Official Title:	**A Phase 2 Study of INCMGA00012 in Participants With Squamous Carcinoma of the Anal Canal Who Have Progressed Following Platinum-Based Chemotherapy (POD1UM-202)**
NCT Number:	NCT03597295
Document Date:	Clinical Study Protocol Version 4: 08 July 2019

Clinical Study Protocol

INCMGA 0012-202

A Phase 2 Study of INCMGA00012 in Participants With Squamous Carcinoma of the Anal Canal Who Have Progressed Following Platinum-Based Chemotherapy (POD1UM-202)

Product:	**INCMGA00012**
IND Number:	**139,333**
EudraCT Number:	**2018-002070-51**
Phase of Study:	**2**
Sponsor:	**Incyte Corporation** **1801 Augustine Cut-Off** **Wilmington, DE 19803**
Original Protocol (Version 0):	**12 JUN 2018**
Amendment (Version) 1:	**06 AUG 2018**
Amendment (Version) 2:	**04 OCT 2018**
Amendment (Version) 2-NL:	**26 NOV 2018**
Amendment (Version) 3:	**21 MAR 2019**
Amendment (Version) 4:	**08 JUL 2019**

INVESTIGATOR'S AGREEMENT

I have read the INCMGA 0012-202 Protocol Amendment 4 (Version 4 dated 08 JUL 2019) and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this Protocol.

_____

(Printed Name of Investigator)

_____ _____

(Signature of Investigator) (Date)

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LIST OF ABBREVIATIONS

Abbreviations and Special Terms	Definition
[redacted]	[redacted]
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
ART	antiretroviral therapy
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
$AUC_{0-\infty}$	area under the single-dose plasma or serum concentration-time curve extrapolated to infinity
AUC_{0-t}	area under the plasma or serum concentration-time curve from time = 0 to the last measurable concentration at time = t
BCG	Bacillus Calmette–Guérin
CFR	Code of Federal Regulations
CI	confidence interval
C_{max}	maximum observed plasma or serum concentration
C_{min}	minimum observed plasma or serum concentration over the dose interval
$C_{min,ss}$	C_{min} at steady state
CNS	central nervous system
CR	complete response
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTFG	Clinical Trial Facilitation Group
DCR	disease control rate
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DOR	duration of response
EBV	Epstein–Barr Virus
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
[redacted]	[redacted]
EOT	end of treatment
[redacted]	[redacted]
FAS	full analysis set
FDA	Food and Drug Administration

Abbreviations and Special Terms	Definition
GCP	Good Clinical Practice
HAV	hepatitis A virus
HBc	hepatitis B core
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HDL	high-density lipoprotein
HIPAA	Health Insurance Portability and Accountability Act of 1996
HIV	human immunodeficiency virus
HPV	human papillomavirus
[redacted]	[redacted]
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICR	Independent Central Radiographic Review
IEC	independent ethics committee
IgG	immunoglobulin G
IgG4	immunoglobulin G4
IgM	immunoglobulin M
IHC	immunohistochemistry
INR	international normalized ratio
irAE	immune-related adverse event
IRB	institutional review board
[redacted]	[redacted]
IRT	interactive response technology
IV	intravenous
LDL	low-density lipoprotein
MedDRA	Medical Dictionary for Regulatory Activities
MTD	maximum tolerated dose
NCI	National Cancer Institute
NSAID	nonsteroidal anti-inflammatory drug
NSCLC	non–small cell lung cancer
ORR	overall response rate
OS	overall survival
PD	progressive disease
PD-1	programmed cell death protein 1
PD-L1	programmed cell death-ligand 1
PFS	progression-free survival
PK	pharmacokinetic
PO	oral

Abbreviations and Special Terms	Definition
PR	partial response
[redacted]	[redacted]
PT	prothrombin time
PTT	partial thromboplastin time
Q2W	every 2 weeks
Q4W	every 4 weeks
Q8W	every 8 weeks
Q12W	every 12 weeks
QLG	Quality of Life Group
[redacted]	[redacted]
[redacted]	[redacted]
RECIST	Response Evaluation Criteria in Solid Tumors
[redacted]	[redacted]
SAE	serious adverse event
SCAC	squamous carcinoma of the anal canal
SD	stable disease
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
$t_{½}$	apparent terminal-phase disposition half-life
T3/FT3	triiodothyronine
T4	thyroxine
TEAE	treatment-emergent adverse event
T_{max}	time to maximum concentration
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
WBC	white blood cell
WMO	World Medical Association

1. PROTOCOL SUMMARY

Protocol Title: A Phase 2 Study of INCMGA00012 in Participants With Squamous Carcinoma of the Anal Canal Who Have Progressed Following Platinum-Based Chemotherapy (POD1UM-202)

Protocol Number: INCMGA 0012-202

Objectives and Endpoints:

Table 1 presents the primary objective and endpoint.

Table 1: Primary Objective and Endpoint

Objective	Endpoint
Primary	
To assess efficacy of INCMGA00012 in terms of the ORR in participants with locally advanced or metastatic SCAC who have progressed after platinum-based chemotherapy.	ORR, defined as the percentage of participants having a CR or PR, according to RECIST v1.1 as determined by ICR.

Overall Design:

Table 2 presents the key study design elements. Further study details are presented after the table.

Table 2: Key Study Design Elements

Study Phase	Phase 2
Clinical Indication	Locally advanced or metastatic SCAC in participants who have progressed after treatment with platinum-based chemotherapy.
Population	Male and female participants at least 18 years of age with locally advanced or metastatic SCAC who have progressed after platinum-based chemotherapy.
Number of Participants	Approximately 81 participants will be enrolled.
Study Design	This is an open-label, single-group, multicenter, Phase 2 study.
Estimated Duration of Study Participation	The study consists of 3 periods: screening, study drug treatment, and follow-up. Participants have up to 28 days to complete screening. Treatment duration with study drug may last up to 2 years in the absence of clinical disease progression, intolerable toxicity, death, withdrawal of consent, lost to follow-up, or premature discontinuation for any other reason.
Independent Central Radiographic Review	Imaging will undergo independent central radiographic review in support of efficacy endpoints.
Data Monitoring Committee (DMC)	Yes (external)

Treatment Groups and Duration:

All participants will receive INCMGA00012 at the recommended Phase 2 dose of 500 mg IV Q4W. Treatment will be administered by IV infusion over 60 minutes on Day 1 of each 28-day cycle. Subsequent treatment cycles should be delayed (for up to 12 weeks, Section 6.5) until the following criteria are met:

- Hemoglobin ≥ 8 gm/dL.
- ANC ≥ 1.0×10^9/L.
- Platelet count ≥ 75×10^9/L.
- ALT/AST/bilirubin ≤ Grade 2.
- Resolution of all immune-related toxicity to ≤ Grade 1 (with the exception of endocrinopathy that is controlled on hormonal replacement), other than unacceptable toxicity per Section 6.5.2.
- Resolution of all non–immune-related toxicity to Grade ≤ 1 or baseline (with the exception of alopecia or non–transfusion-dependent anemia).

  Note: Transient asymptomatic laboratory elevations ≤ Grade 3 do not require dose interruption or reduction if the participant is asymptomatic and the elevation is clinically insignificant and has been discussed with the medical monitor (eg, amylase, lipase).
- Daily dose of corticosteroid ≤ 10 mg prednisone or equivalent.

Table 3 presents the complete study-specific schedule of activities. Details regarding the sample collection for pharmacokinetic [redacted] analyses are defined in Table 4 and Table 5. Table 20 presents the safety laboratory analytes to be evaluated. Adherence to the study design requirements, including those specified in the schedule of activities, is essential and required for study conduct. [redacted]

Table 3: Schedule of Activities

Visit Day (Range)	Screening	Treatment				Follow-Up		Notes
	28 Days	Cycle 1 Day 1	Cycle ≥ 2 Day 1 (± 3 d)	Q8W (± 7 d)	EOT[a]	Safety 28-Days After Last Dose (± 7 d)	Disease/ Survival	
Administrative procedures								
Informed consent	X							
Interactive Response Technology	X	X	X		X			
Inclusion/exclusion criteria	X							
General and disease medical history	X							
Prior/concomitant medications	X	X	X		X	X		
Administer INCMGA00012		X	X					Premedication with acetaminophen/paracetamol and a histamine blocker should be considered for participants who have had previous systemic reactions to protein product infusions or when recommended by institutional policy.
Safety assessments								
AE assessments	X	X	X		X	X	X*	* Immune-related AEs to be collected for 90 days after the last dose of study drug, regardless of whether a new anticancer therapy is started. Reasonable efforts should be made to align the first 12-week follow-up visit with the end of the 90-day irAE reporting period.
Physical examination	X	X	X		X	X	X	A comprehensive examination is performed at screening and at EOT. All other scheduled examinations will be targeted.
Vital signs/body weight/height	X	X	X		X	X		Height at screening only.
12-lead ECG	X	X	X*			X		* Every third cycle (C4, C7, C10, etc).

Table 3: Schedule of Activities (Continued)

Visit Day (Range)	Screening	Treatment				Follow-Up		Notes
	28 Days	Cycle 1 Day 1	Cycle ≥ 2 Day 1 (± 3 d)	Q8W (± 7 d)	EOT[a]	Safety 28-Days After Last Dose (± 7 d)	Disease/ Survival	
Efficacy assessments								
Tumor imaging/response assessments	X			X			X*	* Scans during follow-up will only be performed for participants continuing to be followed for disease status. Complete response or PR should be confirmed by imaging at least 4 weeks after initial documentation.
[redacted]								
ECOG performance status	X	X	X		X			
Post study anticancer therapy status					X	X	X	
Survival status					X	X	X*	* During survival follow-up period, participants should be contacted by telephone, email, or visit at least every 12 weeks per Section 8.8.3.

Table 3: Schedule of Activities (Continued)

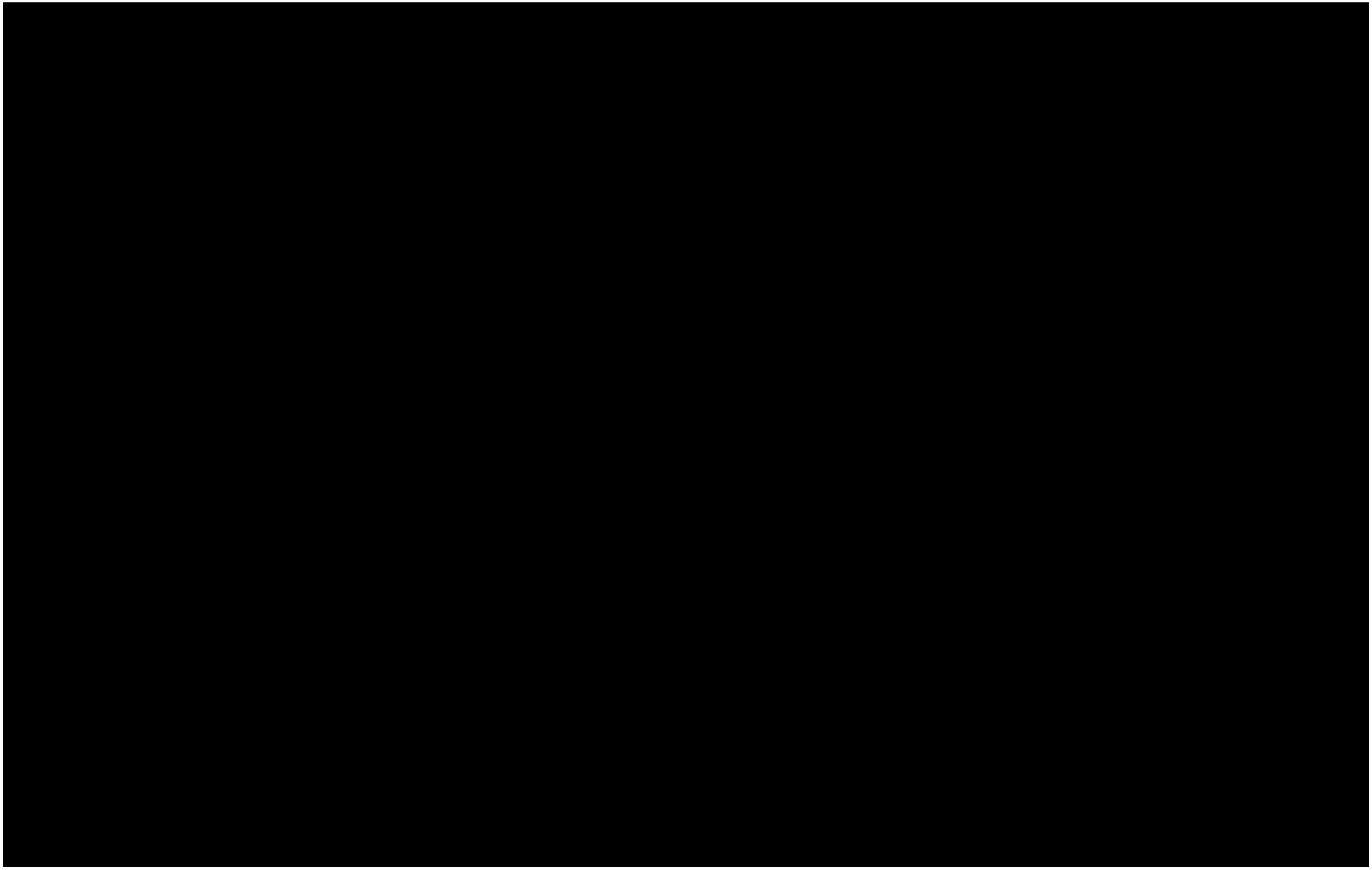
Visit Day (Range)	Screening 28 Days	Treatment Cycle 1 Day 1	Treatment Cycle ≥ 2 Day 1 (± 3 d)	Treatment Q8W (± 7 d)	Treatment EOT[a]	Follow-Up Safety 28-Days After Last Dose (± 7 d)	Follow-Up Disease/ Survival	Notes
Clinical laboratory assessments								
Blood chemistries	X	X*	X			X		* Not necessary on C1D1 if performed during screening within 7 days on C1D1.
Hematology	X	X*	X			X		* Not necessary on C1D1 if performed during screening within 7 days on C1D1.
Lipid panel (fasting)	X		X*			X		* Every third cycle (C4, C7, C10, etc).
Coagulation panel	X		X*			X		* Every third cycle (C4, C7, C10, etc).
Endocrine panel	X		X*			X		* Every third cycle (C4, C7, C10, etc).
Urinalysis	X		X*			X		* Every third cycle (C4, C7, C10, etc).
[redacted]								
Pregnancy testing	X	X*	X		X**	X**		* Not necessary on C1D1 if performed during screening within 7 days on C1D1. ** Can be performed at either EOT visit or 28 days after last dose. Timing and type of testing may be adjusted based on country-specific requirements.

