12.1.5 above.

Clinical Laboratory Changes: Safety laboratory assessments will be evaluated by the investigator to ensure participant safety. Laboratory tests will be graded according to NCI CTCAE v5.0. The investigator is responsible for reviewing the results of all laboratory tests as they become available:

- Laboratory values that fall outside of a clinically accepted reference range or values that differ significantly from previous values must be evaluated by the investigator for clinical significance. The investigator may repeat the laboratory test or request additional tests to verify the results of the original laboratory tests.
- A laboratory abnormality is reported as an AE if it is associated with an intervention. An intervention includes, but is not limited to, discontinuation of study drug, dose

reduction/delay, or concomitant therapy. In addition, any medical important laboratory abnormality may be reported as an AE at the discretion of the investigator. This includes laboratory abnormalities for which there are no interventions, but the abnormal value(s) suggests a disease or organ toxicity. If clinical sequelae are associated with a laboratory abnormality, the diagnosis or medical condition should be reported (eg, renal failure, hematuria) not the laboratory abnormality (eg, elevated creatinine, urine red blood cell increased).

Section 12.2.5 summarizes AE reporting to sponsor timeframes. The sponsor assumes responsibility for appropriate reporting of AEs to regulatory authorities. The sponsor will also notify the investigator of regulatory submissions, as appropriate. The investigator is responsible for notifying the appropriate IEC/IRB that approved the protocol, unless otherwise required and documented by the IEC/IRB.

For this study, the participants must be provided with a study card and instructed to carry this study card with them for the duration of the study indicating the following:

- Study number
- Statement, in the local language(s), that the participant is enrolled in a clinical study
- Investigator's name and 24-hour contact telephone number
- Site number
- Participant number

PD under study is an anticipated occurrence and is part of the efficacy objectives of this study. PD is not an AE. However, any medical event or condition that results from PD, if untoward, should be reported as an AE.

12.2.2. Serious Adverse Events

All SAEs occurring during the study must be reported to the sponsor.

After 30 days following the last dose of study drug administration, if an investigator becomes aware of an SAE that they suspect is related to study drug, the investigator should report the event to the sponsor.

Within 24 hours of becoming aware of an SAE, the investigator should provide a completed SAE report form, via email or fax, to the sponsor. Upon receipt of follow-up information pertaining to an SAE, a follow-up SAE report form should be submitted to the sponsor within 24 hours of becoming aware of the follow-up information. All SAEs should be entered into the eCRFs within 5 calendar days of the site’s awareness.

The investigator must follow all SAEs until resolution and record the date of resolution. Resolution of an event is defined as the return to pre-treatment status or stabilization of the condition with the expectation that it will remain chronic.

All SAEs that have not resolved by the end of the study, or that have not resolved upon discontinuation of the participant from the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- It becomes unlikely that any additional information can be obtained (participant or health care practitioner refusal to provide additional information, LTFU after demonstration of due diligence with follow-up efforts)

Any event requiring hospitalization (or prolongation of hospitalization) that occurs during enrollment in a study must be reported as an SAE, except hospitalizations for the following:

- A standard hospitalization for administration of study drug therapy will not be reported as an SAE
- A procedure for protocol/disease-related investigations (eg, surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling, PK or biomarker blood sampling)
- Hospitalizations not intended to treat an acute illness or AE (eg, social reasons such as pending placement in long-term care or hospice facility)
- Surgery or procedure planned before entry into the study (must be documented in the eCRF)

PD should not be reported as an SAE term; however, any serious medical event/condition that results from progression of underlying disease, if untoward, should be reported as the SAE. The applicable protocol case report form page(s) pertaining to death should be appropriately completed, however, as disease progression. Death should not be reported as an SAE term. Death is an outcome of a specific SAE term. In exceptional cases, “death of unknown cause” may be used as an event term until the cause of death has been determined. If an autopsy was performed, the autopsy report should be provided.

12.2.3. Protocol-Specific Adverse Events of Special Interest

IMGC936 has 1 AESI: IRR. Any symptom or sign occurring within 24 hours of infusion and suggestive of an IRR should be promptly reported as per Section 12.2.5.

Further information on risks can be found in the IMGC936 Investigator’s Brochure.

12.2.4. Pregnancy

All reports of pregnancy in participants or partners of male participants must be reported to the sponsor by study-site personnel within 24 hours of their knowledge of the event using the Pregnancy Exposure Form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and must be reported using the SAE report form. Any participant who becomes pregnant during the study must discontinue further study drug administration.

Because the effect of the study drug on sperm is unknown, pregnancies in partners of male participants included in the study will be reported by the study-site personnel within 24 hours of

their knowledge of the event. If the female partner of a male participant becomes pregnant, the partner must be requested to complete a Pregnant Partner Consent Form so that pregnant partner, fetal, and/or newborn information can be collected.

Upon confirmation of serum or urine pregnancy testing, the participant will be followed for the outcome of pregnancy. Follow-up information will be collected for all live newborns at birth and 6 months after the birth. All necessary information will be collected to assess the effects of study drug on the newborn. If necessary, the follow-up period will be extended for the newborn.

12.2.5. Reporting of Adverse Events to the Sponsor

The investigator must document all AEs in eCRFs in a timely manner. Refer to Table 10 for reporting timeframes.

Note: When reporting an AESI, complete the SAE/AESI form, stating that the event is an AESI.

Table 10: Safety Reporting by Event Type

Type of Event:	**Hard Copy Form/Timeline for Reporting**	**eCRF Timeline for Data Entry**
Serious adverse event (SAE)	SAE/AESI form within 24 hours of awareness	Within 5 calendar days of awareness
Pregnancy	Pregnancy exposure form within 24 hours of awareness	Within 5 calendar days of awareness
AESI	SAE/AESI form within 24 hours of awareness	Within 5 calendar days of awareness

Abbreviations: AESI: adverse event of special interest; eCRF: electronic case report form; SAE: serious adverse event.

13. PRODUCT QUALITY COMPLAINT HANDLING

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity. A PQC may have an impact on participant safety and activity of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of participants, investigators, and the sponsor and are mandated by regulatory agencies worldwide. The sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information; all studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

13.1. Procedure

All initial PQCs must be reported to the sponsor by the study-site personnel, after being made aware of the event, and those that are associated with clinical consequences must be reported within 24 hours.

If the defect is combined with a SAE, the study-site personnel must report the PQC to the sponsor according to the SAE reporting timelines (refer to Section 12.2.2, Serious Adverse Events). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

13.2. Contacting Sponsor Regarding Product Quality

Name(s) and corresponding telephone numbers of the individuals who should be contacted regarding product quality issues are listed on the contact information page(s), which will be provided as a separate document.

14. STATISTICAL ANALYSIS

This section outlines the statistical methodology and principles which will be used for data analysis in this study. A separate statistical analysis plan (SAP) will further describe the details regarding statistical methods and will govern the analysis.