[a] If EOT is ≥ 21 days postdose, the EOT visit will also serve as the 28-day safety follow-up visit. If EOT is < 21 days postdose, the 28-day safety follow-up visit is required.

Table 4: Pharmacokinetic [redacted] Sample Collections [redacted]

Sample	Collection	Purpose/Analysis	Treatment Period							EOT[a]	Notes
			Cycle 1 Day 1	Cycle 2 Day 1 (± 3 d)	Cycle 4 Day 1 (± 3 d)	Cycle 6 Day 1 (± 3 d)	Cycle 7 Day 1 (± 3 d)	Cycle 8 Day 1 (± 3 d)	Cycle 12 Day 1 (± 3 d)		
Serum	PK serum	PK	X*	X	X	X*	X				Samples will be collected preinfusion on Day 1 of Cycles 1, 2, 4, 6, and 7. * Samples are collected 10 minutes postinfusion (± 10 minutes) postinfusion on Day 1 of Cycles 1 and 6. There is a 2-hour window for the preinfusion on Cycle 1 Day 1 and 24 hours at the other visits.
[redacted]											

[a] PK [redacted] samples are only collected at the EOT visit, including if the EOT visit also serves as the 28-day safety follow-up visit.



2. INTRODUCTION

2.1. Background

Monoclonal antibodies that inhibit the interaction of the PD-1 receptor with its ligands have recently been approved for treatment of a wide variety of cancers based on prolonged durable remissions, which, for some tumor types, have been associated with improved progression-free or overall survival (Keytruda® 2017, Opdivo® 2018).

Squamous cell carcinoma of the anal canal accounts for almost 3% of digestive system cancers and is increasing in frequency due to its association with HPV and HIV infection (Ghosn et al 2015). Although most patients have localized disease, systemic metastases will develop in approximately 25% of patients, and 5-year survival is poor in these individuals. Salvage chemotherapy with platinum-based regimens is an accepted standard of care; however, responses are not durable, and progression-free and overall survival after these treatments is measured only in months. There are no accepted salvage treatments for patients who progress after first-line chemotherapy (Eng et al 2014).

Immunotherapy is a promising new approach to treatment of metastatic SCAC. The ORR to single-agent nivolumab in treatment-refractory SCAC was 24% (95% CI: 15, 33), and most of these responses were durable (Morris et al 2017). A pilot study of pembrolizumab in PD-L1+ SCAC showed a similar ORR of 17% (Ott et al 2017). Patients with well-controlled HIV infection were included on the nivolumab study, and no unexpected safety issues were reported. Anecdotal reports suggest that PD-1 inhibitor treatment may actually improve the outcome of chronic HIV infection through multiple mechanisms, including restoration of HIV-specific CD8 T-cell function (Guihot et al 2018).

2.1.1. INCMGA00012

The study drug, INCMGA00012, is a humanized, IgG4 monoclonal antibody that recognizes human PD-1. Phase 1 results of INCMGA00012 in patients with advanced cancer (N = 37) have been presented (Lakhani et al 2017). INCMGA00012 demonstrated acceptable tolerability with no dose-limiting toxicity observed at doses ranging from 1 to 10 mg/kg Q2W and Q4W. A maximum tolerated dose was not reached. $T_{½}$ (β) was approximately 17 days, and steady-state was achieved in approximately 85 days. Full and sustained receptor occupancy of INCMGA00012 on both CD4+ and CD8+ T cells along with complete loss of competing fluorescently labeled anti–PD-1 staining (eJBio105 clone) were seen at all dose levels. INCMGA00012 is currently being evaluated in expansion cohorts and in combination with other potentially immunomodulatory agents.

INCMGA00012 demonstrated acceptable tolerability with no DLTs observed at any dose level up to 10 mg/kg Q2W. An MTD was not reached. Treatment-related ≥ Grade 3 AEs occurred in 4/37 (10.8%) participants and included increased lipase (n = 3) and vulvovaginal ulceration/inflammation (n = 1). The most common treatment-related AEs were fatigue (n = 9, 24.3%), rash (n = 5, 13.5%), nausea (n = 5, 13.5%), tumor flare (n = 4, 10.8%), and pruritus (n = 4, 10.8%). A single, treatment-related SAE of aphasia (occurring in the setting of new brain metastases) was reported. Immune-related AEs were limited to rash (n = 5, 13.5%), hypothyroidism (n = 3, 8.1%), hyperthyroidism (n = 2, 5.4%), vaginal ulceration/inflammation (n = 1, 2.7%), and infusion-related reaction (n = 1, 2.7%).

INCMGA00012 is currently being evaluated in tumor-specific expansion cohorts of 35 participants each in Study INCMGA 0012-101. The expansion cohorts include cervical cancer, NSCLC, selected sarcoma subtypes, and endometrial cancer (including microsatellite instability-high, mismatch repair deficient, and/or DNA polymerase ε exonuclease domain mutation positive disease). As of 23 SEP 2018, 132 participants have been treated with 3 mg/kg INCMGA00012 in one of the above noted cohorts. The most frequently reported TEAEs were fatigue (13.6%), diarrhea (10.6%), and dyspnea (10.6%). Forty-six participants (34.8%) had a TEAE of ≥ Grade 3; the most frequently reported events of ≥ Grade 3 were colitis, hypoalbuminemia, and hyponatremia (2.3% each). Serious AEs occurred in 33 participants (25.0%). SAEs occurring in more than 1 participant included colitis (3.0%), acute kidney injury (2.3%), dyspnea (2.3%), and pleural effusion (1.5%). Immune-related AEs occurred in 16 participants (12.1%); colitis (2.3%) and infusion-related reaction (2.3%) were the only immune-related AEs occurring in more than 1 participant. INCMGA00012 has also been assessed in 2 fixed dose groups (500 mg Q4W and 750 mg Q4W) of 15 participants each. No new safety signals were evident based on fixed doses compared with weight-based doses. Further details are presented in the IB. Preliminary efficacy results indicated that objective responses have been observed in participants with NSCLC, cervical cancer, endometrial cancer, soft-tissue sarcoma, ovarian cancer, and breast cancer (Mehnert et al 2018).

As of 23 SEP 2018, 199 participants have received INCMGA00012 monotherapy in Study INCMGA 0012-101. Preliminary activity based on confirmed RECIST responses has been observed in multiple tumor types, including all of the disease-specific expansion cohorts (previously treated cervical cancer, endometrial cancer, NSCLC, and sarcoma; Mehnert et al 2018).

2.2. Rationale for Study Design

Though initial results with checkpoint inhibitors are encouraging, there still remains an unmet medical need in the treatment of SCAC. In particular, safety, efficacy, and convenience of therapy could be improved by using alternative immunotherapies, either as monotherapy or as part of rational combination strategies.

2.3. Rationale for Fixed Doses of INCMGA00012

Fixed doses have several advantages over weight-based doses, including convenience of preparation and administration, reducing errors in preparation calculation, and minimization of drug waste. Body size–based doses and fixed doses of monoclonal antibodies have been evaluated, and the 2 approaches performed similarly, with body size–based doses not always offering an advantage in reducing variability of exposure (Wang et al 2009, Bai et al 2012).

The proposed flat dose regimen of 500 mg Q4W is based on modeling of preclinical and clinical data from the ongoing first-in-human monotherapy study (NCT03059823). This dose-escalation study of INCMGA00012 was performed and evaluated 37 participants at the following doses: 1 mg/kg Q2W, 3 mg/kg Q2W, 3 mg/kg Q4W, 10 mg/kg/Q2W, and 10 mg/kg Q4W. While supra-dose proportionality was observed for AUC and C_{max} for the first dose from 1 mg/kg to 10 mg/kg, linear PK was shown from 3 mg/kg to 10 mg/kg. No dose-limiting toxicity was observed with any dose level, and an MTD was not reached.

A population PK analysis was performed on these participants to characterize the effect of body weight on the PK of INCMGA00012. The serum concentrations of INCMGA00012 can be adequately described by a 2-compartment model with first-order elimination. Higher clearance of INCMGA00012 was estimated for 1 mg/kg than the other dose groups. Body weight dependence of clearance was characterized by a power relationship with an exponent of 0.911.

A simulation was conducted to investigate the use of body weighted dosing and flat dosing for INCMGA00012, with the aim of targeting a steady-state trough concentration of approximately 21 µg/mL, the median trough concentration for pembrolizumab (Freshwater et al 2017). The median INCMGA00012 exposure and its distribution around the median at 500 mg Q4W were similar to 7 mg/kg Q4W in the simulated population, which justified clinical exploration in an expansion cohort of the study. The median steady-state concentration at 500 mg Q4W is 24.8 µg/mL, and 58% of participants have trough concentrations greater than target concentration.

Pharmacokinetic data were obtained from 15 participants who received INCMGA00012 500 mg Q4W in the cohort expansion phase of Study INCMGA 0012-101. The observed $AUC_{0-\infty}$ for 500 mg Q4W is close to the steady-state AUC_{0-t} based on the population PK analysis of weight-based dosing, as is the estimated clearance. The estimated $t_{½}$ (333 h) is slightly shorter than that from the previous estimate of 409 hours. The mean trough serum concentration on Cycle 2 was 17.1 µg/mL, and the mean projected serum $C_{min,ss}$ is 23.1 µg/mL (which meets or slightly exceeds the targeted concentration based on pembrolizumab data) with mean accumulation index of 1.50. Overall, the 500 mg Q4W dose had very similar PK properties to the 3 mg/kg dosing and has approximately a 58% probability for steady-state trough serum concentration ≥ 21 µg/mL, which is associated with maximum target engagement and greatest probability of efficacy. Based on these observations, 500 mg Q4W was chosen as the dose regimen as the dosing regimen for this study.

2.4. Benefit/Risk Assessment

Treatment directed at the PD-1/PD-L1 axis is a promising approach to SCAC. Phase 2 results with both nivolumab and pembrolizumab in chemotherapy-refractory populations show promising efficacy in terms of durable tumor response (Morris et al 2017, Ott et al 2017). Importantly, no unexpected safety findings have been reported in this population, despite the frequent association of SCAC with chronic HIV and HPV infections. Alternative treatments (eg, chemotherapy) are associated with both inferior activity and serious toxicities. Based on these observations, the benefit/risk for INCMGA00012 should also be favorable, provided efficacy objectives in the proposed study are met.

Close oversight of study conduct will be provided through safety team meetings and contact with participating investigators. Additionally, irAEs will be monitored throughout the study as AEs of special interest with appropriate guidance provided to investigators for their assessment and management.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of INCMGA00012 may be found in the IB.

3. OBJECTIVES AND ENDPOINTS

Table 6 presents the objectives and endpoints.

Table 6: Objectives and Endpoints

Objectives	Endpoints
Primary	
To assess efficacy of INCMGA00012 in terms of the ORR in participants with locally advanced or metastatic SCAC who have progressed after platinum-based chemotherapy.	ORR, defined as the percentage of participants having a CR or PR, according to RECIST v1.1 as determined by ICR.
Secondary	
To determine additional measures of clinical benefit, specifically, DOR, DCR, PFS, and OS.	DOR, defined as the time from an initial objective response (CR or PR) according to RECIST v1.1 until disease progression as determined by ICR or death due to any cause.
	DCR, defined as the number of participants maintaining either an ORR or stable disease.
	PFS, defined as the time from the first dose of study treatment until disease progression by ICR or death due to any cause.
	OS, defined as the time from the start of therapy until death due to any cause.
To evaluate the safety of INCMGA00012 in participants with previously-treated SCAC.	Safety, determined by the number of participants; the frequency, duration, and severity of AEs per CTCAE v5.0; laboratory tests; vital signs; and ECGs.
To determine the PK of INCMGA00012 administered to participants with SCAC.	Population PK, including C_{max}, T_{max}, C_{min}, and AUC_{0-t}, will be summarized.
[redacted]	

4. STUDY DESIGN

4.1. Overall Design

This study is an open-label, single-group, multicenter, Phase 2 study that will enroll participants with locally advanced or metastatic SCAC who have progressed on a standard-of-care platinum-based chemotherapy regimen. Participants with well-controlled HIV infection will be eligible. All participants will receive INCMGA00012 at the recommended Phase 2 dose of 500 mg IV Q4W.

The primary endpoint is ORR as determined by independent central review using RECIST v1.1.

The study consists of 3 periods: screening, study drug treatment, and follow-up. Treatment may continue for up to 2 years in the absence of clinical disease progression (see Section 8.2), intolerable toxicity, death, withdrawal of consent, lost to follow-up, or premature discontinuation for any other reason.

Treatment will be administered by IV infusion over 60 minutes (±15 minutes) on Day 1 of each 28-day cycle. Subsequent treatment cycles should be delayed (for up to 12 weeks, see Section 6.5) until the following criteria are met:

- Hemoglobin ≥ 8 gm/dL.
- ANC ≥ 1.0×10^9/L.
- Platelet count ≥ 75×10^9/L.
- ALT/AST/bilirubin ≤ Grade 2.
- Resolution of all immune-related toxicity to ≤ Grade 1 (with the exception of endocrinopathy that is controlled on hormonal replacement), other than unacceptable toxicity per Section 6.5.
- Resolution of all non–immune-related toxicity to Grade ≤ 1 or baseline (with the exception of alopecia or non–transfusion-dependent anemia).

  Note: Transient asymptomatic laboratory elevations ≤ Grade 3 do not require dose interruption or reduction if the participant is asymptomatic and the elevation is clinically insignificant and has been discussed with the medical monitor (eg, amylase, lipase).
- Daily dose of corticosteroid ≤ 10 mg prednisone or equivalent.

Participants unable to restart study drug treatment ≤ 12 weeks from the start of the treatment delay due to toxicity will be permanently discontinued from study treatment. Treatment interruptions of > 12 weeks for reasons other than toxicity (eg, for targeted radiotherapy or surgical resection of oligometastatic disease) will be considered on a case-by-case basis by the medical monitor.

Participants who have been treated for at least 6 months and achieve a confirmed CR may discontinue INCMGA00012 after 2 additional cycles upon consultation with the medical monitor.

Patient management should follow either RECIST v1.1 (see Section 8.2.1) [redacted] with the decision to treat beyond conventional RECIST progression documented in the study file.

The follow-up period will begin once a participant has completed 2 years of study drug or prematurely discontinued from study drug. Participants will be evaluated for irAEs for 90 days after the last dose of study drug, regardless of whether a new anticancer therapy is started.

Once participants discontinue treatment, they enter the follow-up period and will be assessed for survival until study completion. Participants who discontinue study treatment without experiencing disease progression will enter the follow-up period and continue to undergo tumor assessments according to the schedule of activities (see Table 3) until they experience disease progression, the start of a new anticancer treatment, withdrawal of consent, lost to follow-up, the end of the study, or death.

The complete study-specific assessment schedule required for participants in this clinical study is presented in Table 3. The analytes to be evaluated in the safety laboratory analyses are found in Table 20. Details regarding the sample collection for pharmacokinetic [redacted] analyses are defined in Table 4.

[redacted]

4.2. Overall Study Duration

The study begins when the first participant signs the ICF. The end of the study is defined as the date of the last visit of the last participant in the study. Participants completing treatment or prematurely discontinuing the study drug will be followed for survival until all participants have completed at least 2 years of treatment with INCMGA00012 or discontinued.

A participant is considered to have completed the study if he/she has completed all periods/parts of the study including survival follow-up.

4.3. Study Termination

The investigator retains the right to terminate study participation at any time, according to the terms specified in the study contract. The investigator is to notify the IRB/IEC in writing of the study's completion or early termination, send a copy of the notification to the sponsor or sponsor's designee, and retain 1 copy for the site study regulatory file.

The sponsor may terminate the study electively, if required by regulatory decision, or upon advice of the DMC. If the study is terminated prematurely, the sponsor will notify the investigators, the IRBs and IECs, and the regulatory bodies of the decision and reason for termination of the study.

4.3.1. Data Monitoring Committee

An independent DMC will be formed. The DMC will consist of qualified individuals who are not involved with the conduct of the study. The establishment, composition, roles, duties, and responsibilities of the DMC will be addressed in the DMC Charter.

Preplanned analyses of safety will be provided to the independent DMC as specified in the DMC Charter. In addition, the DMC will make recommendations to the sponsor at a planned interim analysis. In terms of efficacy, the DMC will use the guidelines provided for recommendation of either continuation or early termination of the study at the interim analysis. Additionally, the DMC will review safety data of the ongoing study at regular intervals as specified in the DMC Charter. The process by which the DMC will make recommendations and decisions will be documented in the DMC Charter.

5. STUDY POPULATION

Deviations from eligibility criteria are not allowed, because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability, and/or participant safety. Therefore, adherence to the criteria as specified in the Protocol is essential. Prospective approval of Protocol deviations to recruitment and enrollment criteria, also known as Protocol waivers or exemptions, are not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1. Ability to comprehend and willingness to sign a written ICF for the study.
2. Men and women 18 years of age or older (or as applicable per local country requirements).
3. Confirmed diagnosis of locally advanced or metastatic SCAC.
4. Participants must have had progression on or after platinum-based therapy unless ineligible for or intolerant of platinum.
    a. No more than 2 prior lines of systemic therapy for metastatic disease are permitted.
    b. Participants who are ineligible for platinum must have received at least 1 prior line of systemic therapy.
    c. Participants receiving platinum-based radiosensitizing chemotherapy are eligible if relapse occurs < 6 months from completion of treatment.
5. Must have measurable disease by RECIST v1.1.
6. ECOG performance status 0 to 1.
7. If a participant is known to be HIV-positive, then all of the following criteria must also be met:
    a. CD4+ count ≥ 300/μL.
    b. Undetectable viral load.
    c. Receiving antiretroviral therapy (ART).
8. Willingness to avoid pregnancy or fathering children based on the criteria below.
    a. Men must agree to take appropriate precautions to avoid fathering children (with at least 99% certainty) from screening through 6 months after the last dose of study drug (or longer as appropriate based on country-specific requirements) and must refrain from donating sperm during this period. Permitted methods that are at least 99% effective in preventing pregnancy (see Appendix A) should be communicated to the participants and their understanding confirmed.

b. Women of childbearing potential must have a negative serum pregnancy test at screening and must agree to take appropriate precautions to avoid pregnancy (with at least 99% certainty) from screening through 6 months after the last dose of study drug. Permitted methods that are at least 99% effective in preventing pregnancy (see Appendix A) should be communicated to the participants and their understanding confirmed.
c. Women of nonchildbearing potential (ie, surgically sterile with a hysterectomy and/or bilateral oophorectomy OR ≥ 12 months of amenorrhea and at least 50 years of age) are eligible.

9. [redacted]

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. Receipt of anticancer therapy or participation in another interventional clinical study within 21 days before the first administration of study drug; 6 weeks for mitomycin C.
2. Radiotherapy within 14 days of first dose of study treatment with the following caveats:
   a. 28 days for pelvic radiotherapy.
   b. 6 months for thoracic region radiotherapy that is > 30 Gy in 2 Gy fractions.
3. Prior treatment with PD-1 or PD-L1 directed therapy (other immunotherapies may be acceptable with prior approval from the medical monitor).
4. Toxicity of prior therapy that has not recovered to ≤ Grade 1 or baseline (with the exception of any grade of alopecia and anemia not requiring transfusion support). Endocrinopathy, if well-managed, is not exclusionary and should be discussed with sponsor medical monitor.
5. Participants with laboratory values at screening defined in Table 7.

Table 7: Exclusionary Laboratory Values

Laboratory Parameter		Exclusion Criterion
Hematology		
a	Platelets	$\leq 75 \times 10^9$/L
b	Hemoglobin	≤ 9 g/dL
c	ANC	$\leq 1.5 \times 10^9$/L
Hepatic		
d	ALT	> 2.5 × ULN OR > 5 × ULN for participants with liver metastases
e	AST	> 2.5 × ULN OR > 5 × ULN for participants with liver metastases
f	Bilirubin	≥ 1.5 × ULN unless conjugated bilirubin ≤ ULN (conjugated bilirubin only needs to be tested if total bilirubin exceeds ULN). If there is no institutional ULN, then direct bilirubin must be < 40% of total bilirubin.
Renal		
g	Calculated creatinine clearance	< 30 mL/min
Coagulation		
h	INR or PT	> 1.5 × ULN, for participants not receiving anticoagulant therapy
i	aPTT	> 1.5 × ULN for participants not receiving anticoagulant therapy

6. Known additional malignancy that is progressing or requires active treatment, or history of other malignancy within 3 years of study entry with the exception of cured basal cell or squamous cell carcinoma of the skin, superficial bladder cancer, prostate intraepithelial neoplasm, carcinoma in situ of the cervix, or other noninvasive or indolent malignancy, or cancers from which the participant has been disease-free for > 1 year, after treatment with curative intent.
7. Active autoimmune disease requiring systemic immunosuppression in excess of physiologic maintenance doses of corticosteroids (> 10 mg of prednisone or equivalent).
8. Evidence of interstitial lung disease or active noninfectious pneumonitis.
9. Known active CNS metastases and/or carcinomatous meningitis.

   Note: Participants with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least 28 days before the first dose of study drug and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases or CNS edema, and have not required steroids for at least 14 days before the first dose of study drug.
10. Known active HAV, HBV, or HCV infection, as defined by elevated transaminases with the following serology: positivity for HAV IgM antibody, anti-HCV, anti-HBc IgG or IgM, or HBsAg (in the absence of prior immunization).
11. Active infections requiring systemic therapy.
12. Known hypersensitivity to another monoclonal antibody that cannot be controlled with standard measures (eg, antihistamines and corticosteroids) or known allergy or hypersensitivity to any component of INCMGA00012 or formulation components.

13. Participants with impaired cardiac function or clinically significant cardiac disease:
    a. New York Heart Association Class III or IV cardiac disease, including preexisting clinically significant ventricular arrhythmia, congestive heart failure, or cardiomyopathy.
    b. Unstable angina pectoris.
    c. Acute myocardial infarction ≤ 6 months before study participation.
    d. Other clinically significant heart disease (ie, ≥ uncontrolled Grade 3 hypertension.)
14. Participant is pregnant or breastfeeding.
15. Participant is expecting to conceive or father children within the projected duration of the study, from screening through 6 months after the last dose of study drug.
16. Participant has not recovered adequately from toxicities and/or complications from surgical intervention before starting study drug.
17. Has received a live vaccine within 28 days of the planned start of study drug.

    Note: Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox/zoster, yellow fever, rabies, BCG, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live-attenuated vaccines and are not allowed.
18. Current use of prohibited medication as described in Section 6.6.2.
19. Any condition that would, in the investigator's judgment, interfere with full participation in the study, including administration of study drug and attending required study visits; pose a significant risk to the participant; or interfere with interpretation of study data.

5.3. Lifestyle Considerations

Not applicable.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently assigned to study drug.

Tests with results that fail eligibility requirements may be repeated during screening. Additionally, a participant who fails screening may repeat the screening process once if the investigator believes that there has been a change in eligibility status. Participants who rescreen must reconsent and be assigned a new participant number.

5.5. Replacement of Participants

Not applicable.

6. STUDY TREATMENT

6.1. Study Treatments Administered

Table 8 presents the study drug information.

Table 8: Study Drug Information

Study drug name:	INCMGA00012
Dosage formulation:	liquid formulation
Unit dose strength/dosage level:	500 mg Q4W
Route of administration:	IV
Administration instructions:	Administered IV over 60 minutes (±15 minutes)
Packaging and labeling:	INCMGA00012 will be provided in a 250 mg vial. Each vial will be labeled as required per country requirement.
Storage:	Upright under refrigeration at 2°C-8°C (36°F-46°F) Protected from light

6.2. Preparation, Handling, and Accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study drug received and any discrepancies are reported and resolved before use of the study drug.

Only participants enrolled in the study may receive study drug, and only authorized site staff may supply or administer study drug. All study drug must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator (or designee) is responsible for study drug accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records). Inventory and accountability records must be maintained and readily available for inspection by the study monitor and are open to inspection at any time by any applicable regulatory authorities. The investigator or designee must maintain records that document:

- Delivery of study drug(s) to the study site.
- Inventory of study drug(s) at the site.
- Participant use of the study drug(s) including tablet and vial counts (as appropriate for each study drug) from each supply dispensed.
- Lot numbers and/or vial numbers (as applicable) of study drug used to prepare the infusion solution.
- Return of study drug(s) to the investigator or designee by participants.

The investigational product must be used only in accordance with the Protocol. The investigator will also maintain records adequately documenting that the participants were provided the specified study drug. These records should include dates, quantities, and any available batch or serial numbers or unique code numbers assigned to the investigational product and study participants.

Completed accountability records will be archived by the site. The investigator or designee will be expected to collect and retain all used, unused, and partially used containers of study drug until verified by the study monitor (unless otherwise agreed to by the sponsor). At the conclusion of the study, the investigator or designee will oversee shipment of any remaining study drug back to the sponsor or its designee for destruction according to institutional SOPs. If local procedures mandate on-site destruction of investigational supply, the site should (where local procedures allow) maintain the investigational supply until the study monitor inspects the accountability records in order to evaluate compliance and accuracy of accountability by the investigative site. At sites where the study drug is destroyed before monitor inspection, the monitors rely on documentation of destruction per the site SOP.

Further guidance and information for the final disposition of unused study drug are provided in the Pharmacy Manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

Not applicable.

6.4. Study Treatment Compliance

Compliance with all study-related treatments should be emphasized to the participant by the site personnel, and appropriate steps should be taken to optimize compliance during the study. Compliance with study drug will be calculated by the sponsor based on the drug accountability documented by the site staff and monitored by the sponsor/designee.

6.5. Dose Modifications

Dose reduction is not allowed. Before the start of each treatment cycle, the participant must meet the treatment continuation criteria in Section 4.1.

Infusion or hypersensitivity reactions may be observed with administration of any foreign protein. Premedication with acetaminophen/paracetamol and a histamine blocker should be considered for participants who have had previous systemic reactions to protein product infusions or when recommended by institutional policy.

Guidelines for management of suspected infusion reactions are provided in Table 9.