14.1. Determination of Sample Size

The number of participants who receive study drug cannot be determined precisely in advance. The study plans to treat up to approximately 72 participants in dose escalation. 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. The null hypothesis is that an uninteresting response rate is 9% less. The design has 80% power to detect a target response rate of 25% at the significance level of 1-sided 0.05. Following this design per cohort, the first stage of the futility assessment will be conducted in the first 13 response-evaluable participants in each expansion cohort. If no more than 1 responder is observed in an expansion cohort, no further participants will be recruited to that cohort and the null hypothesis will not be rejected. If there are at least 2 responders out of the 13 response-evaluable participants at the first stage, each may enroll an additional 26 participants to that cohort. If there are at least 7 responders out of a total of 39 response-evaluable participants, the null hypothesis will be rejected for that cohort.

14.2. Analysis Populations

The study analyses will be performed on the following populations:

- Safety Population: All participants who received at least one dose of study drug. This population will be used for analyses of safety, PK, and immunogenicity. It will also be used for summary of baseline data and analyses of PFS.
- Response Evaluable Population: 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.

14.3. Demographics and Baseline Characteristics

Participant disposition, demographics, baseline characteristics, disease history, medical history, and prior cancer treatment will be summarized using descriptive statistics.

14.4. Study Drug Exposures and Concomitant Medications

Study drug exposures and concomitant medications will be summarized by descriptive statistics. The summary of study drug exposure will include descriptive statistics as well as frequency counts for the number of doses or cycles received, the total dose administered as well as the total

dose intended, and the dose intensity, which is calculated as percentage of total dose actually administered divided by total dose intended during the whole treatment period.

14.5. Safety Endpoints and Analyses

14.5.1. Adverse Events

Only treatment-emergent AEs will be summarized in tables. The following AEs will be provided in summary tables as well as displayed in listings:

- All AEs
- AEs with CTCAE severity Grade ≥ 3
- Ocular AEs
- Study drug related AEs
- Study drug related AEs with CTCAE severity Grade ≥ 3
- SAEs
- Study drug related SAEs
- AEs resulting in discontinuation of study drug
- AEs resulting in interruption of study drug
- Study drug related AEs resulting in discontinuation of study drug
- Study drug related AEs resulting in interruption of study drug
- Fatal AEs
- AESIs

All of these tables will display the number and percent of participants that experience the given event and will display events by Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term (PT). Events will be displayed alphabetically for SOC and in descending order of overall PT incidence within each SOC. An overall summary of AEs will display the number and percent of participants who experience at least one event of each of the above types.

14.5.2. Laboratory Values

Summaries of laboratory values will display descriptive statistics for numerically quantified laboratory test results. Summaries will be grouped by laboratory panel (eg, hematology, blood chemistry, and urinalysis) and will be displayed by visit for each laboratory parameter.

14.5.3. Other Safety Endpoints

Twelve lead ECGs will be collected and analyzed for evidence of cardiac toxicity, especially prolongation of QT interval. Change in LVEF from baseline will be summarized. Vital signs will be summarized with descriptive statistics at each visit and time point at which they are collected. Shift tables may be created.

14.6. Pharmacokinetic Biomarker Analysis

14.6.1. Pharmacokinetic Analysis

Study drug concentrations will be summarized. Summary statistics will be tabulated separately for PK parameters by IMGC936 dose. Geometric means and percent coefficients of variation will be reported for C_{max}, AUC from time zero to time t (AUC_{0-t}), AUC_{0-inf}, trough concentration (C_{trough}) and accumulation index (AI); arithmetic means and standard deviations will be reported for half-life ($t_{1/2}$), clearance (CL), and volume of distribution at steady state (V_{ss}); and medians, minimum, and maximum will be reported for time to maximum concentration (T_{max}). Separate scatter plots of C_{max} and AUC may be provided versus dose to assess dose dependency. Dose proportionality may be assessed using a power model.

14.6.2. Immunogenicity Analysis

The proportion of participants who are negative for ADAs at baseline and become positive in this assay, the proportion of participants who are negative at baseline and remain negative, and those who have positive ADA at baseline that increases or decreases in titer over the course of the study will be summarized.

14.6.3. Biomarker Analysis

Summary statistics for biomarker parameters, such as, but not limited to, those listed in Section 10.3 and corresponding changes from baseline will be summarized and/or may also be presented graphically. Biomarker analysis and subsequent results may be reported in separate documents and not included in the SAP or clinical study report, respectively.

14.7. Efficacy and Endpoint Analyses

14.7.1. Response Endpoints and Analyses

For RECIST v1.1, the best overall response (BOR) will be categorized as CR, PR, SD, PD, or NE. To be qualified as BOR, CR and PR require confirmation at least 28 days (4 weeks) after initial observation of such response, and SD requires to be observed at least once after 35 days (6 weeks [- 1 week]) from the first dose of study drug.

The number and percent of participants with their BOR will be summarized. Objective response rate per RECIST v1.1 is estimated as the proportion of participants in the Response Evaluable Population who achieve BOR of CR or PR. Two-sided 95% exact binomial CIs of the response rates will be calculated.

14.7.2. Analysis of Tumor Size Change Over Time

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

14.7.3. Time-to-Event Endpoints and Analyses

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 will be applied to the PFS analysis.

Table 11: Censoring Rules for Primary Analysis of PFS

Situation	Date	Outcome
No baseline tumor assessments	First dose date	Censored
Death prior to first scheduled tumor assessment	Date of death	Progressed
No post-baseline tumor assessments in absence of death prior to first scheduled tumor assessment	First dose date	Censored
Documented progression	Date of progression	Progressed
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	Date of last tumor assessment prior to missed assessments	Censored

Abbreviation: PFS: progression-free survival

DoR is defined as the time from the date of initial response (CR or PR) to the date of first documented progression or death from any cause, whichever occurs first. The DoR is calculated only for the responders. For responders who are not known to be dead or progressed at the time of data cut-off for DoR analysis, the DoR will be censored at the date of the last tumor assessment. Specifically, the last 3 situations described in Table 11 will be applied. DoR analyses will be performed only if there are enough responders to render the analyses meaningful.

The Kaplan-Meier method will be applied to estimate PFS and DoR curves; their median times, and PFS rates at 6 and 12 months, respectively. The method of Brookmeyer and Crowley (3) will be used to construct 95% CIs for median time of each time-to-event endpoint. The 95% CIs for PFS rates at each time point of interest will be calculated by normal approximation after log(-log) transformation.

15. QUALITY CONTROL AND ASSURANCE

Quality review activities will be undertaken to ensure accurate, complete, and reliable data. The sponsor and/or its representatives will do the following:

- Provide instructional material to the study sites, as appropriate.
- Sponsor a start-up training session to instruct investigators and study coordinators. This session will give instruction on the protocol, completion of eCRFs, and study procedures.
- Monitor protocol and GCP compliance on a regular basis (on-site visits and/or remote monitoring).
- Be available for consultation and stay in contact with the study site personnel by mail, e mail, telephone, and/or fax.
- Review and evaluate eCRF data and use standard computer checks to detect and query errors in data collection.
- Conduct a quality review of the database.

15.1. Monitoring, Auditing and Inspections

The sponsor or its designee will monitor the conduct of the trial on a regular basis throughout the duration of the study, according to the monitoring plan and in compliance with current GCP guidelines. Monitoring of the study will serve to ensure: (a) The rights and well-being of human subjects are protected; (b) The reported trial data are accurate, complete, and verifiable from source documentation; and (c) The conduct of the trial complies with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s).