Table 9: Guidelines for Management of Suspected Infusion Reactions

Grade	Description[a]	Treatment	Subsequent Infusions
1	Mild reaction; infusion interruption not indicated; intervention not indicated.	Monitor vital signs closely until medically stable.	Premedication with acetaminophen/paracetamol and a histamine blocker should be considered for participants who have had previous systemic reactions to protein product infusions or when recommended by institutional policy.
2	Requires infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hours.	**First occurrence:** Stop infusion and initiate appropriate medical measures (eg, IV fluids, antihistamines NSAIDS, acetaminophen/paracetamol, narcotics, per institutional preferences). Monitor vital signs until medically stable. If symptoms resolve within 1 hour, infusion may be resumed at 50% of the original infusion rate. **Subsequent occurrences (after recommended prophylaxis):** Permanently discontinue treatment.	Premedicate at least 30 minutes before infusion with antihistamines (eg, diphenhydramine 50 mg PO) and acetaminophen/paracetamol (500-1000 mg PO). Additional supportive measures may be acceptable (per institutional preference) but should be discussed with medical monitor.
3 or 4	**Grade 3:** Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates). **Grade 4:** Life-threatening; pressor or ventilatory support indicated.	Stop infusion and initiate appropriate medical therapy (eg, IV fluids, antihistamines NSAIDS, acetaminophen/paracetamol, narcotics, oxygen, pressors, epinephrine, corticosteroids, per institutional preferences). Monitor vital signs frequently until medically stable. Hospitalization may be indicated.	Discontinue study drug.

[a] Per NCI CTCAE v5.0, appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of study drug administration.

6.5.1. Procedures for Participants Exhibiting Immune-Related Adverse Events

Adverse events of a potential immunologic etiology or irAEs may be defined as an AE of unknown etiology, associated with drug exposure, and consistent with an immune phenomenon. Immune-related AEs may be predicted based on the nature of the compounds, their mechanism of action, and reported experience with immunotherapies that have a similar mechanism of action. Special attention should be paid to AEs that may be suggestive of potential irAEs. An irAE can occur shortly after the first dose or several months after the last dose of treatment.

If an irAE is suspected, efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes before labeling an AE as an irAE.

Recommendations for management of specific immune-mediated AEs known to be associated with other PD-1 inhibitors (eg, pembrolizumab, nivolumab) are detailed in the sections below.

Management guidance for irAEs not detailed elsewhere in the Protocol should follow the ASCO Clinical Practice Guideline (Brahmer et al 2018), provided in the Study Procedures Manual.

6.5.1.1. Immune-Mediated Pneumonitis

Participants with symptomatic pneumonitis should immediately stop receiving study drug and have an evaluation. The evaluation may include bronchoscopy and pulmonary function tests to rule out other causes such as infection. If the participant is determined to have study drug–associated pneumonitis, the suggested treatment plan is detailed in Table 10.

Table 10: Recommended Approach to Handling Pneumonitis

Study Drug–Associated Pneumonitis	**Withhold/Discontinue Study Drug** *Criteria for restarting study drug are in Section 4.1.*	**Supportive Care**
Grade 1 (asymptomatic)	No action.	Intervention not indicated.
Grade 2	Withhold study drug.	Systemic corticosteroids are indicated (initial dose of 1-2 mg/kg per day of prednisone or equivalent). Taper as appropriate.
Grades 3 and 4 or recurrent Grade 2	Permanently discontinue study drug.	Systemic corticosteroids are indicated.

6.5.1.2. Immune-Mediated Colitis

Participants should be carefully monitored for signs and symptoms of colitis (such as diarrhea, abdominal pain, mucus, or blood in stool, with or without fever). In symptomatic participants, infectious etiologies should be ruled out, and endoscopic evaluation should be considered for persistent or severe symptoms. Recommendations for management of enterocolitis are shown in Table 11.

Table 11: Recommended Approach for Handling Enterocolitis/Diarrhea

Study Drug–Associated Enterocolitis/Diarrhea	**Withhold/Discontinue Study Drug** *Criteria for restarting study drug are located in Section 4.1.*	**Supportive Care**
Grade 1	No action.	All participants who have diarrhea should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. An antidiarrheal can be started.
Grade 2	Withhold study drug.	Systemic corticosteroids are indicated (initial dose of 1 mg/kg to 2 mg/kg per day of prednisone or equivalent). Taper as appropriate. Treatment with infliximab is acceptable per institutional guidelines.
Grade 3	Withhold study drug.	Treatment with systemic corticosteroids should be initiated. Treatment with infliximab is acceptable per institutional guidelines.
Grade 4 or recurrent Grade 3	Permanently discontinue study drug.	

6.5.1.3. Immune-Mediated Hepatitis

Liver chemistry testing (hepatic transaminase and bilirubin levels) should be monitored and participants assessed for signs and symptoms of hepatotoxicity before each dose of INCMGA00012. In participants with hepatotoxicity, infectious or malignant causes should be ruled out, and frequency of liver chemistry monitoring should be increased until resolution. Recommendations for management of hepatitis are shown in Table 12.

Table 12: Recommended Approach for Handling Hepatitis

Study Drug–Associated Hepatitis	**Withhold/Discontinue Study Drug** *Criteria for restarting study drug are located in Section 4.1.*	**Supportive Care**
Grade 1	No action.	Increase frequency of liver chemistry monitoring to twice per week until liver chemistry tests return to baseline.
Grade 2	Withhold study drug.	Systemic corticosteroids are indicated (initial dose of 0.5 mg/kg to 1 mg/kg per day of prednisone or equivalent). Taper as appropriate.
Grades 3 and 4	Permanently discontinue study drug.	Treatment with systemic corticosteroids should be initiated (initial dose of 1 mg/kg to 2 mg/kg per day of prednisone or equivalent). Taper as appropriate.

6.5.1.4. Immune-Mediated Endocrinopathies

6.5.1.4.1. Hypophysitis

Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency). Recommendations for management of hypophysitis are shown in Table 13.

Table 13: Recommended Approach for Handling Hypophysitis

Study Drug–Associated Hypophysitis	**Withhold/Discontinue Study Drug** *Criteria for restarting study drug are located in Section 4.1.*	**Supportive Care**
Grade 1	No action.	Administer corticosteroids and hormone replacement as clinically indicated.
Grade 2	Withhold study drug.	
Grade 3	Withhold or discontinue study drug.	
Grade 4	Permanently discontinue study drug.	

6.5.1.4.2. Thyroid Disorders

Monitor participants for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders. Recommendations for management of thyroid disorders are shown in Table 14.

Table 14: Recommended Approach for Handling Thyroid Disorders

Study Drug–Associated Thyroid Disorders	**Withhold/Discontinue Study Drug** *Criteria for restarting study drug are located in Section 4.1.*	**Supportive Care**
Grades 1 and 2	No action.	Administer replacement hormones for hypothyroidism and manage hyperthyroidism with thionamides and beta-blockers as appropriate.
Grade 3	Withhold or discontinue study drug.	
Grade 4	Permanently discontinue study drug.	

6.5.1.4.3. New Onset Diabetes Mellitus

Monitor participants for hyperglycemia or other signs and symptoms of diabetes. Recommendations for management of diabetes mellitus are shown in Table 15.

Table 15: Recommended Approach for Handling New Onset Diabetes Mellitus

Study Drug–Associated Diabetes Mellitus	**Withhold/Discontinue Study Drug** *Criteria for restarting study drug are located in Section 4.1.*	**Supportive Care**
Grades 1 and 2	No action.	Intervention not indicated.
Grade 3	Withhold study drug.	Administer insulin for Type 1 diabetes and administer antihyperglycemics in participants with severe hyperglycemia.
Grade 4	Permanently discontinue study drug.	

6.5.1.5. Immune-Mediated Nephritis and Renal Dysfunction

Monitor participants for changes in renal function. Recommendations for management of nephritis and renal dysfunction are shown in Table 16.

Table 16: Recommended Approach for Handling Nephritis and Renal Dysfunction

Study Drug–Associated Nephritis and Renal Dysfunction	**Withhold/Discontinue Study Drug** *Criteria for restarting study drug are located in Section 4.1.*	**Supportive Care**
Grade 1	No action.	Intervention not indicated.
Grade 2	Withhold study drug.	Treatment with systemic corticosteroids should be initiated (initial dose of 1 mg/kg to 2 mg/kg per day of prednisone or equivalent). Taper as appropriate.
Grades 3 or 4	Permanently discontinue study drug.	

6.5.1.6. Immune-Mediated Skin Reactions

Immune-mediated rashes, including Stevens-Johnson syndrome, toxic epidermal necrolysis (some cases with fatal outcome), exfoliative dermatitis, and bullous pemphigoid, can occur. Monitor participants for suspected severe skin reactions and exclude other causes. Recommendations for management of skin reactions are shown in Table 17.

Table 17: Recommended Approach for Handling Skin Reactions

Study Drug–Associated Skin Reactions	**Withhold/Discontinue Study Drug** *Criteria for restarting study drug are located in Section 4.1.*	**Supportive Care**
Grade 1	No action.	Intervention not indicated.
Grade 2	Withhold study drug.	Treatment with systemic corticosteroids should be initiated (initial dose of 1 mg/kg to 2 mg/kg per day of prednisone or equivalent). Taper as appropriate. *Note:* May consider IV immunoglobulin (IVIG) or cyclosporine as an alternative or in corticosteroid-refractory cases, for Grade for SCARs, DRESS/DIHS.
Grade 3 or suspected Stevens-Johnson syndrome or toxic epidermal necrolysis	Withhold study drug.	
Grade 4 or confirmed Stevens-Johnson syndrome or toxic epidermal necrolysis	Permanently discontinue study drug.	

6.5.1.7. Immune-Mediated Myocarditis

Immune-mediated myocarditis can occur (some cases with fatal outcome). Monitor participants for suspected myocarditis and exclude other causes. Recommendations for management of myocarditis are shown in Table 18.

Table 18: Recommended Approach for Handling Myocarditis

Study Drug–Associated Myocarditis	Withhold/Discontinue Study Drug *Criteria for restarting study drug are located in Section 4.1.*	Supportive Care
Grades 2, 3, and 4	Permanently discontinue study drug.	Upon signs and symptoms, all grades warrant work-up and intervention given potential for cardiac compromise. Treatment with systemic corticosteroids should be initiated (initial dose of 1 mg/kg to 2 mg/kg per day of prednisone or equivalent). Taper as appropriate. Management of cardiac symptoms according to standard of care and with guidance from cardiology. Consider cardiac MRI and myocardial biopsy for diagnosis.

6.5.2. Permanent Discontinuation of Study Drug Due to Toxicity

The occurrence of unacceptable toxicity not caused by the underlying disease will require that the study treatment be permanently discontinued. Unacceptable toxicity is defined as follows:

- Occurrence of an AE that is related to study treatment that, in the judgment of the investigator or the sponsor's medical monitor, compromises the participant's ability to continue study-specific procedures or is considered to not be in the participant's best interest.
- Persistent AE requiring a delay of therapy for more than 12 weeks.
- Any AE defined in the dose modifications management guidelines (see Section 6.5) requiring the study treatment be discontinued.

A complete list of study treatment discontinuation reasons and procedures is found in Section 7.

6.6. Concomitant Medications and Procedures

All concomitant medications and treatments (including over-the-counter or prescription medicines, vitamins, vaccines, and/or herbal supplements) must be recorded in the eCRF. Any medication received up to 30 days before the first dose of study drug and 28 days after the last dose of study drug (unless associated with the treatment of an AE), or until the participant begins a new anticancer therapy, whichever occurs first, will be recorded in the eCRF. Any addition, deletion, or change in the dose of these medications will also be recorded. Concomitant medications administered for the management of SAEs or irAEs should be recorded regardless of when they are provided. Concomitant treatments/procedures that are required to manage a participant's medical condition during the study will also be recorded in the eCRF. The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.6.1. Permitted Medications and Procedures

Antiretroviral therapy (ART) should be continued for participants who are known to be HIV-positive.

Recommended supportive measures for specific toxicities are described in Section 6.5.

Growth factors, bisphosphonates, anticoagulants, and transfusional support will also be permitted and must be reported into the eCRF.

Premedication with acetaminophen/paracetamol and a histamine blocker should be considered for participants who have had previous systemic reactions to protein product infusions or when recommended by institutional policy.

6.6.2. Prohibited Medications and Procedures

- Other anticancer therapies, including investigational treatments within 21 days before the first administration of study drug (6 weeks for mitomycin C), and throughout the treatment period of the study.
- Immunosuppression in excess of physiologic maintenance corticosteroid doses (> 10 mg of prednisone or equivalent) within 14 days of first dose and throughout the treatment period of the study (with the exception of acute treatment for an AE).
- Probiotic dietary supplements.
- Live vaccines within 28 days before first administration of study drug, throughout the treatment period of the study, and for a duration of 90 days after the last dose of study drug.

  Note: Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox/zoster, yellow fever, rabies, BCG, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live-attenuated vaccines and are not allowed.

6.7. Treatment After the End of the Study

Once a participant has discontinued study treatment, no further treatment will be provided in this study. Participants who discontinue study drug will enter the follow-up period to be evaluated for safety and survival. Any participants entering the follow-up period for any reason other than PD will continue to be evaluated for disease status according to the scheduled assessments found in Table 3.

7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Drug

7.1.1. Reasons for Discontinuation

Participants **must** be withdrawn from study drug for the following reasons:

- Clinical disease progression.
- Unacceptable toxicity as noted in Section 6.5.2.
- Consent is withdrawn.

  Note: Consent withdrawn means that the participant has explicitly indicated that they do not want to participate in the study or be followed any longer; in this case no further data, except data in public domain, may be solicited from or collected on the participant. Participants who discontinue study drug will remain in the study to be followed for progression and survival.
- Further study treatment would be injurious to the participant's health or well-being, in the investigator's medical judgment.
- The study is terminated by the sponsor.
- The study is terminated by the local health authority, IRB, or IEC.

A participant **may** be discontinued from study drug as follows:

- The participant becomes pregnant. If the female participant is no longer pregnant and meets the treatment continuation criteria within 12 weeks of the scheduled start of a cycle, study treatment may be resumed after approval has been received from the medical monitor (see Section 9.7).
- If a participant is noncompliant with study procedures or study drug administration in the investigator's opinion, the sponsor should be consulted for instruction on handling the participant.

7.1.2. Discontinuation Procedures

In the event that the decision is made to permanently discontinue the study drug, the EOT visit should be conducted. Reasonable efforts should be made to have the participant return for a follow-up visit. These visits are described in Table 3. The last date of the last dose of study drug and the reason for discontinuation of study drug will be recorded in the eCRF.

If a participant is discontinued from study drug:

- The study monitor or sponsor must be notified.
- The reason(s) for discontinuation from study drug must be documented in the participant's medical record, and the primary reason must be included in the eCRF.
- The EOT visit should be performed.
- The date of the EOT visit should be recorded in the IRT.
- After the EOT visit, participants will remain in the study to be followed for progression and survival and will be followed for safety and AEs per Sections 8.8 and 9.

Discontinuation from study drug does not mean withdrawal from the study, and remaining study procedures should be completed as indicated by the study Protocol.

If the participant discontinues study drug, the participant will complete the EOT visit and move into the follow-up portion of the study per Table 3. However, if a participant actively withdraws consent for collection of follow-up data (safety follow-up or disease assessment), then no additional data collection should occur (with the exception of data in the public domain.)

7.2. Participant Withdrawal From the Study

A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.

If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

See Table 3 for data to be collected at the time of study withdrawal.

7.3. Lost to Follow-Up

A participant will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and at least 1 certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Administrative and General Procedures

8.1.1. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
  - Informed consent must be obtained before any study-related procedures are conducted, unless otherwise specified by the Protocol.
  - Informed consent must be obtained using the IRB/IEC-approved version in a language that is native and understandable to the participant. A template will be provided by the sponsor or its designee. The sponsor or its designee must review and acknowledge the site-specific changes to the ICF template. The ICF must include a statement that the sponsor or its designee and regulatory authorities have direct access to participant records.
  - The ICF must contain all required elements and describe the nature, scope, and possible consequences of the study in a form understandable to the study participant.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the applicable requirements and regulations for the countries in which the study is being conducted as well as the IRB/IEC or study center.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection laws. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must provide consent to the most current version of the ICF(s) during their participation in the study
- [redacted]
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

Participants who are rescreened are required to sign a new ICF.

[redacted]

8.1.2. Screening Procedures

Screening is the interval between signing the ICF and the day the participant is enrolled in the study (Cycle 1 Day 1). Screening may not exceed 28 days. Assessments that are required to demonstrate eligibility may be performed over the course of 1 or more days during the screening process.

Procedures conducted as part of the participant's routine clinical management (eg, blood count, imaging study) and obtained before signing of informed consent may be used for screening or baseline purposes provided the procedure meets the Protocol-defined criteria and has been performed in the timeframe of the study (ie, within 28 days of Cycle 1 Day 1). For participants who are enrolled in the study, information associated with eligibility requirements must be entered into the appropriate eCRF pages.

Tests with results that fail eligibility requirements may be repeated. For screening assessments that are repeated, the most recent available result before treatment assignment will be used to determine eligibility.

See Sections 5.4 and 5.5 for information regarding screen failures and replacement of participants, respectively.

8.1.3. Interactive Response Technology Procedure

Each participant will be identified in the study by a participant ID number, which is a combination of the site ID and participant number. After determining that the participant is eligible for study entry at screening, site staff should contact the IRT to obtain the participant ID number. Additionally, the IRT will be contacted at each regular study visit to track the status of participation (eg, completion or premature discontinuations as well as to update the study drug supply. Additional details are provided in the IRT manual.

8.1.4. Distribution of Reminder Cards

Participants will be provided with a reminder card at each visit. The reminder card will indicate the date/time of the next visit and will also inform the participant about visit-specific procedures.

8.1.5. Demography and Medical History

8.1.5.1. Demographics and General Medical History

Demographic data and general medical history will be collected at screening by the investigator or qualified designee and will include age, race, ethnicity, medical and surgical history, and current illnesses.

8.1.5.2. Disease Characteristics and Treatment History

A disease-targeted medical and treatment history will be collected at screening. Details regarding the participant's malignancy under study, including date of diagnosis, initial and current cancer stage, tumor histology, and relevant disease characteristics, and prior treatments, including systemic treatments, radiation, and surgical procedures, will be recorded.

8.2. Efficacy Assessments

Objective assessment of disease status will be evaluated according to RECIST v1.1 (Eisenhauer et al 2009) and entered into the eCRF. [redacted]

Efficacy assessments of response should be performed according to schedule found in Table 3. Scans should follow calendar days and remain on the 8-week schedule, established on Cycle 1 Day 1, and should not be delayed for treatment holds or interruptions. Confirmation of CR or PR should be confirmed by imaging at least 4 weeks after initial documentation. For participants who discontinue study treatment for reasons other than disease progression, every effort should be made to continue monitoring their disease status by radiographic imaging according to the follow-up schedule.

Participants who continue study participation in the follow-up period without experiencing disease progression will continue to have efficacy assessments every 12 weeks until they complete participation in the study, start a new anticancer therapy, experience disease progression, or death.

8.2.1. Tumor Imaging

Disease assessment and tumor response to study drug will be evaluated according to RECIST v1.1 guidelines (Eisenhauer et al 2009) as described in Appendix B. The recommended method for measuring and following tumor burden will be CT scan, which should be performed using consistent techniques and facilities. The CT portion of PET-CT may be acceptable if it is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast.) Alternative modalities such as MRI may be substituted for a CT scan at the discretion of the investigator, provided that the same modality is used throughout the study and the methodology is consistent with RECIST v1.1. Initial tumor imaging must be performed within 28 days before the first dose of study drug. Imaging performed as part of routine clinical management are acceptable for use as the screening images if they are of diagnostic quality and performed within 28 days before the first dose of study drug. Tumor lesions that are located in a previously irradiated area or in an area subjected to other loco regional therapy should not be selected as target lesions unless there has been demonstrated progression in the lesion. Additionally, it is recommended that tumor lesions selected for excisional biopsy not be selected as target lesions. Imaging of the chest, abdomen, and pelvis are required for all participants. Imaging of other anatomical sites (ie, head, neck, and extremities) should be performed as applicable if participant has disease or suspected disease in those areas.

Computed tomography or MRI scan of the brain will be performed at screening if there are signs or symptoms suggesting that the participant has disease involvement in the CNS.

[redacted]

8.2.3. Health Economics

Not applicable.

[redacted]

[redacted]

[redacted]

8.3. Safety Assessments

See Section 6.5 for guidelines regarding the management of relevant laboratory or other safety assessment abnormalities.

8.3.1. Adverse Events

Adverse events will be monitored from the time the participant signs the ICF until at least 28 days after the last dose of study drug, regardless of whether a new anticancer therapy is started. Immune-related AEs will be collected until 90 days after the last dose of study drug. Adverse events that begin or worsen after informed consent should be recorded on the Adverse Events Form in the eCRF regardless of the assumption of a causal relationship with the study drug. Conditions that were already present at the time of informed consent should be recorded on the Medical History Form in the eCRF. Adverse events (including laboratory abnormalities that constitute AEs) should be described using a diagnosis whenever possible rather than by individual underlying signs and symptoms. Adverse events judged to be potentially immune-related should be described on the appropriate eCRF (recommended diagnostic algorithms are provided in the Study Procedures Manual).

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative). The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following-up on AEs that are serious, considered related to the study drug/procedures, or that caused the participant to discontinue the study drug. Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant, such as "How are you feeling?" is the preferred method to inquire about AE occurrences. Adverse events may also be detected when they are volunteered by the participant during the screening process or between visits, or through physical examinations, laboratory tests, or other assessments. The definition, reporting, and recording requirements for AEs are described in Section 9.

All SAEs will be recorded and reported to the sponsor or designee within 24 hours. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and nonserious AEs of special interest (as defined in Section 9.5), will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

The severity of adverse events will be determined per CTCAE v5.0.

8.3.2. Physical Examinations

Physical examinations must be performed by a medically qualified individual, such as a licensed physician, physician's assistant, or an advanced registered nurse practitioner, as local law permits. Abnormalities identified after the first dose of study drug constitute an AE if they are considered clinically meaningful, induce clinical signs or symptoms, require concomitant therapy, or require changes in study drug (with the exception of abnormalities associated with disease progression). Investigators should pay special attention to clinical signs related to previous serious illnesses.

At the screening visit and EOT, a comprehensive physical examination should be conducted. The comprehensive physical examination will include height and body weight and assessment of the following organ or body systems: skin; head, eyes, ears, nose, and throat; thyroid; lungs; cardiovascular system; abdomen (liver, spleen); extremities; and lymph nodes; as well as a brief neurological examination.

During the study, participants will be assessed by the investigator or medically qualified designee per institutional standard of care. These assessments should be an evaluation as indicated by participant symptoms, AEs, or other findings and documented on the AE eCRF. Weight will also be assessed at each study visit.

In addition, a disease-related clinical assessment should be performed at each study visit.

8.3.3. Vital Signs

Vital sign measurements (to be taken before blood collection for laboratory tests) include blood pressure, pulse, respiratory rate, and body temperature. Blood pressure and pulse will be taken with the participant in the recumbent, semirecumbent, or sitting position after 5 minutes of rest. Abnormal vital sign results identified after the first dose of study drug constitute an AE if they are considered clinically meaningful, induce clinical signs or symptoms, require concomitant therapy, or require changes in study drug.

8.3.4. ECOG Performance Status

ECOG performance status will be assessed according to the criteria in Table 19.

Table 19: ECOG Performance Status

Grade	Performance Status
0	Fully active, able to carry on all pre-disease 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, 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.

Source: Oken et al 1982.

8.3.5. Electrocardiograms

Electrocardiograms will be obtained as outlined in Table 3 according to the institutional standard of care. A 12-lead machine that automatically calculates heart rate and measures PR, QRS, QT, and QTc intervals is recommended. All ECGs should be performed with the participant in a recumbent or semirecumbent position after 5 minutes of rest.

The 12-lead ECGs will be interpreted by the investigator at the site to be used for immediate participant management. Additional 12-lead ECGs may be performed as clinically indicated to manage participant safety. The decision to include or exclude a participant or withdraw a participant from the study drug based on an ECG flagged as "Abnormal, Clinically Significant" is the responsibility of the investigator, in consultation with the sponsor's medical monitor, as appropriate. Clinically notable abnormalities that are considered clinically significant in the judgment of the investigator are to be reported as AEs.

8.3.6. Laboratory Assessments

Clinical safety laboratory analyses (ie, blood chemistries, hematology assessments, coagulation tests, endocrine function, lipid panel [fasting], and urinalysis) will be performed in certified local laboratories associated with study sites. Blood and urine samples will be collected for laboratory analyses during study visits, before study treatment administration, according to the schedule in Table 3. The laboratory analytes to be evaluated are presented in Table 20. Additional testing may be required by the sponsor based on emerging safety data. Additional tests may also be performed if clinically indicated.

Analysis by local laboratories for study treatment–related decisions are acceptable using a certified laboratory available to the investigative site. The investigative site will enter the results and normal ranges into the eCRF from any local laboratory analysis.

Further detailed information regarding collection, processing, and shipping of laboratory assessments is provided in the Laboratory Manual.

Clinically significant abnormal laboratory findings are those that are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. All abnormal laboratory values considered clinically significant up to 90 days after the last dose of study treatment should be repeated until the values are no longer considered clinically significant by the investigator, regardless of whether a new anticancer therapy is started.

Screening laboratory assessments for study eligibility evaluation must be performed within 28 days of Cycle 1 Day 1. If screening laboratory analyses are performed less than 7 days before initial administration of study treatment, laboratory analyses do not need to be repeated if the requirements for receiving study drug are met.

If performed more than 7 days before Cycle 1 Day 1, then the tests must be repeated before the initial study treatment administration on Cycle 1 Day 1. After Cycle 1, predose laboratory procedures can be conducted up to 72 hours before study treatment administration, and results should be reviewed by the investigator or qualified designee and found to be acceptable before a new cycle of treatment is initiated.

A final laboratory analysis is required during the 28-day follow-up safety visit. These laboratory assessments should only be performed at the EOT visit if the EOT visit is also serving as the 28-day safety visit.

[redacted]

8.3.6.1. Pregnancy Testing

Serum pregnancy tests are required for all women of childbearing potential during screening and either EOT or the safety follow-up visit 28 days after the last dose. Pregnancy testing is required on Day 1 of all cycles and can be either serum- or urine-based and will be performed before administration of study treatment. If a pregnancy test is performed during screening within 7 days of Cycle 1 Day 1, it is not necessary to repeat on Cycle 1 Day 1 (unless necessary based on country-specific requirements).

A positive urine pregnancy should be confirmed with a serum pregnancy test. If a pregnancy is confirmed by a serum pregnancy test, see Section 9.7.

Timing and type of pregnancy testing may be adjusted based on country-specific requirements.

Table 20: Required Laboratory Analytes

Blood Chemistries	Hematology	Urinalysis With Microscopic Examination	Coagulation	Pregnancy Testing
Albumin Alkaline phosphatase ALT AST Amylase Bicarbonate or CO_2[a] Blood urea nitrogen or urea[a] Calcium Chloride Creatinine Glucose Lactate dehydrogenase Lipase Phosphate Potassium Sodium Total bilirubin Direct bilirubin (if total bilirubin is elevated above ULN) Total protein Uric acid	Complete blood count, including: • Hemoglobin • Hematocrit • Platelet count • Red blood cell count • WBC count Differential count, including: • Basophils • Eosinophils • Lymphocytes • Monocytes • Neutrophils Absolute values must be provided for: • WBC differential laboratory results	Color and appearance pH and specific gravity Bilirubin Glucose Ketones Leukocytes Nitrite Occult blood Protein	PT PTT or aPTT INR	Women of childbearing potential
		Lipid Panel (Fasting)	**Endocrine Function**	**HIV Management Testing**[b] (Only participants who are known to be HIV-positive)
		Total cholesterol Triglycerides LDL HDL	TSH T4 T3/FT3[a]	[redacted]

[a] If considered standard by the region.