The study monitor will educate site personnel on the conduct of the trial. The monitor will assess the trial site's compliance with the protocol and will periodically review and verify a sample of the participant data recorded on eCRFs against source documentation. The study monitor will also review documents that provide evidence of proper consent and eligibility of enrolled participants, compliant conduct of study procedures, administration and disposition of investigational product(s), reporting of SAEs and AEs, and continued maintenance of trial records.

The investigator will allocate adequate time to support such monitoring activities. The Investigator will also ensure that the monitor is given reasonable access to study-related documents, source documents (regardless of media) and study-related facilities (eg, investigational pharmacy, etc.). Queries may be raised if any datum is unclear or contradictory. The Investigator and site personnel must address all queries in a timely manner.

Sponsor personnel and the designee (ie, representative from the contract research organization) will review the protocol and clinical trial database with the investigator and the site staff at a site initiation visit. Monitoring procedures that comply with current GCP guidelines will be followed. On-site and/or remote monitoring will be performed by a representative of the sponsor (clinical study monitor). Review of the clinical trial database for completeness and clarity, cross-checking with source documents, and clarification of administrative matters will be performed. During

monitoring activities, the clinical study monitor will check the progress of enrollment, and ensure that study drug is being stored, dispensed, and accounted for according to specifications. Key study personnel from the site must be available to assist the clinical study monitor during these activities. The clinical study monitor will ensure that the investigation is conducted according to protocol design and regulatory requirements on a regular basis per the study monitoring plan.

The investigator must maintain source documents for each participant in the study, consisting of (but not limited to) all visit notes, laboratory data, ECGs, and the results of any other tests or assessments. The investigator must also keep the original signed informed consent form (ICF); a signed copy is given to the participant. The investigator must give the monitor access to all relevant source documents to confirm their consistency with clinical trial database entries. Full verification for the presence of informed consent, adherence to inclusion/exclusion criteria and documentation of SAEs is required. Additional checks of the consistency of source data with the clinical trial database are performed according to the study-specific monitoring plan.

Participation as an investigator in this study implies acceptance of the potential for inspection by the study sponsor/representatives, US or non-US government regulatory authorities, IRB/IEC, and applicable compliance and quality assurance offices. The investigator will permit study-related audits and inspections and will provide access to all study-related documents (eg, source documents, regulatory documents, data collection instruments, study data). The investigator will ensure the capability for inspections of applicable study related facilities (eg, pharmacy, diagnostic laboratory).

15.2. Data Collection and Management

The investigator is responsible for maintaining accurate, complete, and up-to-date records for each participant. The investigator is also responsible for maintaining any source documentation related to the study, including any films, tracings, or other media containing data pertaining to this protocol.

The anonymity of participants must be maintained. For data collection, and management purposes, participants are to be identified by participant number only. Documents that identify the participant beyond participant number (eg, participant initials) will not be submitted to the sponsor (eg, the signed informed consent document) and must be maintained in strict confidence by the investigator, except to the extent to allow auditing by the regulatory authorities, study monitor, or sponsor representatives.

Site personnel record all data for each participant through eCRFs using an EDC system provided and approved by the sponsor. Study sites must complete eCRFs for each participant in a timely manner shortly after each participant visit. As the person ultimately responsible for the accuracy of all eCRF data, the investigator must sign the Investigator's Statement in each participant's eCRF.

The EDC system automatically generates queries resulting from the computer checks embedded into the system to ensure data accuracy, quality, consistency, and completeness. Manual queries resulting from review by monitors, medical coders, and Data Management staff are also generated from within the EDC system, where they are tracked. Study sites resolve the queries

and correct the entered data accordingly. Every change to data is captured in the EDC system audit trail. Adverse events are coded using MedDRA, whereas concomitant medications are coded using the World Health Organization (WHO) Drug Dictionary. Upon completion of the study, or after reaching a pre-specified point in the study, Data Management will lock the database and generate the SAS datasets necessary for analysis and reporting. Upon completion of the study, each study site will be provided with the eCRFs for each of their participants.

16. ADMINISTRATIVE CONSIDERATIONS

16.1. Institutional Review Board or Independent Ethics Committee Approval

The investigator should provide the sponsor with a statement of compliance from the IRB/IEC indicating compliance with the applicable regulations in the region and International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). Any documents that the IRB/IEC may need to fulfill its responsibilities, such as the protocol and any amendments, Investigator's Brochure, and information concerning participant recruitment, payment or compensation procedures, or information from the sponsor will be submitted to the IRB/IEC. The IRB/IEC's written approval of the study protocol and the ICFs will be in the possession of the investigator and the sponsor before the study drug is initiated at the investigator's site. The investigator will transmit the IRB/IEC's approval statement to the sponsor. This approval must include the date of review and refer to the study by protocol title and/or study number and version number and refer to the ICFs by version number or date. If the IRB/IEC or institution uses its own unique number for the protocol instead of the sponsor's number, that unique number should be noted on the approval statement. If approval of the ICFs is stamped on the forms (instead of documented in the IRB/IEC approval statement), the date of approval and/or expiration must be included.

Protocol modifications or changes may not be initiated without approval from the sponsor and prior written IRB/IEC approval (when required), except when necessary to eliminate immediate hazards to the participant. Such modifications will be submitted to the IRB/IEC; and written verification that the modification was submitted should be obtained.

The investigator must, where required by local regulations, submit the following to the IRB/IEC:

- The protocol, Investigator's Brochure, and any amendments or updates.
- The informed consent form(s) and any amendments or changes.
- Any documents given to participants or potential participants (eg, recruitment materials, diary cards) and the plan for distribution/use.
- Revisions of other documents originally submitted for review or for notification.
- Serious and/or unexpected AEs occurring during the study.
- New information that may adversely affect the safety of participants or conduct of the study.
- At minimum, an annual update and/or request for re-approval of study, unless otherwise specified by IRB/IEC.
- Protocol deviations.
- Notification when the study has been completed.
- Proof of indemnity/liability insurance.
- Other documents required by the IRB/IEC.

16.2. Ethical Conduct of the Study

The investigational study will be conducted according to the Protection of Human Patients (21 CFR [Code of Federal Regulations] 50), Institutional Review Boards (21 CFR 56), Obligations of Clinical Investigators (21 CFR 312.60–312.69), current ICH guideline for GCP (ICH E6), and all other applicable regulations.

16.3. Participant Information and Consent

It is the responsibility of the investigator to obtain and document written informed consent from the participant. Informed consent in compliance with the principles of informed consent in ICH E6 and all applicable local regulations should be obtained before any protocol-specified procedures or interventions are conducted. The sponsor reserves the right to delay initiation of the study at a site where ICFs do not meet the standards of applicable local regulations or ICH E6.

Information should be given to the participant in both oral and written form, and participants must be given ample opportunity to inquire about details of the study.

The consent form generated by the investigator must be approved by the IRB/IEC. The investigator will provide the sponsor with a copy of the IRB/IEC-approved consent forms and a copy of the IRB/IEC's written approval before the start of the study.

Consent forms must be written (and appropriately translated in the participant's native language or language in which the participant has fluency) so as to be understood by the prospective participant. Informed consent will be documented by the use of a written consent form approved by the IRB/IEC. The form must be signed and dated by the participant and by the person who conducted the discussion of the informed consent.