[redacted]

Note: Additional tests may be required, as agreed by investigator and sponsor, based on emerging safety data.

8.4. Pharmacokinetic Assessments

Blood samples for PK [redacted] analysis will be obtained at the visits and timepoints indicated in Table 4 and Table 5. After the preinfusion PK sample is drawn, participants will begin the study drug infusion. Adjustments to the timing of blood sampling may be made based on emerging PK data. The exact dates and times of the PK blood collection will be recorded in the eCRF. Instructions for sample preparation and shipping will be provided in the Laboratory Manual.

8.5. Pharmacodynamic [redacted] Assessments

[redacted]

8.5.2. Tissue Biopsies

Tumor tissue should be collected during screening (fresh or archival tissue) according to the schedule outlined in Table 4. Detailed information regarding procedures for handling and shipping of tissue samples will be provided in a separate laboratory manual.

[redacted]

8.5.3. Blood Sample Collection

Whole blood, serum, and plasma will be collected according to the schedule outlined in Table 4. Detailed information regarding procedures for handling and shipping of specimens will be provided in a separate laboratory manual.

[redacted]

8.6. Unscheduled Visits

Unscheduled study visits may occur at any time if medically warranted. Any assessments performed at those visits should be recorded in the eCRF.

8.7. End of Treatment and/or Early Termination

Once a participant permanently discontinues study treatment, the EOT visit should be conducted, and the data should be entered in the EOT visit in the eCRF. If the EOT visit coincides with a regular study visit, the EOT evaluations will supersede those of that scheduled visit. Should study treatment discontinuation occur < 21 days after the final dose of study treatment, a 28-day safety follow-up visit is required and should be conducted according to Table 3 and Table 4. If the EOT visit occurs ≥ 21 days after the last study treatment, only a single EOT/28-day safety follow up is required; otherwise, the EOT visit will also serve as the 28-day safety follow-up visit, and the EOT assessment schedule will be followed.

[redacted]

8.8. Follow-Up

The study design includes a follow-up period for participants subsequent to the end of the study treatment period. After discontinuation of study treatment, all study participants continue in the follow-up period of the study as described in Table 3.

[redacted]

8.8.1. Safety Follow-Up

The safety follow-up period starts once the participant discontinues study treatment. Approximately 28 days after the final dose of study drug (± 7 days), participants are to attend a clinical visit for a safety evaluation. During this visit, blood will be collected for safety laboratory analysis, a physical exam will be performed, and AEs and concomitant medications will be assessed according to the scheduled assessments found in Table 3. Participants will be followed for irAEs for 90 days after the last dose of study drug, regardless of whether a new anticancer therapy is started. Reasonable efforts should be made to align the first 12-week follow-up visit with the end of the 90-day irAE reporting period. However, if necessary, contact by phone or other methods of communication are acceptable in order for the participant to report any AEs that may occur during this period.

If a participant is scheduled to begin a new anticancer therapy before the end of the 28-day safety follow-up period, the safety follow-up visit should be performed before a new anticancer therapy is started. Once a new anticancer therapy has been initiated, the participant will move into the survival follow-up period.

8.8.2. Post-Treatment Disease Follow-Up

Participants who discontinue study drug for a reason other than disease progression will move into the disease status follow-up period and should be assessed every 12 weeks ± 7 days by radiologic imaging to monitor disease status. Every effort should be made to collect information regarding disease status until:

- The start of new anticancer therapy.
- Disease progression.
- Death.
- The end of the study.
- Participant is lost to follow-up.

8.8.3. Survival Follow-Up

Once a participant has received the last dose of study drug, has confirmed disease progression, or starts a new anticancer therapy, the participant moves into the survival follow-up period and should be contacted by telephone, email, or visit at least every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

For participants having entered the survival follow-up period of the study, the site will use continuing participant records to supply data on subsequent treatment regimens, tumor assessments (if discontinued treatment for a reason other than progression), and OS in the eCRF. For participants who do not intend to return to the study investigator for their ongoing care, follow-up should be maintained by phone contact, patient records, and public records/databases at intervals of no longer than 12 weeks.

9. ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

9.1. Definition of Adverse Event

Adverse Event Definition
• An AE is any untoward medical occurrence 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), symptom, or disease (new or exacerbated) temporally associated with the use of study drug.
Events Meeting the Adverse Event Definition
• Any safety assessments (eg, ECG, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • Abnormal laboratory test results constitute an AE if they are considered clinically meaningful, induce clinical signs or symptoms, require concomitant therapy, or require changes in study drug. Whenever possible, a diagnosis (eg, anemia, thrombocytopenia) should be recorded in the eCRF rather than the abnormal lab result (eg, low hemoglobin, platelet count decreased). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study drug administration even though they may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study drug or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
Events NOT Meeting the Adverse Event Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition or considered to be treatment-related by the investigator. • Efficacy endpoints as outlined in Section 3 will not be reported as AE/SAEs, specifically, any event that is related to disease progression of the cancer under study. Unblinded aggregated efficacy endpoint events and safety data will be monitored to ensure the safety of the participants in the study. Any suspected endpoint that upon review is not progression of the cancer under study will be forwarded to Incyte Pharmacovigilance as a SAE within 24 hours of determination that the event is not progression of the cancer under study. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE if it occurred after signing informed consent. If present before entering the study, the condition should be captured as medical history. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

9.2. Definition of Serious Adverse Event

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A Serious Adverse Event is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an adverse drug experience that places the participant, in the opinion of the initial reporter, at immediate risk of death from the adverse experience as it occurred. This does not include an adverse drug experience that, had it occurred in a more severe form, might have caused death.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle), that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations (Important Medical Event)

An event that may not result in death, be immediately life-threatening, or require hospitalization, but may be considered serious when, based on appropriate medical judgment, the event may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in the above definition. Examples of such events include invasive or malignant cancers (excluding the disease[s] under study in oncology protocols), intensive treatment in an emergency department or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

9.3. Recording and Follow-Up of Adverse Events and/or Serious Adverse Events

Adverse Event and Serious Adverse Event Recording

- An AE/SAE that begins or worsens after informed consent is signed should be recorded on the Adverse Event Form in the eCRF. Conditions that were present at the time informed consent was given should be recorded on the Medical History Form in the eCRF.
- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator (or delegate) will then record all relevant AE/SAE information in the eCRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records in lieu of completing the AE eCRF page.
- There may be instances when copies of medical records for certain cases are requested. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate AE/SAE.

To the extent possible, each AE/SAE should be evaluated to determine:

- The severity grade (CTCAE Grade 1 to 5). See below for further instructions on the assessment of intensity.
- Whether there is at least a reasonable possibility that the AE is related to the study drug: suspected (yes) or not suspected (no). See below for further instructions on the assessment of causality.
- The start and end dates, unless unresolved at final follow-up.
- The action taken with regard to each study drug as a result of the AE/SAE(s).
- The event outcome (eg, not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown).
- The seriousness, as per the SAE definition provided in Section 9.2.
- The action taken with regard to the event. Note: If an AE is treated with a concomitant medication or nondrug therapy, this action should be recorded on Adverse Event Form and the treatment should be specified on the appropriate eCRF (eg, Prior/Concomitant Medications, Procedures and Non-Drug Therapy).

Assessment of Intensity

The severity of AEs will be assessed using CTCAE v5.0 Grades 1 through 5. If an event is not classified by CTCAE, the severity of the AE will be graded according to the scale below to estimate the grade of severity:

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- **Grade 1:** Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; treatment not indicated.
- **Grade 2:** Moderate; minimal, local, or noninvasive treatment indicated; limiting age appropriate activities of daily living.
- **Grade 3:** Severe or medical significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.
- **Grade 4:** Life-threatening consequences; urgent treatment indicated.
- **Grade 5:** Fatal.

Assessment of Causality

- The investigator is obligated to assess the relationship between each study drug and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than that a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- The investigator will also consult the Reference Safety Information in the IB and/or Product Information, for marketed products, in his/her assessment.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study drug administration, will be considered and investigated.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- With regard to assessing causality of SAEs:
  - There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report. However, the causality assessment is one of the criteria used when determining regulatory reporting requirements. **Therefore, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE.**
  - The investigator may change his/her opinion of causality in light of follow-up information and send a follow-up SAE report with the updated causality assessment.

Follow-Up of Adverse Events and Serious Adverse Events

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the originally completed eCRF.
- Any updated SAE data will be submitted to the sponsor (or designee) within 24 hours of receipt of the information.
- Once an AE is detected, it should be followed until it has resolved or until it is judged to be permanent; assessment should be made at each visit (or more frequently if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat the event, and the outcome.
- When the severity of an AE changes over time for a reporting period (eg, between visits), each change in severity will be reported as a separate AE until the event resolves.

9.4. Reporting of Serious Adverse Events

Regardless of suspected causality (eg, relationship to study drug or study procedures), all SAEs occurring after the participant has signed the ICF through 28 days after the last dose of study drug, regardless of whether a new anticancer therapy is started, must be reported to the sponsor (or designee) within **24 hours** of learning of its occurrence, unless otherwise specified by the Protocol. Serious AEs that are irAEs must be reported until 90 days after the last dose of study drug. The investigator will submit any updated SAE data to the sponsor (or designee) within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE information after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study drug or study participation, the investigator must notify the sponsor (or designee) within 24 hours of becoming aware of the event.

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, [and nonserious AEs of special interest (as defined in Section 9.5), will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study drug under clinical investigation are met.

If the SAE is not documented in the IB for the study drug (new occurrence) and is thought to be related to the sponsor's study drug, the sponsor or its designee may urgently require further information from the investigator for reporting to health authorities. The sponsor or its designee may need to issue an Investigator Notification to inform all investigators involved in any study with the same drug that this SAE has been reported. SUSARs will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC, or as per national regulatory requirements in participating countries.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study drug under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

Serious Adverse Event Reporting

- Information about all SAEs is collected and recorded on the Adverse Event Form in the eCRF.
- The investigator must also complete the Incyte Serious Adverse Event Report Form, in English. Refer to the Incyte Reference Guide for Completing the Serious Adverse Event Report Form.
- Facsimile or email transmission of the Serious Adverse Event Report Form is the preferred method to transmit this information to PhV/designee. The contact information of the sponsor's study-specific representatives is listed in the Study Procedures Manual provided to each site. The original copy of the Serious Adverse Event Report Form and the confirmation sheet must be kept at the study site.
- Follow-up information is recorded on an amended or new Serious Adverse Event Report Form, with an indication that it is follow-up to the previously reported SAE and the date of the original report. The follow-up report should include information that was not provided on the previous Serious Adverse Event Report Form, such as the outcome of the event (eg, resolved or ongoing), treatment provided, action taken with each study drug because of the SAE (eg, dose reduced, interrupted, or discontinued), or participant disposition (eg, continued or withdrew from study participation). Each recurrence, complication, or progression of the original event should be reported as follow-up to that event, regardless of when it occurs.
- In rare circumstances and in the absence of facsimile or computer equipment, notification by telephone is acceptable with a copy of the Incyte Serious Adverse Event Report Form sent by overnight mail or courier service. Initial notification via telephone does not replace the need for the investigator to complete and sign the Serious Adverse Event Report Form within the designated reporting time frames.
- Contacts for SAE reporting can be found in the Study Procedures Manual.

9.5. Adverse Events of Special Interest

Not applicable.

9.6. Emergency Unblinding of Treatment Assignment

Not applicable.

9.7. Pregnancy

Pregnancy, in and of itself, is not regarded as an AE unless there is suspicion that study drug may have interfered with the effectiveness of a contraceptive medication or method. When a pregnancy has been confirmed in a participant during maternal or paternal exposure to study drug, the following procedures should be followed in order to ensure safety:

- The study drug must be interrupted immediately (female participants only).
- If the female participant is no longer pregnant and meets the treatment continuation criteria within 12 weeks of the scheduled start of a cycle, study drug may be resumed after approval has been received from the sponsor medical monitor.
- The investigator must complete and submit the Incyte Clinical Trial Pregnancy Form to the sponsor or its designee within **24 hours** of learning of the pregnancy.

Data on fetal outcome are collected for regulatory reporting and drug safety evaluation. Follow-up should be conducted for each pregnancy to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications, by following until the first well-baby visit. Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the sponsor or its designee. Pregnancy follow-up information should be recorded on the same form and should include an assessment of the possible causal relationship to the sponsor's study drug to any pregnancy outcome, as well as follow-up to the first well-baby visit or the duration specified in local regulations, whichever is later. Refer to the Incyte Reference Guide for Completing the Clinical Trial Pregnancy Form.

Any SAE occurring during pregnancy of a study participant must be recorded on the Serious Adverse Event Report Form and submitted to the sponsor or designee.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, or ectopic pregnancy) are considered SAEs (if occurring in the study participant) and must be reported as described in Section 9.4. If an abnormal pregnancy outcome is reported in a study participant's partner, the event should be reported to the sponsor on the Clinical Trial Pregnancy Form.

9.8. Warnings and Precautions

Special warnings or precautions for study drug, derived from safety information collected by the sponsor or its designee, are presented in the IB. Additional safety information collected between IB updates will be communicated in the form of Investigator Notifications. Any important new safety information should be discussed with the participant during the study, as necessary. If new significant risks are identified, they will be added to the ICF.

9.9. Product Complaints

The sponsor collects product complaints on study drug and drug delivery systems used in clinical studies in order to ensure the safety of study participants, monitor quality, and facilitate process and product improvements.

All product complaints associated with material packaged, labeled, and released by the sponsor or its designee will be reported to the sponsor. All product complaints associated with other study material will be reported directly to the respective manufacturer.

The investigator or his/her designee is responsible for reporting a complete description of the product complaint via email or other written communication to the sponsor contact or respective manufacturer as noted in the packaging information. Any AE associated with a product complaint should be recorded as described in Section 9.3.