All versions of each participant's signed ICF must be kept on file by the investigator for possible inspection by regulatory authorities and/or authorized sponsor monitoring and regulatory compliance persons. The participant should receive a copy of the signed and dated written ICF and any other written information provided to the participant.

16.4. Participant Confidentiality

To maintain confidentiality of participants, all laboratory specimens, evaluation forms, reports, and other records will be identified by a coded number. Clinical information will not be released without written permission of the participant or an individual with legal decision-making authority for the participant or the participant's interests, except as necessary for monitoring by the relevant regulatory authorities, the sponsor of the clinical study, or the sponsor's representative. The investigator must comply with all local applicable privacy regulations for protection of personal data (eg, US Health Insurance Portability and Accountability Act of 1996 or European Union General Data Protection Regulation).

16.5. Case Report Forms and Study Records

Source data in a clinical study are the original records or certified copies where clinical observations are first recorded, which may include, but are not limited to, the participant's

medical file, original laboratory reports, histology, and pathology reports (as applicable). The investigator is responsible for maintaining adequate and accurate medical records from which accurate information will be entered into the eCRFs designed to capture data pertinent to the clinical investigation. Data should be recorded on paper source documents or electronic in an electronic medical records system. The eCRFs should be completed in their entirety by the investigator or their designee. Prior to eCRF database lock, the investigator will verify the completeness and accuracy of the data and indicate that he/she has done so by providing an electronic signature on the appropriate eCRF. The investigator will retain a copy of all source documents.

16.6. Access to Source Documentation

The investigator and study center will permit the sponsor, its representatives, IRB/IEC, and all relevant regulatory agencies access to all original source data and documents regardless of media, for study monitoring audits and inspections.

16.7. Retention of Data

Per ICH guidelines, all essential documents, including eCRFs, source documents (regardless of media), signed ICFs, and laboratory test results, must be retained by the investigator for at least 2 years after last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since formal discontinuation of clinical development of the investigational product. There may be other circumstances for which the sponsor is required to maintain study records for longer periods; therefore, the sponsor must be contacted before study records are removed from the control of the study site for any reason. The investigator must obtain written permission from the sponsor prior to destruction of study documents.

16.8. Sample Retention and Further Testing

Samples acquired for protocol-specified assays will be retained for at least 1 year following the end of the study and may be retained up to 2 years after last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since formal discontinuation of clinical development of the investigational product. If the participant consents, or an individual with legal decision-making authority for the participant or the participant's interests consent, to the use of their study samples for non-study research purposes, these samples may also be used for exploratory testing (including assay development/optimization) and may be retained up to 15 years from the end of the study.

16.9. Financial Disclosure

The investigator and sub-investigators will be required to disclose any applicable financial arrangement as defined in US regulations (ie, 21 CFR 54).

The following information will be collected about the investigators, their spouse, and each dependent child: any significant payments of other sorts from sponsor, or any alliance partner, such as a grant to fund ongoing research, compensation in the form of equipment, retainer for

ongoing consultation or honoraria; any proprietary interest in the study drug; and any significant equity interest in sponsor, as defined in 21 CFR 54. Investigators are obliged to update the sponsor with any changes in reported information up to 1 year following the end of the study.

Investigators and sub-investigators will be required to disclose if they are an employee of the sponsor, or an immediate family member of a sponsor employee, officer, or director. This is to assist the sponsor with its compliance with Securities and Exchange Commission rules requiring disclosure of certain transactions with related persons as defined in 17 CFR 229.404. "Immediate family member of a sponsor employee" means a child, stepchild, parent, stepparent, spouse, sibling, mother-in-law, father-in-law, son-in-law, brother-in-law, or sister-in-law of any sponsor employee, officer, or director or any person sharing the household of such sponsor employee, officer, or director.

In consideration of participation in the study, the sponsor will pay the investigator or nominated payee the sums set out in the payment schedule attached to the investigator agreement.

Financial disclosure information will be documented in writing and signed and dated by the investigator. This information will be collected prior to that investigator taking part in the research.

16.10. Publication and Disclosure Policy

Data collected in this clinical study belong to the sponsor. The publication terms regarding use of the study data will be noted in the clinical trial agreement. This includes authorship: scheduling and prioritizing analyses for reports, publications, and presentations; and developing a review and approval process.

16.11. Discontinuation of the Study or Study Sites

16.11.1. Discontinuation of Study Sites

Site participation may be discontinued if the sponsor, the investigator, a regulatory authority, or the IRB/IEC of the study sites deems it necessary for any reason.

16.11.2. Discontinuation of the Study

The study may be discontinued by a regulatory authority or at the discretion of the sponsor. Changes in the risk/benefit profile will prompt a review of the study in conjunction with the local regulatory authority.

The investigator maintains the right to discontinue their participation in the study should their clinical judgment so dictate. The investigator will notify the IRB/IEC of any study discontinuation. Study records must be retained as noted above.

16.12. Identification of the Coordinating Principal Investigator

A coordinating principal investigator will be appointed by the sponsor prior to the end of the study.

As part of his or her responsibilities, the coordinating principal investigator will review the final clinical study report. Agreement with the final clinical study report will be documented by the dated signature of the coordinating principal investigator.

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18. APPENDICES

APPENDIX 1. TIME AND EVENTS SCHEDULE (SCHEDULE A - 21 DAY CYCLE)

EVALUATION/ PROCEDURE	Screening (within 28 days)	Cycle 1					≥ Cycle 2			EOTV	Follow-up
		Day 1	Day 2	Day 3 (+ 1d)	Day 8 (± 1d)	Day 15 (± 1d)	Day 1 (+ 3d)	Day 8 (± 1d)	Day 15 (± 1d)		
Informed consent	X										
Eligibility criteria review	X										
Medical/cancer history	X										
Tumor specimen [a]	X										
Physical examination [b]	X	X			X	X	X	X	X	X	
Concomitant medications/procedures	Continuous									X	
ECOG performance status [c]	X	X					X			X	
12-lead ECG [d]	X	X			X		X			X	
Echocardiogram/MUGA [e]	X									X	
Ophthalmic examination [f]	X	Asymptomatic participants have exams at the end of Cycle 2 and every 3 cycles (ie, Cycle 5, 8, 11, etc.). Participants with ocular symptoms or signs follow Table 7.								X	
Ocular symptoms assessment [g]		X			X	X	X	X	X	X	
Pregnancy test [h]	X	X					X			X	
Assess for AEs	Continuous										
Vital signs [i]	X	X		X	X	X	X	X	X	X	
Hematology/chemistry [j]	X	X		X		X	X	X		X	
Coagulation [j]	X	X		X		X	X	X		X	
Endocrine [j]	X									X	
Urinalysis [j]	X	X					X			X	

EVALUATION/ PROCEDURE	Screening (within 28 days)	Cycle 1					≥ Cycle 2			EOTV	Follow-up
		Day 1	Day 2	Day 3 (+ 1d)	Day 8 (± 1d)	Day 15 (± 1d)	Day 1 (+ 3d)	Day 8 (± 1d)	Day 15 (± 1d)		
PK/ADA/Biomarker		See Appendix 4									
Tumor markers eg, CEA or CA19-9 [k]	X	Q6W (± 3 days) starting Cycle 1 Day 1 [k]								X	
Disease assessment	X	Q6W (± 7 days) while on study drug then Q12W (± 21 days) [l]								X [l]	
Follow-up assessments [m]											X [m]
Administer IMGC936		X					X				

Abbreviations: ADA: antidrug antibody; AE: adverse events; C: cycle; CA19-9: carbohydrate antigen 19-9; CEA: carcinoembryonic antigen; D/d: day; ECG: electrocardiography; ECOG: Eastern Cooperative Oncology Group; EOI: end of infusion; EOTV: end of treatment visit; LTFU: lost to follow-up; LVEF: left ventricular ejection fraction; MUGA, multigated acquisition scan; PD: progressive disease; PK: pharmacokinetic; QxW: every x weeks; RECIST: Response Evaluation Criteria in Solid Tumors; RP2D: recommended Phase 2 dose.

[a] All participants to be enrolled in the study must have an identified formalin-fixed, paraffin embedded tumor specimen or slides as detailed in the laboratory manual; see Section 9.13. Participants may undergo a low-risk, medically routine procedure to obtain a specimen for testing if a suitable archival sample cannot be identified. The specimens will be analyzed retrospectively and will not be used to determine eligibility.

[b] Includes height (screening only) and weight. Weight may be obtained within 24 hours of Cycle 1 Day 1. Full physical examinations are performed at screening, Cycle 1 Day 1 (or within 24 hours before the first infusion), and EOTV. All other physical examinations are directed physical examinations based on symptoms, tumor location, and as clinically indicated. Participants in dose escalation cohorts will have weekly directed physical examination through treatment Cycle 3. Beginning on Cycle 4, physical examination is only required on Day 1 of each cycle. Participants in the dose expansion cohorts should have physical examination recorded on Day 1 of each treatment cycle.

[c] ECOG performance status should be the primary performance measure for participant enrollment. If ECOG performance status is an inappropriate performance measurement for participant enrollment (eg, chronically nonambulatory), then Karnofsky performance status may be used. A description of the scale is in Appendix 8. ECOG assessment at C1D1 can be performed within 24 hours before the infusion.

[d] On Day 1 of Cycle 1, 2 and 3, ECGs are recorded pre-infusion (within 30 minutes before) and EOI (within 30 minutes after EOI). During selected non-dosing visits (eg, screening, C1D8, and EOTV), ECGs will be recorded.

[e] The Investigator to choose appropriate modality (eg, echocardiogram or MUGA) to assess LVEF.

[f] Ophthalmic examinations are performed at screening by an ophthalmologist per Section 9.12. All participants will have a complete ophthalmological examination when ocular symptoms and signs develop, repeated per Table 7. Participants without ocular symptoms or signs should have an ophthalmic examination at the end of Cycle 2, followed with ophthalmic exams every 3 cycles/ 9 weeks (at the end of Cycle 5 ,8, etc.) in both dose escalation and expansion phases. Participants with Grade 2 or greater ocular AEs which have not resolved to Grade 1 or baseline must have an ophthalmic examination at EOTV. All other participants are recommended to have an ophthalmic examination at EOTV to document any subclinical findings.

[g] Ocular symptom assessment at C1D1 can be performed within 24 hours before the infusion. For participants in dose escalation cohorts, ocular symptoms assessment should occur weekly during the first 3 cycles and subsequently Day 1 of each cycle. During the Dose Expansion Phase (at RP2D), if limited ocular

toxicity is observed during escalation, ocular symptom assessment will occur on Day 1 of each cycle or more frequently if ocular symptoms and signs are observed. Phone-based ocular symptom assessments are acceptable if no clinic visit is scheduled.

[h] Females of childbearing potential only. Serum pregnancy test is required for eligibility. Subsequent pregnancy tests may use serum or urine. Results must be reviewed before study drug infusion on Day 1 of Cycle 1 and all subsequent cycles. If screening test is performed within 72 hours of first infusion, repeat of the test on Day 1 may be deferred.

[i] During non-dosing visits (eg, screening and EOTV), vital signs will be taken at one timepoint. For Cycle 1 Day 1, vitals are measured pre-infusion (within 30 minutes before); 15 and 30 minutes after start of infusion (± 5 minutes); EOI (± 10 minutes); and 2, 4, and 6 hours after EOI (± 10 minutes). For Cycle 2 Day 1 and subsequent cycles, vitals are measured pre-infusion (within 30 minutes before), EOI (± 10 minutes), and 1 hour after EOI (± 10 minutes). Participants in dose escalation cohorts must have vital signs recorded on both dosing and non-dosing days through treatment Cycle 3. Beginning on Cycle 4, vital signs must be recorded on Day 1 of each treatment cycle. Participants in expansion cohorts must have vital signs recorded on Day 1 of each treatment cycle.

[j] To be obtained pre-infusion. Day 1 laboratory samples can be obtained up to 3 days before infusion. Chemistry and hematology results must be reviewed before study drug administration. See Appendix 3 for assessments. Beginning on Cycle 4, laboratory samples only required on Day 1 of each cycle.

[k] Tumor markers are obtained as indicated for each specific tumor type, eg, CEA for colorectal cancer and CA19-9 for pancreatic cancer. Repeat collection on Cycle 1 Day 1 if screening collection > 7 days prior.

[l] Tumor assessments are Q6W (± 7 days) while participant is on study drug, then Q12W (± 21 days). Assessments continue until discontinuation criteria are met. Tumor assessments are performed at EOTV except if prior assessment was ≤ 30 days of EOTV and results are available for RECIST v1.1 assessment.

[m] Tumor assessments will occur after participant has discontinued study drug Q12W (± 21 days) until evidence of PD, initiation of another anticancer therapy, withdrawal of consent, LTFU, death, or end of study, whichever occurs first.

APPENDIX 2. TIME AND EVENTS SCHEDULE (SCHEDULE B - 28 DAY CYCLE)

EVALUATION/ PROCEDURE	Screen-ing (within 28 d)	Cycle 1 and Cycle 2								≥Cycle 3				Follow -up
		Day 1	Day 2	Day 3 (+ 1d)	Day 8 (± 1d)	Day 15 (± 1d)	Day 16 (± 1d) *(Cycle 1 PK only)*	Day 17 (±1d) *(Cycle 1 PK only)*	Day 22 (± 1d)	Day 1 (±3d)	Day 8 (±1d)	Day 15 (±1d) (Cycle 3 only)	EOTV	
Informed consent	X													
Eligibility criteria review	X													
Medical/ cancer history	X													
Tumor specimen [a]	X													
Physical examination [b]	X	X			X	X			X	X	X	X	X	
Concomitant medications/ procedures	Continuous												X	
ECOG performance status [c]	X	X		X	X	X			X	X	X		X	
12-lead ECG [d]	X	X			X	X				X			X	
Echocardiogram/MUGA [e]	X													
Ophthalmic examination [f]	X	Asymptomatic participants have exams the end of Cycle 2, then every 3 cycles (ie, Cycle 5, 8, 11, etc.). Participants with ocular symptoms or signs follow Table 7.											X	
Ocular Symptoms Assessment [g]		X			X	X			X	X	X	X	X	
Pregnancy test [h]	X	X			X	X				X	X		X	
Assess for AEs	Continuous													
Vital signs [i]	X	X		X	X	X			X	X	X	X	X	
Hematology/chemistry [j]	X	X		X	X	X			X	X	X	X	X	
Coagulation [j]	X	X		X	X	X			X	X	X	X	X	