If the investigator is asked to return the product for investigation, he/she will return a copy of the product complaint communication with the product.

10. STATISTICS

10.1. Sample Size Determination

In a recent single-arm Phase 2 study, nivolumab achieved an ORR of 24% in participants with unresectable metastatic anal cancer (Morris et al 2017).

Based on a target ORR of 25% and a sample size of 81, the study has 80% power to exclude a lower confidence limit of 13% with alpha equal to 0.025 (1-sided). The sample size calculation is based on participants' full analysis set defined in the next section.

10.2. Populations for Analysis

Table 21 presents the populations for analysis.

Table 21: Populations for Analysis

Population	Description
Full analysis set	The FAS includes all participants enrolled in the study who received at least 1 dose of study drug. The FAS will be used for the summary of demographics, baseline characteristics, and participant disposition as well as efficacy analysis.
Safety evaluable	The safety evaluable population includes all enrolled participants who received at least 1 dose of study drug. All safety analyses will be conducted using the safety evaluable population.
PK evaluable	The PK evaluable population will include all participants who received at least 1 dose of study drug and provided at least 1 postdose serum sample (1 PK measurement).
[redacted]	[redacted]

10.3. Level of Significance

There is no formal hypothesis testing in this study. Response rate as well as the associated 95% CI will be provided.

10.4. Statistical Analyses

The Statistical Analysis Plan will be developed and finalized before database lock and will describe the participant populations to be included in the analyses and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

10.4.1. Primary Analysis

10.4.1.1. Overall Response Rate

The primary endpoint of the study is ORR, defined as the percentage of participants with CR or PR, according to RECIST v1.1 (Eisenhauer et al 2009) as determined by an ICR. The primary analysis of ORR will be based on the FAS. Objective response rate and its exact 95% CI will be presented.

10.4.1.2. Handling of Missing Data in Primary Analysis

Complete response or PR reported before any additional anticancer therapy will be considered as response in the calculation of ORR irrespective of the number of missed assessments before response.

10.4.2. Secondary Analysis

10.4.2.1. Duration of Response

Duration of response is defined as the time from first documented response (CR or PR) to the time of first documented disease progression or death due to any cause. If a participant does not have an event before data cutoff or new anticancer therapy, DOR is censored at the date of the last adequate tumor assessment before data cut off or new anticancer therapy. The Kaplan-Meier estimate of the distribution function will be constructed for DOR. The estimated median along with 95% CIs will be reported.

10.4.2.2. Disease Control Rate

Disease control rate defined as the proportion of participants with an overall response (CR and PR), or stable disease per RECIST v1.1, according the ICR. The DCR will be estimated, and the exact 95% CI will be reported.

10.4.2.3. Progression-Free Survival

Progression-free survival, defined as the time from the first dose of study treatment to the date of the first documented progression per RECIST v1.1 or death due to any cause. Progression-free survival data will be analyzed by the Kaplan-Meier method, including estimated median with 95% CI and Kaplan-Meier estimated probabilities at several timepoints. If participants have no observed death or disease progression before data cutoff or new anticancer therapy, the participants will be treated as censored at their last adequate tumor assessment before cutoff or new anticancer therapy.

10.4.2.4. Overall Survival

Overall survival is defined as the time from first dose of study treatment to the date of death due to any cause. Participants still alive at the time of analysis will be censored at the date of last known alive. Kaplan-Meier curves, medians, and 95% CIs of the medians will be presented.

10.4.3. Safety Analyses

10.4.3.1. Adverse Events

Safety analyses will be conducted for the safety population. Adverse events will be coded by the MedDRA dictionary, and TEAEs (ie, AEs reported for the first time or worsening of a pre-existing event after first dose of study drug) will be tabulated by preferred term and system organ class for all events, related events, and events of Grade 3 or higher.

10.4.3.2. Adverse Events of Special Interest

Adverse events of special interest will include irAEs.

10.4.3.3. Clinical Laboratory Tests

The clinical laboratory data will be analyzed using summary statistics. In addition, distributions of key laboratory parameters may be plotted over time; these values will also be classified into CTCAE toxicity grades and tabulated.

Laboratory test values outside the normal range will be assessed for severity based on the normal ranges for the clinical reference laboratory. The incidence of abnormal laboratory values and shift tables relative to baseline will be tabulated. The following summaries will be produced for the laboratory data:

- Number and percentage of participants with worst postbaseline CTCAE grade (regardless of baseline value). Each participant will be counted only for the worst grade observed postbaseline.
- Shift tables from baseline to the worst postbaseline value using CTCAE grade.
- For laboratory parameters where CTCAE grades are not defined, shift tables to the worst postbaseline value using the low/normal/high classifications based on laboratory reference ranges.

10.4.3.4. Vital Signs

Descriptive statistics and mean change from baseline will be determined for vital signs (blood pressure, pulse, respiratory rate, and body temperature) at each assessment time. Vital sign results will be reviewed for clinically notable abnormalities, and participants exhibiting clinically notable vital sign abnormalities will be listed.

10.4.3.5. Electrocardiograms

Descriptive statistics and mean change from baseline will be determined for each ECG parameter at each assessment time. Electrocardiogram results will be reviewed for clinically notable abnormalities according to predefined criteria as described in the Statistical Analysis Plan.

10.4.3.6. Dose Intensity

Measures of exposure (eg, days of exposure, dose intensity, etc) of study drug will be summarized by means of summary statistics.

10.4.4. Pharmacokinetics

If there is a sufficient amount of serum concentration data from this study, the data will be analyzed by standard population PK methods using appropriate software (eg, NONMEM). Otherwise, the data will be pooled with data from other studies for a population PK analysis.

10.5. Interim Analysis

An analysis is planned after approximately 25 participants are assessable for response according to RECIST v1.1. The primary intent of this analysis is to minimize unnecessary exposure of participants to INCMGA00012 in the event of futility. The study will be stopped for futility at the interim analysis if conditional power based on interim result is lower than 20%, which is equivalent to less than 2 participants responded. All participants enrolled with a postbaseline response assessment or participants early discontinued will be included in the futility analysis. Participants enrolled in the study without any postbaseline response assessment but are ongoing in the study will not be included in the futility analysis for calculation of conditional power. Enrollment will continue while the analysis is being conducted. This futility analysis will be reviewed by an independent DMC as specified in the DMC Charter. The process by which the DMC will review data and make recommendations and decisions will be documented in the DMC Charter. The Statistical Analysis Plan will describe the planned interim analyses in greater detail.

[redacted]

11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

11.1. Investigator Responsibilities

- The Protocol, Protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- The investigator is responsible for ensuring that the safety reports provided by the sponsor are reviewed and processed in accordance with regulatory requirements, the policies and procedures established by the IRB/IEC, and institutional requirements.
- Any amendments to the Protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
  - Providing oversight of the conduct of the study at the site and adherence to GCP, IRB/IEC requirements, institutional requirements, and applicable laws and country-specific regulations.
- Adhering to the Protocol as described in this document and agreeing that changes to the Protocol procedures, with the exception of medical emergencies, must be discussed and approved, first, by the sponsor or its designee and, second, by the IRB/IEC. Each investigator is responsible for enrolling participants who have met the specified eligibility criteria.
- Retaining records in accordance with all local, national, and regulatory laws, but for a minimum period of at least 2 years after the last marketing application approval in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or if not approved, 2 years after the termination of the test article for investigation to ensure the availability of study documentation should it become necessary for the sponsor or a regulatory authority to review.
  - The investigator must not destroy any records associated with the study without receiving approval from the sponsor. The investigator must notify the sponsor or its designee in the event of accidental loss or destruction of any study records. If the investigator leaves the institution where the study was conducted, the sponsor or its designee must be contacted to arrange alternative record storage options.
  - All eCRF data entered by the site (including audit trail), as well as computer hardware and software (for accessing the data), will be maintained or made available at the site in compliance with applicable record retention regulations. The sponsor will retain the original eCRF data and audit trail.

11.2. Data Management

Data management will be performed in a validated EDC system. The investigator will be provided with access to an EDC system so that an eCRF can be completed for each participant.

The site will be provided eCRF completion guidelines for instructions on data entry in the eCRF. The study monitor will reference the Monitoring Plan in order to ensure that each issue identified is appropriately documented, reported, and resolved in a timely manner in accordance with the plan's requirements. Other data outside the EDC system required in the study conduct of the protocol such as documents or results transmitted to the sponsor via a central laboratory or specialized technical vendors, and as designated by the sponsor, will have their own data flow management plans, or study charters, [redacted] as applicable.

The sponsor (or designee) will be responsible for:

- Managing the integrity of the data and the quality of the conduct of the study, such as ensuring that study monitors perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Managing and reconciling the data generated, and/or collected including documents and results such as laboratory or imaging data analyzed centrally by a designated vendor of the sponsor.

The investigator will be responsible for:

- Recording, or ensuring the recording of, all relevant data relating to the study in the eCRF.
- Delivering, or ensuring the delivery of, all other results, documents, data, know-how, or formulas relating to the study to the sponsor or designee electronically and/or centrally (eg, laboratory data, imaging data, [redacted], photographs, diary data), or as otherwise specified in the Protocol.
- Verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- Maintaining accurate documentation (source data) that supports the information entered in the eCRF, or sent to a central vendor designated by the sponsor, or as described in other study and data flow manuals.
  - Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
  - Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current applicable medical records must be available.

- May have responsibility for sending participants' data, either as unique samples, or copies, or photographs, to be evaluated centrally or analyzed centrally, or both, by a qualified vendor designated by the sponsor.
- Permitting study-related monitoring, sponsor audits, IRB/IEC review, and regulatory inspections by providing direct access to source data and other relevant clinical study documents.
  - Monitoring: Qualified representatives of the sponsor or its designee, study monitors, will monitor the study according to a predetermined plan. The investigator must allow the study monitors to review any study materials and participant records at each monitoring visit.
  - Auditing: Qualified representatives of the sponsor or its designee may audit the clinical study site and study data to evaluate compliance with the Protocol, applicable local clinical study regulations, and overall study conduct. The investigator must allow the auditors to review original source records and study documentation for all participants.
  - Regulatory inspection: Regulatory authorities may conduct an inspection of the study and the site at any time during the development of an investigational product. The investigator and staff are expected to cooperate with the inspectors and allow access to all source documents supporting the eCRFs and other study related documents. The investigator must immediately notify the sponsor when contacted by any regulatory authority for the purposes of conducting an inspection.

11.3. Data Privacy and Confidentiality of Study Records

The investigator and the sponsor or its designee must adhere to applicable data privacy laws and regulations. The investigator and the sponsor or its designee are responsible for ensuring that sensitive information is handled in accordance with local requirements (eg, HIPAA). Appropriate consent and authorizations for use and disclosure and/or transfer (if applicable) of protected information must be obtained.

Participant names will not be supplied to the sponsor or its designee. Only the participant number will be recorded in the eCRF; if the participant's name appears on any other document (eg, laboratory report), it must be obliterated on the copy of the document to be supplied to the sponsor or its designee. Study findings stored on a computer will be stored in accordance with local data protection laws.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 10 years after study completion unless local regulations or institutional policies require a longer retention period. In the Netherlands, it is mandatory to keep the data for 15 years after the end of the research. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

11.4. Financial Disclosure

Before study initiation, all clinical investigators participating in clinical studies participant to FDA Regulation Title 21 CFR Part 54 – Financial Disclosure by Clinical Investigators (ie, "covered studies") are required to submit a completed Clinical Investigator Financial Disclosure form that sufficiently details any financial interests and arrangements that apply. For the purpose of this regulation, "clinical investigator" is defined as any investigator or subinvestigator who is directly involved in the treatment or evaluation of research participants, including the spouse and each dependent child of the clinical investigator or subinvestigator. These requirements apply to both US and foreign clinical investigators conducting covered clinical studies.

Any new clinical investigators added to the covered clinical study during its conduct must also submit a completed Investigator Financial Disclosure Form. During a covered clinical study, any changes to the financial information previously reported by a clinical investigator must be reported to the sponsor or its designee. At the conclusion of the covered clinical study, the clinical investigators will be reminded of their obligations. In the event that the clinical investigator is not reminded, they nevertheless will remain obligated to report to the sponsor or its designee any changes to the financial information previously reported, as well as any changes in their financial information for a period of 1 year after completion of the covered clinical study.

11.5. Publication Policy

By signing the study Protocol, the investigator and his/her institution agree that the results of the study may be used by the sponsor, Incyte Corporation (Incyte), for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals. Study results will be published in accordance with applicable local and national regulations. If necessary, the authorities will be notified of the investigator's name, address, qualifications, and extent of involvement. The terms regarding the publication of study results are contained in the agreement signed with the sponsor or its designee. A signed agreement will be retained by the sponsor or its designee.

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined in line with International Committee of Medical Journal Editors authorship requirements.

11.6. Study and Site Closure

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of participants by the investigator.
- Discontinuation of further study drug development.

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APPENDIX A. INFORMATION REGARDING EFFECTIVENESS OF CONTRACEPTIVE METHODS

For male participants in the study:
Male participants should use a condom during treatment and through 6 months after the end of systemic exposure. If the male participant has a partner that is of child-bearing potential, the partner should also use contraception through 6 months after the end of relevant systemic exposure. In addition, male participants must refrain from donating sperm during the study through 6 months after the end of relevant systemic exposure. Males who have had a vasectomy qualify as having met the requirement for a highly effective birth control method.

For female participants in the study:
The following methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods.
Such methods include:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[1]
  - oral
  - intravaginal
  - transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation[1]
  - oral
  - injectable
  - implantable[2]
- Intrauterine device (IUD)[2]
- Intrauterine hormone-releasing system (IUS)[2]
- Bilateral tubal occlusion[2]
- Vasectomised partner[2,3]
- Sexual abstinence[4]

Acceptable birth control methods that result in a failure rate of more than 1% per year include:

- progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
- male or female condom with or without spermicide[5]
- cap, diaphragm or sponge with spermicide[5]
- tubal ligation

[1] Hormonal contraception may be susceptible to interaction with the IMP, which may reduce the efficacy of the contraception method.
[2] Contraception methods that in the context of this guidance are considered to have low user dependency.
[3] Vasectomised partner is a highly effective method of avoiding pregnancy provided that partner is the sole sexual partner of the woman of childbearing potential trial participant and that the vasectomised partner has received medical assessment of the surgical success.
[4] In the context of this guidance, sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. 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.
[5] A combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier methods) are also considered acceptable, but not highly effective, birth control methods.
Source: CTFG 2014.

APPENDIX B. RESPONSE EVALUATION CRITERIA FOR SOLID TUMORS VERSION 1.1

Evaluation of Target Lesions

CR	Disappearance of all target lesions.
PR	At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD.
PD	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started, and the sum must also demonstrate an absolute increase of at least 5 mm or the appearance of 1 or more new lesions.
SD	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.

CR = complete response; LD = longest diameter; PD = progressive disease; PR = partial response; SD = stable disease.

Evaluation of Nontarget Lesions

CR	Disappearance of all nontarget lesions and normalization of tumor marker level.
Incomplete non-CR/ non-PD/SD	Persistence of 1 or more nontarget lesion(s) and/or maintenance of tumor marker level above the normal limits.
PD	Appearance of 1 or more new lesions and/or unequivocal progression of existing nontarget lesions.[a]

CR = complete response; PD = progressive disease; SD = stable disease.

[a] Although a clear progression of "nontarget" lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail, and the progression status should be confirmed later on by the review panel (or study chair).

Evaluation of Best Overall Response

- The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the participant's best response assignment will depend on the achievement of both measurement and confirmation criteria.
- Note: In nonrandomized studies where response is the primary endpoint, confirmation of PR or CR is needed to deem either one the ‘best overall response’.

Target Lesions	Nontarget Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD or NE	No	PR
SD	Non-PD or NE	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

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

- Participants with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment.
- In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of CR depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the CR status.

Source: Eisenhauer et al 2009.

APPENDIX C. PROTOCOL AMENDMENT SUMMARY OF CHANGES

Document	Date
Amendment (Version) 1:	06 AUG 2018
Amendment (Version) 2:	04 OCT 2018
Amendment (Version) 2-NL:	26 NOV 2018
Amendment (Version) 3:	21 MAR 2019
Amendment (Version) 4:	08 JUL 2019

Amendment 4 (08 JUL 2019)

Overall Rationale for the Amendment: Clarification of eligibility criteria.

[redacted]

3. **Section 5.1, Inclusion Criteria**

   Description of change: Revised inclusion criterion #4 as follows:

   Participants must have had progression on or after platinum-based therapy unless ineligible for or intolerant of platinum.

   a. No more than 2 prior lines of systemic therapy **for metastatic disease** are permitted**.** ~~(this includes radiosensitizing chemotherapy).~~

   b. Participants who are ineligible for platinum must have received at least 1 prior line of systemic therapy.

   c. **Participants receiving platinum-based radiosensitizing chemotherapy are eligible if relapse occurs < 6 months from completion of treatment.**

   Rationale for change: To clarify the relationship of prior anticancer therapy to eligibility.

4. **Section 5.2, Exclusion Criteria(Table 7: Exclusionary Laboratory Values)**

   Description of change: Changed hemoglobin units from L to dL in exclusion criterion #5, Table 7.

   Rationale for change: To provide consistency throughout the document.

5. **Section 5.2, Exclusion Criteria**

   Description of change: Revised exclusion criterion #13 as follows:

   Participants with impaired cardiac function or clinically significant cardiac disease:

   a. New York Heart Association Class III or IV cardiac disease, including preexisting clinically significant ventricular arrhythmia, congestive heart failure, or cardiomyopathy.
   b. Unstable angina pectoris**.** ~~≤ 6 months before study participation.~~
   c. Acute myocardial infarction ≤ 6 months before study participation.
   d. Other clinically significant heart disease (ie, ≥ **uncontrolled** Grade 3 hypertension**).**~~,~~ ~~history of labile hypertension, or poor compliance with an antihypertensive regimen) must have recovered (to baseline or ≤ Grade 1) from toxicity associated with prior treatment.~~

   Rationale for change: To further clarify eligibility as it relates to cardiac diagnoses.

6. **Section 6.6.2, Prohibited Medications and Procedures**

   Description of change: Added probiotic dietary supplements as a prohibited medication.

   Rationale for change: To clarify that probiotic dietary supplements are prohibited while on study.

7. **Incorporation of administrative changes.** Other minor, administrative changes have been incorporated throughout the Protocol and are noted in the redline version of the amendment.

Amendment 3 (21 MAR 2019)

Overall Rationale for the Amendment:

[redacted] to remove requirement for premedication prophylaxis.

1. **Incorporate changes from Amendment 2-NL (26 NOV 2018)**

   Description of change: Changes as listed in Amendment 2-NL (26 NOV 2018).

   Rationale for change: To align Protocol Amendment 3 as appropriate for all regions.

2. **Section 1, Protocol Summary (Table 3: Schedule of Activities); Section 6.5.1, Management of Suspected Infusion Reactions (Table 9: Guidelines for Management of Suspected Infusion Reactions); Section 6.6.1, Permitted Medications and Procedures**

   Description of change: Removed the requirement for premedication prophylaxis before the first dose of INCMGA00012.

   Rationale for change: Updated for consistency with the INCMGA00012 IB.

3. **Section 1, Protocol Summary (Table 3: Schedule of Activities); Section 6.6, Concomitant Medications and Procedures; Section 8.3, Safety Assessments; Section 9.4, Reporting of Serious Adverse Events**

   Description of change: Clarified that irAEs are collected up to 90 days after last dose of study drug.

   Rationale for change: Immune-related adverse events are collected up to 90 days after last dose of study drug.

4. **Section 1, Protocol Summary (Table 5: Pharmacokinetic [redacted] Sample Collections [redacted]); Section 3, Objectives and Endpoints (Table 6); [redacted]; Section 5.1, Inclusion Criteria (Criterion #9); Section 8.1.1 Informed Consent Process; Section 8.5, Pharmacodynamic [redacted] Assessments; Section 8.7, End of Treatment and/or Early Termination; Section 8.8, Follow-Up; Section 10.4.5.5, HIV Viral Control; [redacted]**

   Description of change: [redacted]

   Rationale for change: [redacted]

5. **Section 2.1.1, INCMGA00012**

   Description of change: Updated INCMGA00012 safety data.

   Rationale for change: To provide updated data and align with the current IB.

6. **Incorporation of administrative changes.** Other minor, administrative changes including updates to the Schedule of Activities (Table 3) have been incorporated throughout the Protocol and are noted in the redline version of the amendment.

Amendment 2-NL (26 NOV 2018)

Overall Rationale for the Amendment:

The purpose of this amendment is to address comments regarding the design of the study.

1. **Cover Page**

   Description of change: Added the following statement: "The research in the Netherlands is carried out in accordance with the Declaration of Helsinki (Brazil, 2013) and the WMO (Medical Research Involving Human Subjects Act)."

   Rationale for change: To clarify.

2. **Section 8.5.1, Description of Analyses**

   Description of change: Added the following text: "Biological samples will be stored for up to 10 years from the first clinical study report publication. The research performed on those samples will be study-related. Additional research outside of study-related research will not be performed."

   Rationale for change: To clarify how long the body material is stored after the investigation and for which purpose this material is stored.

3. **Section 11.3, Data Privacy and Confidentiality of Study Records**

   Description of change: Added the following text: "In the Netherlands, it is mandatory to keep the data for 15 years after the end of the research."

   Rationale for change: To clarify how long the data will be stored at the research location in the Netherlands.

4. **Incorporation of administrative changes.** Other minor, administrative changes have been incorporated throughout the Protocol and are noted in the redline version of the amendment.

Amendment 2 (04 OCT 2018)

Overall Rationale for the Amendment:

The purpose of this amendment is to address comments regarding the design of the study.

1. **Section 1, Protocol Summary; Section 4.3, Study Termination; Section 4.3.1, Data Monitoring Committee; Section 10.5 Futility Analysis**

   Description of change: Added a DMC.

   Rationale for change: To clarify that an independent DMC will be formed.

2. **Section 5.1, Inclusion Criteria**

   Description of change: Inclusion criterion #4 was revised as follows:

   Participants must have received no more than 2 prior lines of therapy and must have progressed after at least 1 platinum-based regimen. Participants ineligible for platinum-based therapy must have received at least 1 line of prior systemic therapy.
   a. Participants ineligible for platinum-based therapy may enroll.
   b. Participants intolerant of platinum-based therapy may enroll.
   c. Participants who developed advanced, recurrent, or metastatic disease within 6 months of completing platinum-based chemoradiation with curative intent may enroll.

   ~~Must have received (or been intolerant to or ineligible for) at least 1 prior line of platinum-based chemotherapy and received no more than 2 prior systemic treatments~~.

   Rationale for change: To clarify that participants will be included if they progressed after standard-of-care platinum-based chemotherapy.

3. **Section 5.2, Exclusion Criteria**

   Description of change: Exclusion criterion #2 was revised as follows:

   Radiotherapy within 14 days of first dose of study treatment with the following caveats:
   a. 28 days for pelvic radiotherapy.
   b. 6 months for thoracic region radiotherapy that is > 30 Gy in 2 Gy fractions.

   Rationale for change: To clarify that the limit is a total dose equivalent to 30 Gy in 2 Gy fractions.

4. **Section 5.2, Exclusion Criteria**

   Description of change: Exclusion Criterion #12 was revised as follows:

   Known hypersensitivity to another monoclonal antibody that cannot be controlled with standard measures (eg, antihistamines and corticosteroids) or known allergy or hypersensitivity to any component of INCMGA00012 or formulation components.

   Rationale for change: To clarify that known hypersensitivity to any excipient contained in the INCMGA00012 drug formulation is exclusionary.

5. **Section 6.5.2.7, Immune-Mediated Myocarditis (Table 17: Recommended Approach for Handling Myocarditis)**

   Description of change: Added Section 6.5.2.7, Immune-Mediated Myocarditis.

   Rationale for change: To add guidance regarding management of immune-mediated myocarditis.

6. **Section 10.5, Futility Analysis**

   Description of change: Added additional details to clarity the stopping rules and responsibilities of the futility analysis.

   Rationale for change: To clarify criteria for stopping the trial for futility.

Amendment 1 (06 AUG 2018)

Overall Rationale for the Amendment:

The primary purpose of this amendment is to address comments regarding the design of the study.

1. **Section 1, Protocol Summary (Table 3, Schedule of Activities); Section 4.1, Overall Design; Section 8.3.1, Adverse Events; Section 8.3.6, Laboratory Assessments; Section 8.8.1, Safety Follow-Up; Section 9.4, Reporting of Serious Adverse Events**

   Description of change: Updated text to reflect that participants will be evaluated for AEs for 90 days after the last dose of study drug regardless of whether a new anticancer therapy is started~~, or until the start of another anticancer therapy, whichever occurs first~~.

   Rationale for change: Participants will be followed for AEs for 90 days after the last dose of study drug, regardless of whether a new anticancer therapy is started.

2. **Section 5.1, Inclusion Criteria (Inclusion Criterion #4)**

   Description of change: Updated Inclusion Criterion #4:

   ~~4. No more than 2 prior systemic treatments, at least 1 of which must have included platinum-based chemotherapy unless the participant is intolerant of platinum therapy, is ineligible for platinum, or has refused platinum-based chemotherapy (with medical monitor approval).~~

   4. Must have received (or been intolerant to or ineligible for) at least 1 prior line of platinum-based chemotherapy and received no more than 2 prior systemic treatments.

   Rationale for change: To clarify the eligibility criteria to explicitly state that participants must have received (or been intolerant to or ineligible for) at least 1 prior line of platinum-based systemic therapy to be eligible.

3. **Section 1, Protocol Summary (Table 3, Schedule of Activities); Section 8.3.6, Laboratory Assessments; Section 8.3.6, Laboratory Assessments (Table 18, Required Laboratory Analytes)**

   Description of change: Added: [redacted]

   Rationale for change: [redacted]

4. **Section 1, Protocol Summary (Table 4, Pharmacokinetic [redacted] Sample Collection); Section 8.5.1, Description of Analysis**

   Description of change: [redacted]

   Rationale for change: [redacted]

5. **Section 1, Protocol Summary (Table 4, Pharmacokinetic [redacted] Sample Collections)**

   Description of change: [redacted]

   Rationale for change: [redacted]

6. **Section 6.6.1, Permitted Medications and Procedures**

   Description of change: Added: Highly active antiretroviral therapy (HAART) should be continued for participants who are known to be HIV positive.

   Rationale for change: To clarify that HAART is a permitted medication in this study.

[redacted]

8. **Section 10.2, Population for Analysis; Section 10.4.1.2, Handling of Missing Data in Primary Analysis**

   Description of change: Edited Full Analysis Set (FAS): The FAS includes all participants enrolled in the study ~~have measurable disease per RECIST v1.1~~who received at least 1 dose of study drug. The FAS will be used for the summary of demographics, baseline characteristics, and participant disposition as well as efficacy analysis.

   Rationale for change: Measurable disease by RECIST v1.1 is an eligibility criterion.

9. **Section 3, Objectives and Endpoints (Table 5, Objectives and Endpoints); Section 10.4.2.2, Disease Control Rate**

   Description of change: Edited Disease Control Rate (DCR): DCR, defined as the number of participants maintaining either an ORR or stable disease ~~lasting at least 6 months~~.

   Rationale for change: In SCAC, DCR does not require maintaining SD for 6 months.

10. **Incorporation of administrative changes.** Other minor, administrative changes have been incorporated throughout the Protocol and are noted in the redline version of the amendment.