EVALUATION/ PROCEDURE	Screen-ing (within 28 d)	Cycle 1 and Cycle 2								≥Cycle 3				Follow -up
		Day 1	Day 2	Day 3 (+ 1d)	Day 8 (± 1d)	Day 15 (± 1d)	Day 16 (± 1d) *(Cycle 1 PK only)*	Day 17 (±1d) *(Cycle 1 PK only)*	Day 22 (± 1d)	Day 1 (±3d)	Day 8 (±1d)	Day 15 (±1d) (Cycle 3 only)	EOTV	
Endocrine [j]	X													
Urinalysis [j]	X	X								X				
PK/ADA/Biomarker		See Appendix 5												
Tumor markers eg, CEA or CA19-9 [k]	X	Q8W (± 3 days) starting Cycle 1 Day 1 [k]											X	
Disease assessment	X	Q8W (± 7 days) while on study drug then Q12W (± 21 days) [l]											X [l]	
Follow-up assessments [m]														X [m]
Administer IMGC936		X			X	X[n]				X	X			

Abbreviations: ADA: antidrug antibody; AE: adverse events; C: Cycle; CA19-9: carbohydrate antigen 19-9; CEA: carcinoembryonic antigen; D/d: day; ECG: electrocardiography; ECOG: Eastern Cooperative Oncology Group; EOI: end of infusion; EOTV: end of treatment visit; LTFU: lost to follow-up; LVEF: left ventricular ejection fraction; MUGA, multigated acquisition scan; PD: progressive disease; PK: pharmacokinetic; QxW: every x weeks; RECIST: Response Evaluation Criteria in Solid Tumors; RP2D: recommended Phase 2 dose.

[a] All participants to be enrolled in the study must have an identified formalin-fixed, paraffin embedded tumor specimen or slides as detailed in the laboratory manual; see Section 9.13. Participants may undergo a fresh tumor biopsy using a low-risk, medically routine procedure to obtain a specimen for testing if a suitable sample cannot be identified. The specimens will be analyzed retrospectively and will not be used to determine eligibility.

[b] Includes height (screening only) and weight. Weight may be obtained within 24 hours of Cycle 1 Day 1. Full physical examinations are performed at screening, Cycle 1 Day 1 (or within 24 hours before the first infusion), and EOTV. All other physical examinations are directed physical examinations based on symptoms, tumor location, and as clinically indicated. Participants in dose escalation cohorts will have weekly directed physical examination through in Cycles 1 and 2, and directed physical examinations on Cycle 3 Day 1, Day 8, and Day 15. Beginning on Cycle 4, physical examination is only required on each dosing visit of each cycle, ie, Day 1 and Day 8. Participants in the dose expansion cohorts will have a physical examination recorded on each dosing visit.

[c] ECOG performance status should be the primary performance measure for participant enrollment. If ECOG performance status is an inappropriate performance measurement for participant enrollment (eg, chronically nonambulatory), then Karnofsky performance status may be used. A description of the scale is in Appendix 8. ECOG assessment at C1D1 can be performed within 24 hours before the infusion.

[d] For Cycle 1 Day 1, 8, and 15, ECGs are recorded pre-infusion (within 30 minutes before) and EOI (within 30 minutes after EOI). For Cycle 2 Day 1 and Cycle 3 Day 1, ECGs are recorded pre-infusion (within 24 hours before) and at EOI (within 30 minutes after EOI). During selected non-dosing visits (eg, screening and EOTV), ECGs will be recorded.

[e] The Investigator to choose appropriate modality (eg, echocardiogram or MUGA) to assess LVEF.

[f] Ophthalmic examinations are performed at screening by an ophthalmologist per Section 9.12. All participants will have a complete ophthalmological examination when ocular symptoms or signs develop, repeated per Table 7. Participants without ocular symptoms or signs should have an ophthalmic examination at the end of Cycle 2, followed with ophthalmic examinations every 3 cycles/ 12 weeks (at the end of Cycle 5, 8, etc.) in both dose escalation and expansion phases. Participants with Grade 2 or greater ocular AEs which have not resolved to Grade 1 or baseline must have an ophthalmic examination at EOTV. All other participants are recommended to have an ophthalmic examination at EOTV to document any subclinical findings.

[g] Ocular symptom assessment at C1D1 can be performed within 24 hours before the infusion. For participants in dose escalation cohorts, ocular symptoms assessment should occur weekly in Cycle 1 and 2, and occur on Day 1 and Day 8 in each subsequent cycle. Participants' ocular symptoms and signs are also evaluated on C3D15. During the Dose Expansion Phase (at RP2D), if limited ocular toxicity is observed during escalation, ocular symptom assessment will occur on Day 1 of each cycle or more frequently if ocular symptoms or signs are observed. Phone-based ocular symptom assessments are acceptable if no clinic visit is scheduled.

[h] Females of childbearing potential only. Serum pregnancy test is required for eligibility. Subsequent pregnancy tests may use serum or urine. Results must be reviewed before study drug infusion on Day 1 of Cycle 1 and all subsequent cycles. If screening test is performed within 72 hours of first infusion, repeat of the test on Day 1 may be deferred.

[i] Participants in dose escalation cohorts must have vital signs recorded on both dosing and non-dosing days through treatment Cycle 3. During non-dosing visits (eg, screening and EOTV), vital signs will be taken at one timepoint. For Cycle 1 Day 1, vitals are measured pre-infusion (within 30 minutes before); 15 and 30 minutes after start of infusion (± 5 minutes); EOI (± 10 minutes); and 2, 4, and 6 hours after EOI (± 10 minutes). During other dosing visits up to Cycle 3, vitals are measured pre-infusion (within 30 minutes before), EOI (± 10 minutes), and 1 hour after EOI (± 10 minutes). Beginning on Cycle 4, vital signs must be recorded on each dosing visit. Participants in expansion cohorts must have vital signs recorded on each dosing visit.

[j] To be obtained pre-infusion. Day 1 laboratory samples can be obtained up to 3 days before infusion. Chemistry and hematology results must be reviewed before study drug administration. See Appendix 3 for assessments.

[k] Tumor markers are obtained as indicated for each specific tumor type, eg, CEA for colorectal cancer and CA19-9 for pancreatic cancer. Repeat collection on Cycle 1 Day 1 if screening collection > 7 days prior.

[l] Tumor assessments are Q8W (± 7 days) while participant is on study drug, then Q12W (± 21 days). Assessments continue until discontinuation criteria are met. Tumor assessments are performed at EOTV except if prior assessment was ≤ 30 days of EOTV and results are available for RECIST v1.1 assessment.

[m] Tumor assessments will occur after participant has discontinued study drug Q12W (± 21 days) until evidence of PD, initiation of another anticancer therapy, withdrawal of consent, LTFU, death, or end of study, whichever occurs first.

[n] Day 15 dose may be omitted in Cycle 2 if significant ocular events occurred in Cycle 1, at the discretion of the investigator.

APPENDIX 3. CLINICAL LABORATORY TESTS

Pregnancy test: Serum or urine human chorionic gonadotropin **Hematology:** Hemoglobin Hematocrit Platelet count White blood cell count Absolute neutrophils, lymphocytes, monocytes, eosinophils, and basophils (report in absolute value or percentile) **Serum chemistry:** Albumin Alkaline phosphatase Alanine aminotransferase Aspartate aminotransferase Amylase Bicarbonate Bilirubin (total and direct) Blood urea nitrogen Calcium Chloride Creatinine Glucose Lipase Magnesium Phosphate Potassium Sodium Uric acid	**Coagulation:** Prothrombin time – preferred test International normalized ratio – acceptable test Activated partial thromboplastin time **Endocrine tests:** Free thyroxine Thyroid-stimulating hormone **Urinalysis:** Protein Occult blood If abnormal, reflex test for microscopic evaluation

APPENDIX 4. PHARMACOKINETICS, IMMUNOGENICITY, AND BIOMARKERS BLOOD SAMPLING SCHEDULE A FOR 21 DAY CYCLE

Blood samples for PK, ADA, and biomarkers will be collected per the schedule below. Please note:

- Blood samples should be collected from the arm contralateral to the site of IV infusion. If an indwelling catheter is used, the fluid in the catheter will be removed and discarded prior to collection of the blood sample for PK and immunogenicity assessment.
- Both actual start and end of infusion times and blood sample collection times will be recorded on the eCRFs.

Cycle	Day	Time Point	Window	IMGC936 PK (Total and ADC) Serum	IMGC936 PK (DM50/DM51) Plasma	ADA (IMGC936)	Blood Biomarkers Soluble ADAM9	Blood Biomarkers Cell-free Tumor DNA	Blood Biomarkers FcγR
Cycles 1 and 3	01	Pre-Infusion	N/A	X	X	X [a]	Cycle 1 only[a]	Cycle 1 only	Cycle 1 only
		EOI	+ 5 min	X	X				
		2 h after EOI	± 10 min	X	X				
		4 h after EOI	± 10 min	X	X				
		6 h after EOI	± 1 h	X	X				
	02	24 h after EOI	± 4 h	X	X				
	03	48 h after EOI	± 6 h	X	X				
	08	168 h after EOI	± 24 h	X	X		Cycle 1 only[a]		
	15	336 h after EOI	± 24 h	X	X	X [a]			
Cycles 2, 4, 5, and 6	01	Pre-Infusion	N/A	X	X	X [a]	Cycle 2 only[a]		
		EOI	+ 5 min	X	X				

Cycle	Day	Time Point	Window	IMGC936 PK (Total and ADC) Serum	IMGC936 PK (DM50/DM51) Plasma	ADA (IMGC936)	Blood Biomarkers Soluble ADAM9	Blood Biomarkers Cell-free Tumor DNA	Blood Biomarkers FcγR
	15	336 h after EOI	± 24 h	X	X				
Cycle 9 and beyond [b]	01	Pre-Infusion	N/A	X	X	X [a]			
EOTV		EOTV	N/A	X	X	X [a]	X [a]		

Abbreviations: ADA: antidrug antibody; ADAM9: a disintegrin and metalloprotease domain-containing protein 9; ADC: antibody-drug conjugate; EOI: end of infusion; EOTV: end of treatment visit; FcγR: Fc-gamma receptor; N/A: not applicable; PK: pharmacokinetics.

[a] ADA and soluble ADAM9 will be evaluated from an aliquot of the PK blood draw and does not require a separate blood draw. Please see the laboratory manual for details.

[b] PK and ADA samples will be collected and tested at every 3 cycles beyond Cycle 6 until EOTV, for example Cycle 9, Cycle 12, Cycle 15, etc.

APPENDIX 5. PHARMACOKINETICS, IMMUNOGENICITY, AND BIOMARKERS BLOOD SAMPLING SCHEDULE B FOR A 28 DAY CYCLE

Cycle	Day	Time Point	Window	IMGC936 PK (Total and ADC) Serum	IMGC936 PK (DM50/DM51) Plasma	ADA (IMGC936)	Blood Biomarkers Soluble ADAM9	Blood Biomarkers Cell-free Tumor DNA	Blood Biomarkers FcγR
Cycle 1	1	Pre-Infusion	N/A	X	X	X [a]	X [a]	X	X
		EOI	+ 5 min	X	X				
		2 h after EOI	± 10 min	X	X				
		4 h after EOI	± 10 min	X	X				
		6 h after EOI	± 1 h	X	X				
	2	24 h after EOI	± 4 h	X	X				
	3	48 h after EOI	± 6 h	X	X				
	8	Pre-Infusion	N/A	X	X	X [a]	X [a]		
		EOI	+ 5 min	X	X				
	15	Pre-Infusion	N/A	X	X	X [a]			
		EOI	+ 5 min	X	X				
		2 h after EOI	± 10 min	X	X				
		4 h after EOI	± 10 min	X	X				
		6 h after EOI	± 1 h	X	X				
	16	24 h after EOI	± 4 h	X	X				
	17	48 h after EOI	± 6 h	X	X				

Cycle	Day	Time Point	Window	IMGC936 PK (Total and ADC) Serum	IMGC936 PK (DM50/DM51) Plasma	ADA (IMGC936)	Blood Biomarkers Soluble ADAM9	Blood Biomarkers Cell-free Tumor DNA	Blood Biomarkers FcγR
	22	168 h after EOI	± 24 h	X	X				
Cycle 2	1	Pre-Infusion	N/A	X	X	X [a]	X [a]		
		EOI	+ 5 min	X	X				
	8	Pre-Infusion	N/A	X	X	X [a]			
		EOI	+ 5 min	X	X				
	15	Pre-Infusion	N/A	X	X	X [a]			
		EOI	+ 5 min	X	X				
Cycles 3-6	1	Pre-Infusion	N/A	X	X	X [a]			
		EOI	+ 5 min	X	X				
	8	Pre-Infusion	N/A	X	X	X [a]			
		EOI	+ 5 min	X	X				
Cycle 9 and beyond [b]	1	Pre-Infusion	N/A	X	X	X [a]			
	8	Pre-Infusion	N/A	X	X	X [a]			
EOTV		EOTV	N/A	X	X	X [a]	X [a]		

Abbreviations: ADA: antidrug antibody; ADAM9: a disintegrin and metalloprotease domain-containing protein 9; ADC: antibody-drug conjugate; EOI: end of infusion; EOTV: end of treatment visit; FcγR: Fc-gamma receptor; N/A: not applicable; PK: pharmacokinetics.

[a] ADA and soluble ADAM9 will be evaluated from an aliquot of the PK blood draw and does not require a separate blood draw. Please see the laboratory manual for details.

[b] PK and ADA samples will be collected and tested at every 3 cycles beyond Cycle 6 until EOTV, for example Cycle 9, Cycle 12, Cycle 15, etc.

APPENDIX 6. RECIST V1.1 GUIDELINES

RECIST v1.1 guidelines are adapted from Eisenhauer et al. 2009 ( ).

1. Measurability of Tumor at Baseline

1.1 Definitions

At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows:

1.1.1 Measurable

Tumor lesions: Must be accurately measured in at least one dimension (*longest* diameter in the plane of measurement is to be recorded) with a *minimum* size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm).
- 10 mm caliper measurement by clinical examination (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).
- 20 mm by chest X-ray.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the *short* axis will be measured and followed. See also notes below on 'Baseline documentation of target and non-target lesions' for information on lymph node measurement.

1.1.2 Non-measurable

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

1.1.3 Special Considerations Regarding Lesion Measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require comment:

Bone lesions:

- Bone scan, positron emission tomography scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.

- Blastic bone lesions are non-measurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same participant, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are not considered measurable unless there has been demonstrated progression in the lesion prior to study enrollment.

1.2 Specifications by Methods of Measurements

1.2.1 Measurement of Lesions

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

1.2.2 Method of Assessment

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesions(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm diameter as assessed using calipers (eg, skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical examination and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

Chest X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (eg, for body scans).

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review later and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised.

Tumor markers: Tumor markers alone cannot be used to assess objective tumor response.

2. Tumor Response Evaluation

2.1 Assessment of Overall Tumor Burden and Measurable Disease

To assess objective response or future progression, it is necessary to estimate the *overall tumor burden at baseline* and use this as a comparator for subsequent measurements. Only participants with measurable disease at baseline should be included. Measurable disease is defined by the presence of at least one measurable lesion (as detailed above).

2.2 Baseline Documentation of 'Target' and 'Non-target' Lesions

Where more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as *target lesions* and will be recorded and measured at baseline. For example, in instances where participants have only one or two organ sites involved, a maximum of two and four lesions respectively will be recorded). Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to *reproducible repeated measurements*. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesions which can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. As noted above, pathological nodes which are defined as measurable and may be identified as target lesions must meet criterion of a short axis of ≥ 15 mm by CT scan. Only the *short* axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm x30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

A *sum of the diameters* (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline *sum diameters*. If lymph nodes are to be included in the sum, then as noted above, only the *short* axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as *non-target lesions* and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression. In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (eg, 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

2.3 Response Criteria

This section provides the definitions of the criteria used to determine objective tumor response for target lesions.

2.3.1 Evaluation of Target Lesions

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

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

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

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

2.3.2 Special Notes on Assessment of Target Lesions

Lymph nodes. Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. In order to qualify for CR, each node must achieve a short axis < 10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Target lesions that become 'too small to measure'. While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (eg, 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs, it is important that a value be recorded on the case report form. If it

is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (*Note:* It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error. However, if the radiologist can provide an actual measure, that should be recorded, even if it is below 5 mm.

Lesions that split or coalesce on treatment. When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesions. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

2.3.3 Evaluation of Non-target Lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. While some non-target lesions may be measurable, they need not be measured and instead should be assessed only *qualitatively* at the time points specified in the protocol.

Complete Response (CR): Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (< 10 mm short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesions(s).

Progressive Disease (PD): *Unequivocal progression* (see comments below) of existing non-target lesions. (*Note*: the appearance of one or more new lesions is also considered progression).

2.3.4 Special Notes on Assessment of Progression of Non-target Disease

The concept of progression of non-target disease requires additional explanation as follows:

When a participant also has measurable disease. In this setting, to achieve 'unequivocal progression; on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to quality for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the participant has only non-measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-

target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing participants for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: ie, an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localized to widespread, or may be described in protocols as 'sufficient to require a change in therapy'. If 'unequivocal progression' is seen, the participant should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore, the increase must be substantial.

2.3.5 New Lesions

The appearance of new malignant lesions denotes disease progression. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: ie, not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the participant's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was *not* scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the participant who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals brain metastases. The participant's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

2.4 Evaluation of Best Overall Response

The BOR is the best response recorded from the start of study drug administration until the end of treatment taking into account any requirement for confirmation. The participant's BOR assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions.

2.4.1 Time Point Response

It is assumed that at each protocol specified time point, a response assessment occurs. Table A-1 provides a summary of the overall response status calculation at each time point for participants who have measurable disease at baseline.

2.4.2 Missing Assessments and Inevaluable Designation

When no imaging/measurement is done at all at a particular time point, the participant is NE at that time point. If only a subset of lesion measurements is made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD. For example, if a participant had a baseline sum of 50 mm with three measured lesions and at follow-up only two lesions were assessed, but those gave a sum of 80 mm, the participant will have achieved PD status, regardless of the contribution of the missing lesion.

2.4.3 Best Overall Response: All Time Points

The *best overall response* is determined once all the data for the participant is known.

Table A-1 Time Point Response: Participants with Target (+/- Non-target) Disease

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Abbreviations: CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; NE: non evaluable.

Best response determination in trials where confirmation of complete or partial response IS required: Complete or partial responses may be claimed only if the objective response is confirmed on a follow-up scan obtained no less than 4 weeks after the initial scan demonstrating an objective response. In this circumstance, the BOR can be interpreted as in Table A-2.

Table A-2 Best Overall Response when Confirmation of CR and PR Required		
Overall Response First Time Point	**Overall Response Subsequent Time Point**	**Best Overall Response**
CR	CR	CR
CR	PR	SD, PD or PR [a]
CR	SD	SD
CR	PD	SD
CR	NE	SD
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
NE	NE	NE

Abbreviations: CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; NE: not evaluable.

[a] If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the participant had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

Special Notes on Response Assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (< 10 mm), they may still have a measurement reported on scans This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that participants with CR may not have a total sum of 'zero' on the eCRF.

Participants with a global deterioration of health status requiring discontinuation of study drug without objective evidence of disease progression at that time should be reported as 'symptomatic deterioration". Every effort should be made to document objective progression even after discontinuation of study drug. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study drug. The objective response status of such participants is to be determined by evaluation of target and non-target disease as shown in Table A-1 and Table A-2.

For equivocal findings of progression (eg, very small and uncertain new lesions; cystic changes or necrosis in existing lesions), study drug may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

2.5 Confirmation/Duration of Response

2.5.1 Confirmation

Objective responses should be confirmed by CT and/or MRI scans obtained no less than 4 weeks after the original scan.

2.5.2 Duration of Overall Response

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

2.5.3 Duration of Stable Disease

SD is measured from the start of study drug administration until criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD).

APPENDIX 7. EXAMPLES OF CLINICAL SUBSTRATES FOR CYP3A-MEDIATED METABOLISM

CYP Enzyme	Clinical substrate
CYP3A Strong Inhibitor	boceprevir, cobicistat, danoprevir and ritonavir, elvitegravir and ritonavir, grapefruit juice, indinavir and ritonavir, itraconazole, ketoconazole, lopinavir and ritonavir, paritaprevir and ritonavir and (ombitasvir and/or dasabuvir), posaconazole, ritonavir, saquinavir and ritonavir, telaprevir tipranavir and ritonavir, telithromycin, troleandomycin, voriconazole
CYP3A Strong Inducer	apalutamide, carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's wort

Source: FDA drug development resources (as of 29 July 2020)

APPENDIX 8. ECOG AND KARNOFSKY PERFORMANCE SCALES

ECOG Performance Scale

Grade	Description
0	Fully active, able to carry on all predisease performance without restriction.
1	Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light house work or office work).
2	Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry-on any self-care. Totally confined to bed or chair.
5	Dead.

Karnofsky Performance Scale

Able to carry on normal activity and to work; no special care needed.	100	Normal no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on normal activity or to do active work.
	60	Requires occasional assistance but is able to care for most of his personal needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	40	Disabled; requires special care and assistance.
	30	Severely disable; hospital admission is indicated, although death not imminent.
	20	Very sick; hospital admission necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead.