Official Title: **A Phase 2 Study of INCMGA00012 (PD-1 Inhibitor) in Participants With Selected Solid Tumors (POD1UM-203)**

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Clinical Study Protocol

INCMGA 0012-203

A Phase 2 Study of INCMGA00012 (PD-1 Inhibitor) in Participants With Selected Solid Tumors (POD1UM-203)

Product:	**INCMGA00012**
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EudraCT Number:	**2018-002941-12**
Phase of Study:	**2**
Sponsor:	**Incyte Corporation** **1801 Augustine Cut-Off** **Wilmington, DE 19803**
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INVESTIGATOR'S AGREEMENT

I have read the INCMGA 0012-203 Protocol Amendment 5 (Version 5 dated 23 JUN 2021) 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
ALK	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
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
BSA	body surface area
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
CPS	combined positive score
CR	complete response
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTL	cytotoxic T-lymphocyte
DCR	disease control rate
[redacted]	[redacted]
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EGFR	epidermal growth factor receptor
EOT	end of treatment
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
HSD	Hwang-Shih-DeCani
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
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
iRECIST	modified RECIST v1.1 for immune-based therapeutics
IRT	interactive response technology
IV	intravenous
LDL	low-density lipoprotein
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
NCI	National Cancer Institute
NSAID	nonsteroidal anti-inflammatory drug
NSCLC	non-small cell lung cancer
ORR	overall response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PD	progressive disease

Abbreviations and Special Terms	Definition
PD-1	programmed cell death protein 1
PD-L1	programmed cell death-ligand 1
PFS	progression-free survival
PK	pharmacokinetic(s)
PO	oral
PR	partial response
PT	prothrombin time
PTT	partial thromboplastin time
Q2W	every 2 weeks
Q4W	every 4 weeks
Q8W	every 8 weeks
Q12W	every 12 weeks
RECIST	Response Evaluation Criteria in Solid Tumors
RCC	renal cell carcinoma
RNA	ribonucleic acid
RNAseq	ribonucleic acid sequencing
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SD	stable disease
SoA	schedule of activities
SOP	standard operating procedure
$t_{½}$	apparent terminal-phase disposition half-life
TEAE	treatment-emergent adverse event
TIL	tumor-infiltrating lymphocyte
TMB	tumor mutational burden
TPS	tumor proportion score
UC	urethelial carcinoma
ULN	upper limit of normal
WBC	white blood cell

1. PROTOCOL SUMMARY

Protocol Title: A Phase 2 Study of INCMGA00012 (PD-1 Inhibitor) in Participants With Selected Solid Tumors (POD1UM-203)

Protocol Number: INCMGA 0012-203

Objectives and Endpoints:

Table 1 presents the primary objective and endpoint.

Table 1: Primary Objective and Endpoint

Objective	Endpoint
Primary	
To assess the efficacy of INCMGA00012 in terms of the ORR in tumor types of interest.	ORR, defined as the percentage of participants having a CR or PR, according to RECIST v1.1 as determined by the investigator.

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	Treatment-naive metastatic NSCLC with high PD-L1 expression (TPS ≥ 50%) and no EGFR, ALK, or ROS activating genomic tumor aberrations. Locally-advanced or metastatic UC in cisplatin ineligible patients whose tumors express PD-L1 (CPS ≥ 10 of PD-L1). Unresectable or metastatic melanoma. Locally advanced or metastatic clear-cell RCC without prior systemic treatment.
Population	Male and female participants at least 18 years of age.
Number of Participants	Approximately 120 participants will be enrolled into disease-specific cohorts of approximately 30 participants per cohort.
Study Design	This is a Phase 2, open-label, multiple group, multicenter 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 disease progression, intolerable toxicity, death, withdrawal of consent, lost to follow-up, or premature discontinuation for any other reason. Participants completing treatment or prematurely discontinuing the study drug will be followed for survival until death, withdrawal of consent, or the end of the study, whichever occurs first. Survival follow-up is not required of participants who have discontinued active treatment after the primary efficacy analysis is completed.
Coordinating Principal Investigator	[redacted] MD, [redacted] Hungary

Treatment Groups and Duration:

All eligible participants will receive INCMGA00012 at the RP2D of 500 mg IV Q4W. Treatment will be administered by IV infusion over 30 minutes on Day 1 of each 28-day cycle. Subsequent treatment cycles may be delayed due to toxicity for up to 12 weeks (see Section 6.5 and Table 10).

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 breaks of greater than 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.

Table 3 presents the complete study-specific SoA. Details regarding the sample collection for PK [redacted] analyses are defined in Table 4. Table 12 presents the safety laboratory analytes to be evaluated. Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

Some study procedures may be conducted by phone call, where appropriate, or as per institutional guidelines during the COVID-19 pandemic. This information will be described in detail in the ICF. Some tests such as ECG or CT scan assessments may require longer time-windows due to the COVID-19 pandemic and thus may be done outside the regularly scheduled visits or may be conducted at the next scheduled visit. These delays will not be considered protocol deviations if they are due to administrative difficulties or travel restrictions during the COVID-19 pandemic and are documented accordingly.

Table 3: Schedule of Activities

	Screening	Treatment				Follow-Up	
Visit Day (Range)	28 Days	Cycle 1 Day 1	Cycle ≥ 2 Day 1 (± 3 d)	Q8W (± 7 d)	EOT[a]	28 Days After Last Dose (± 7 d)	Notes
Administrative procedures							
Informed consent	X						
IRT	X	X	X		X		
Inclusion/exclusion criteria	X						
General and disease medical history	X						
Prior/concomitant medications	X	X	X		X	X	
Distribute reminder cards	X	X	X		X	X	
Administer INCMGA00012*		X	X				* Premedication with antipyretic (eg, acetaminophen/paracetamol) and a histamine blocker (eg, diphenhydramine) 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*	* Immune-related AEs to be collected for 90 days after the last dose of study drug or until a new anticancer therapy is started, whichever occurs first.
Physical examination	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	Either Fridericia or Bazett method of correction is acceptable for QT.
Efficacy assessments							
Tumor imaging/response assessments	X			X*			* After efficacy analysis is complete, imaging to be performed per standard of care. Complete response or PR should be confirmed by imaging at least 4 weeks after initial documentation.
ECOG performance status	X	X	X		X		
Post study anticancer therapy status					X	X	
Survival status					X	X	

Table 3: Schedule of Activities (Continued)

	Screening	Treatment				Follow-Up	
Visit Day (Range)	28 Days	Cycle 1 Day 1	Cycle ≥ 2 Day 1 (± 3 d)	Q8W (± 7 d)	EOT[a]	28 Days After Last Dose (± 7 d)	Notes
Clinical laboratory assessments							
Serum 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						
Coagulation panel	X						
Thyroid panel	X		X*			X	* Every third cycle (C4, C7, C10, etc).
Urinalysis	X						
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.
[redacted]							

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

Table 4: Pharmacokinetic [redacted] Sample Collections

Sample	Collection	Purpose/Analysis	Treatment Period							EOT	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[a] *	Samples will be collected preinfusion and 10 minutes postinfusion (± 10 minutes) on Day 1 of Cycles 1, 2, 4 and 6. * Additional PK samples will be collected 4 hours (± 15 minutes) postinfusion on Day 1 of Cycle 1 and at EOT.
[redacted]											

[a] A sample will be collected at the EOT visit or, if no separate EOT visit is performed, at the 28-day safety follow-up visit.

2. INTRODUCTION

2.1. Background

Immunotherapy has had a major impact on the treatment of advanced cancer. Monoclonal antibodies against the immune checkpoints such as cytotoxic T-lymphocyte antigen-4 (CTLA-4) and PD-1 and its ligand, PD-L1, have been approved for many indications (Keytruda® 2018, Opdivo® 2018). The PD-1 receptor is an inhibitory receptor expressed by T cells, which is engaged by the ligands PD-L1 and PD-L2, expressed by antigen presenting cells and, in many cases, tumor cells. Interaction of PD-1 with its ligands leads to the delivery of a negative signal to the T-cell expressing PD-1, and inhibits T-cell function. This pathway helps the body maintain self-tolerance. Many tumor cells however have co-opted this pathway and express high levels of PD-L1 and thereby evade T-cell attack. Within the tumor microenvironment, PD-1/PD-L1 interactions inhibit CTL activity. Programmed cell death protein 1 activation inhibits CD8+ CTL proliferation, survival, and their effector function and can also induce apoptosis of TILs and promote differentiation of CD4+ T-cells into Treg cells.

The immunotherapy treatment paradigm is characterized by deep and evolving clinical responses in association with the development of durable and specific immunity against the tumor (Topalian et al 2012). In many settings, this has led to improved survival (Robert et al 2015, Brahmer et al 2017, Herbst et al 2016, Bellmunt et al 2017, and Motzer et al 2015).

2.1.1. INCMGA00012

INCMGA00012 is a humanized, hinge-stabilized, IgG4κ monoclonal antibody that recognizes human PD-1. INCMGA00012 contains a human IgG4 Fc domain to limit effector function while retaining neonatal Fc receptor binding to extend circulating half-life. INCMGA00012 is designed to target PD-1–expressing cells, including T cells, and to sustain/restore their effector function by blocking checkpoint inhibitory interactions between PD-1 and its 2 ligands, PD-L1 and PD-L2.

Results of the dose-escalation portion of Study INCMGA 0012-101 (POD1UM-101, NCT03059823) demonstrated acceptable tolerability with no DLTs observed at any dose level up to 10 mg/kg Q2W. A maximum tolerated dose was not reached. For both the 3 and 10 mg/kg dose levels, C_{max} and $AUC_{0-\infty}$ were dose-proportional. The $t_{½}$ (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 were seen at all dose levels (Condamine et al 2019, Lakhani et al 2017).

POD1UM-101 had 4 tumor-specific dose-expansion cohorts (endometrial, cervical, sarcoma, and NSCLC) treated with 3 mg/kg Q2W and 3 fixed-dose cohorts (500 mg Q4W, 750 mg Q4W, and 375 mg Q3W). One hundred thirty-two participants were treated in the initial 4 tumor-specific expansion groups (Mehnert et al 2018). Safety was favorable with an overall irAE incidence of 12%. Most irAE were transient, with the exception of endocrine-related irAE. Nonendocrine irAEs that did not resolve were lipase increased, stomatitis, proctitis, diarrhea, ALT increased, and blood bilirubin increased (all 1 participant each). There were no fatal AEs attributed to treatment with INCMGA00012. The 375 mg Q3W and 500 mg Q4W doses were selected as the RP2Ds for further development.

Confirmed RECIST responses were observed in all of the expansion cohorts, none of which had been enriched by a predictive biomarker (eg, microsatellite instability or PD-L1 status). Specifically, 5 of 27 (19%) of the evaluable participants with NSCLC had confirmed RECIST responses, as did 4 of 29 (14%) of participants with cervical cancer, 4 of 23 (17%) with endometrial cancer, and 1 of 28 (4%) with sarcoma. The ORR and median duration of responses have not yet been established.

2.2. Rationale for Study Design

The study is an open-label, nonrandomized, multi-cohort trial that is designed to provide proof of concept for INCMGA00012 in key indications where other PD-1 inhibitors have already shown efficacy. Clinical studies are an important mechanism for providing access to promising therapies where it may otherwise be limited (eg, due to labeling restrictions or insufficient reimbursement).

2.2.1. Population

Overall response to PD-1 directed therapy is an important early indication of whether a new immunotherapy is likely to prove useful in the clinic. Since ORRs of 30% to 40% have been shown with other PD-1 inhibitors against the indications to be studied (see Table 5), this provides a useful benchmark for the development of new checkpoint therapies, like INCMGA00012, which can readily be evaluated in a screening trial.

Table 5: Activity of Other PD-1 Inhibitors

Indication	Pembrolizumab ORR (95% CI)	Nivolumab ORR (95% CI)
1L NSCLC (TPS ≥ 50%)	45 (37, 53)[a]	34 (24, 45)[b]
Cisplatin ineligible UC (CPS ≥ 10)	39 (28, 50)[c]	28 (19, 39)[d,e]
1L melanoma	33 (27, 39)[a]	40 (34, 46)[f]
1L RCC	38 (29, 48)[g]	42 (37, 47)[h,i]

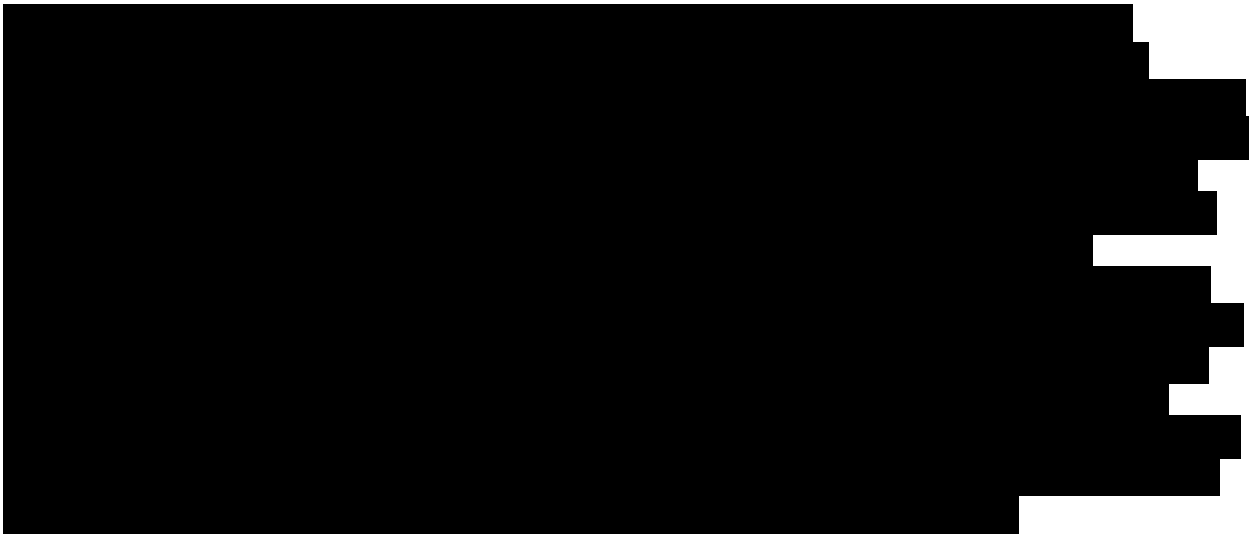
[a] Refer to Keytruda 2018.
[b] Refer to Carbone et al 2017.
[c] Refer to Balar et al 2017.
[d] TPS ≥ 5%.
[e] Refer to Escudier et al 2017.
[f] Refer to Robert et al 2015.
[g] Refer to McDermott et al 2018.
[h] In combination with ipilimumab.
[i] Refer to Motzer et al 2018.

2.2.2. Dose and Schedule

Fixed doses of therapeutics have several advantages over weight-based doses, including convenience of preparation and administration, reduced errors in preparation calculation, and minimization of drug waste. Body size–based doses and fixed doses of mAbs have been evaluated, and the 2 approaches perform similarly in terms of efficacy and safety (Wang et al 2009, Bai et al 2012).

The flat dose regimen of 500 mg Q4W is based on clinical data from the ongoing first-in-human monotherapy study (INCMGA 0012-101; 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 a maximum tolerated dose 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.



2.3. Benefit/Risk Assessment

Treatment directed at the PD-1/PD-L1 axis is a promising approach to the diseases under study. Monoclonal antibodies against PD-1 have shown benefit for these and other indications and safety of these agents has been well characterized (Keytruda 2018, Opdivo 2018). Based on published experience from more than 200 study participants, the pharmacologic and clinical profile of INCMGA00012 is comparable to the approved PD-1 inhibitors; thus, similar efficacy can be anticipated where PD-1 inhibitors have already been shown to be active (Chen et al 2019, Condamine et al 2019, Lakhani et al 2017, Mehnert et al 2018).

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 the efficacy of INCMGA00012 in terms of the ORR in tumor types of interest.	ORR, defined as the percentage of participants having a CR or PR, according to RECIST v1.1 as determined by the investigator.
Secondary	
To determine the DOR to INCMGA00012.	DOR, defined as the time from an initial objective response (CR or PR) according to RECIST v1.1 until first observation of documented disease progression as determined by investigator or death due to any cause.
To determine the DCR.	DCR, defined as the proportion of participants with either an objective response (CR and PR) or SD, according to RECIST v1.1.
To determine the PFS of INCMGA00012.	PFS, defined as the time from the start of therapy until disease progression, as determined by investigator or death due to any cause.
To determine the OS of INCMGA00012.	OS, defined as the time from the start of therapy until death due to any cause.
To evaluate the safety of INCMGA00012.	Safety, determined by the number of participants, frequency, duration, and severity of AEs, laboratory tests, vital signs, and ECGs.
To determine the PK of INCMAG00012 when administered as a 30-minute infusion.	The PK of INCMAG00012 including C_{max}, t_{max}, C_{min}, and AUC_t, will be summarized.
[redacted]	
[redacted]	[redacted]
[redacted]	[redacted]

4. STUDY DESIGN

4.1. Overall Design

This study is a Phase 2, open-label, multicenter study designed to assess the clinical activity and safety of INCMGA00012 in participants with advanced solid tumors where the efficacy of PD-1 inhibitors has previously been established. Participants with the following tumor types will be enrolled into disease-specific cohorts:

- Treatment-naive metastatic NSCLC with high PD-L1 expression (TPS ≥ 50%) and no EGFR, ALK, or ROS activating genomic tumor aberrations.
- Locally-advanced or metastatic urothelial cancer in cisplatin ineligible patients (determined by the investigator) whose tumors express PD-L1 (CPS ≥ 10) of PD-L1).
- Unresectable or metastatic melanoma.
- Locally advanced or metastatic clear–cell RCC without prior systemic treatment.

The primary endpoint is ORR as determined by RECIST v1.1 as determined by the investigator.

The study consists of 3 periods: screening, study drug treatment, and follow-up.

All eligible participants will receive INCMGA00012 at the RP2D of 500 mg IV Q4W. Treatment will be administered by IV infusion over 30 minutes on Day 1 of each 28-day cycle. Subsequent treatment cycles may be delayed due to toxicity for up to 12 weeks (see Section 6.5 and Table 10).

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 breaks of greater than 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. Treatment with study drug may continue up to 2 years in the absence of disease progression (see Section 8.2), intolerable toxicity, death, withdrawal of consent, lost to follow-up, or premature discontinuation for any other reason. 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) or iRECIST (see Section 8.2.2), with the decision to treat beyond conventional RECIST progression documented in the study file.

A participant may receive up to 2 years of study drug in the absence of disease progression or unacceptable toxicity. Participants will be evaluated for AEs/SAEs for approximately 28 days after the last dose of study drug and will be followed for irAEs for approximately 90 days after the last dose of study drug or until the start of a new anticancer therapy, whichever occurs first. The 90-day visit may be conducted via phone call. Survival follow-up is not required of participants who have discontinued study drug once the primary efficacy analysis is completed. The primary efficacy analysis will be performed once all participants have been followed for at least 6 months from the start of treatment or have prematurely discontinued study treatment. Thereafter, participants will be treated with INCMGA00012 if they derive clinical benefit as per standard of care for the disease and local guidelines.

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 12. Details regarding the sample collection for PK [redacted] analyses are defined in Table 4.

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. The study will end when the last participant completes 90 days of safety follow-up for irAEs. No participant will be followed for longer than 27 months (ie, 2 years of study treatment followed by 90 days of observation for irAEs in the event the participant does not discontinue treatment prematurely or start a new anticancer therapy).

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 or if required by regulatory decision. 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.

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 one of the following:
   a. Treatment-naive metastatic NSCLC with high PD-L1 expression (TPS ≥ 50%) and no EGFR, ALK, or ROS activating genomic tumor aberrations.
   b. Locally-advanced or metastatic UC in participants who are not eligible for cisplatin therapy (determined by the investigator) and whose tumors express PD-L1 with a CPS ≥ 10.
   c. Unresectable or metastatic melanoma.
   d. Locally advanced or metastatic RCC with clear cell component (with or without sarcomatoid features) and having received no prior systemic therapy
4. Measurable disease per RECIST v1.1.
5. ECOG performance status 0 to 1.
6. 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.

5.2. Exclusion Criteria

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

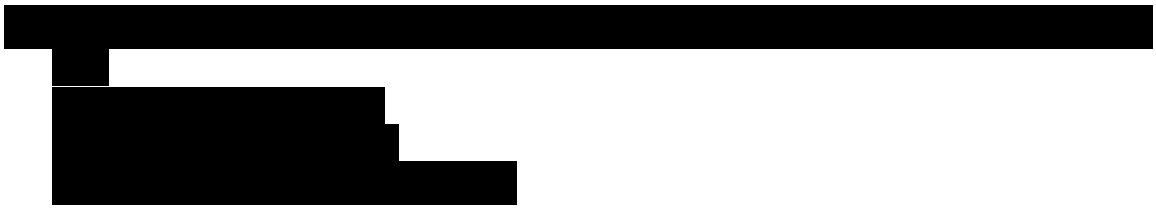
1. Receipt of anticancer therapy or participation in another interventional clinical study within 21 days before the first administration of study drug.
2. Prior treatment with PD-1 or PD-L1 directed therapy (other immunotherapies may be acceptable with prior approval from the medical monitor).
    a. Adjuvant therapy that was completed ≥ 12 months before study entry may be acceptable but should be discussed with the medical monitor before enrolling the participant on study.
3. 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.
    c. 14 days for palliative radiation therapy.
    Note: Participants must have recovered from all radiation-related toxicities, not require corticosteroids for this purpose, and not have had radiation pneumonitis.
4. Toxicity of prior therapy that has not recovered to ≤ Grade 1 or baseline (with the exception of anemia not requiring transfusion support and any grade of alopecia). Endocrinopathy, if well-managed, is not exclusionary and should be discussed with sponsor medical monitor.
5. Participant has not recovered adequately from toxicities and/or complications from surgical intervention before starting study drug.
6. Participants with laboratory values at screening defined in Table 7.

Table 7: Exclusionary Laboratory Values

Laboratory Parameter		Exclusion Criterion
Hematology		
a	Platelets	≤ 100 × 10^9/L
b	Hemoglobin	≤ 9 g/dL
c	ANC	≤ 1.5 × 10^9/L
Hepatic		
d	ALT	> 2.5 × ULN
e	AST	> 2.5 × ULN
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

7. 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.
8. Active autoimmune disease requiring systemic immunosuppression in excess of physiologic maintenance doses of corticosteroids (> 10 mg of prednisone or equivalent).
    a. Physiologic corticosteroid replacement therapy at doses > 10 mg/day of prednisone or equivalent for adrenal or pituitary insufficiency and in the absence of active autoimmune disease is permitted.
    b. Participants with asthma that requires intermittent use of bronchodilators, inhaled steroids, or local steroid injections may participate.
    c. Participants using topical, ocular, intra-articular, or intranasal steroids (with minimal systemic absorption) may participate.
    d. Brief courses of corticosteroids for prophylaxis (eg, contrast dye allergy) or study treatment–related standard premedication are permitted.
9. Evidence of interstitial lung disease or active noninfectious pneumonitis.
10. 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.
11. 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).
12. Active infections requiring systemic therapy.



14. Known hypersensitivity to another mAb that cannot be controlled with standard measures (eg, antihistamines and corticosteroids).
15. 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 (eg, ≥ Grade 3 uncontrolled hypertension).

16. Participant is pregnant or breastfeeding.
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.
20. History of organ transplant, including allogeneic stem cell transplantation.
21. The following patients are excluded in France: vulnerable populations according to article L.1121-6 of the French Public Health code and adults under legal protection or who are unable to express their consent per article L.1121-8 of the French Public Health code.

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
Dosage level:	500 mg Q4W
Route of administration:	IV
Administration instructions:	Administered intravenously over 30 minutes (- 5/+ 15 minutes)
Packaging and labeling:	INCMGA00012 25 mg/mL will be provided in a glass vial for single use 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 to the study site.
- Inventory of study drug at the site.
- Lot numbers and/or vial numbers (as applicable) of study drug used to prepare the infusion solution.
- Return of study drug 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 (see Section 4.1). Management guidelines for immune-related adverse reactions commonly observed with other PD-1 inhibitors are provided in the following sections.

6.5.1. Management of Suspected Infusion Reactions

Infusion or hypersensitivity reactions may be observed with administration of any foreign protein. Premedication with an antipyretic (eg, acetaminophen/paracetamol) and a histamine blocker (eg, diphenhydramine) 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. Grade 3 or 4 infusion reactions should be reported within 24 hours to the study medical monitor regardless of whether criteria for reporting as an SAE are met.

Table 9: Guidelines for Management of Suspected Infusion Reactions

Grade	Description[a]	Treatment	Subsequent Infusions
1	Mild reaction; interrupt or slow the rate of infusion; intervention not indicated.	Monitor vital signs closely until medically stable.	Premedication with an antipyretic (eg, acetaminophen/ paracetamol) and a histamine blocker (eg, diphenhydramine) 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, antipyretic, 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 antipyretic (eg, acetaminophen/ paracetamol 500-1000 mg PO). Additional supportive measures may be acceptable (per institutional preference). Next infusion should start at 50% of the original infusion rate. If no reaction, rate of infusion can be increased by 25% every 15 minutes until a rate of 100% has been reached. Subsequent infusions can begin at 100%.
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, antipyretic, 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.

6.5.2. Management of Suspected 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 INCMGA00012 and other PD-1 inhibitors (eg, pembrolizumab, nivolumab) are provided in Table 10.

Management guidance for irAEs not detailed elsewhere in the Protocol should follow the ASCO or ESMO Clinical Practice Guidelines (Brahmer et al 2018, Haanen et al 2017, Haanen et al 2018, NCCN 2021).

Table 10: Dose Modification and Toxicity Management Guidelines for Immune-Related Adverse Events

Immune-Related Adverse Event	Toxicity Grade or Conditions (CTCAE v5.0)	Action Taken With INCMGA00012	AE Management With Corticosteroid and/or Other Supportive Care Therapies
Pneumonitis	Grade 1	No action.	None.
	Grade 2	Withhold until ≤ Grade 1.	• Administer systemic corticosteroids per local practice followed by taper. • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment. • Add prophylactic antibiotics for opportunistic infections.
	Grades 3 or 4, or recurrent Grade 2	Permanently discontinue.	
Diarrhea/colitis	Grade 1	No action.	None.
	Grades 2 or 3	Withhold until ≤ Grade 1.	• Consider prompt initiation of standard antidiarrheal agents and other necessary supportive care as needed (eg, oral and/or IV fluids). • Administer systemic corticosteroids per local practice followed by taper. • Consider prophylactic antibiotics per local practice. • Consider gastrointestinal consultation and performing endoscopy to rule out colitis.
	Grade 4 or recurrent Grade 3	Permanently discontinue.	

Table 10: Dose Modification and Toxicity Management Guidelines for Immune-Related Adverse Events (Continued)

Immune-Related Adverse Event	Toxicity Grade or Conditions (CTCAE v5.0)	Action Taken With INCMGA00012	AE Management With Corticosteroid and/or Other Supportive Care Therapies
Hepatitis with no tumor involvement of the liver[a]	AST or ALT increases to more than 3 and up to 8 times ULN or Total bilirubin increases to more than 1.5 and up to 3 times ULN	Withhold.	• Administer systemic corticosteroids per local practice followed by taper. • Consider monitoring liver enzymes weekly (or more frequently) until liver enzyme value returns to baseline or is stable.
	AST or ALT increases to more than 8 times ULN or Total bilirubin increases to more than 3 times ULN	Permanently discontinue.	
Hepatitis with tumor involvement of the liver	Baseline AST or ALT is more than 1 and up to 3 times ULN and increases to more than 5 and up to 10 times ULN or Baseline AST or ALT is more than 3 and up to 5 times ULN and increases to more than 8 and up to 10 times ULN	Withhold.	• Administer systemic corticosteroids per local practice followed by taper. • Consider monitoring liver enzymes weekly (or more frequently) until liver enzyme value returns to baseline or is stable.
	ALT or AST increases to more than 10 times ULN or Total bilirubin increases to more than 3 times ULN	Permanently discontinue.	
Endocrinopathies • Type 1 diabetes mellitus • Hyperglycemia • Hyperthyroidism • Hypothyroidism • Adrenal insufficiency	Grades 1 and 2	No action.	None.
	Grades 3 or 4 Type 1 diabetes mellitus (or hyperglycemia)	Withhold until ≤ Grade 1 or is otherwise clinically stable.	Initiate treatment with antihyperglycemics as clinically indicated.
	Grades 3 and 4 hyperthyroidism	Withhold until ≤ Grade 1 or is otherwise clinically stable.	Initiate symptomatic management.
	Grades 3 and 4 hypothyroidism	Withhold until ≤ Grade 1 or is otherwise clinically stable.	Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care.
	Grade 2 adrenal insufficiency	Withhold until ≤ Grade 1 or otherwise clinically stable.	Initiate treatment with hormone replacement as clinically indicated.
	Grades 3 and 4 adrenal insufficiency	Withhold until ≤ Grade 1 after corticosteroid taper to ≤ 10 mg/day prednisone or equivalent or is otherwise clinically stable.	Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper and hormone replacement as clinically indicated.

Table 10: Dose Modification and Toxicity Management Guidelines for Immune-Related Adverse Events (Continued)

Immune-Related Adverse Event	Toxicity Grade or Conditions (CTCAE v5.0)	Action Taken With INCMGA00012	AE Management With Corticosteroid and/or Other Supportive Care Therapies
Endocrinopathies (continued) • Hypophysitis	Grade 1	No action.	None.
	Grade 2 (asymptomatic)	Withhold until ≤ Grade 1. May restart INCMGA00012 treatment after controlled by hormone replacement therapy.	Administer hormonal replacement.
	Grade 2 (symptomatic, eg, headaches, visual disturbances)	Withhold until ≤Grade 1. May restart INCMGA00012 treatment after controlled with hormone replacement, if indicated, and steroid taper is complete.	• Administer corticosteroids at initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper, and initiate other hormonal replacements as clinically indicated. • Consult with endocrinologist as needed.
	Grade 3 or 4 (symptomatic)	Permanent discontinuation should occur if after withholding INCMGA00012 the toxicity does not resolve to ≤ Grade 1 within 12 weeks after last dose of INCMGA00012 treatment, or if corticosteroid dosing cannot be reduced to ≤ 10 mg prednisone or equivalent per day within 12 weeks. Permanent discontinuation of INCMGA00012 should take place earlier at the investigator's discretion, if corticosteroids and/or hormone replacement therapy cannot balance the participant's pituitary function.	• Administer corticosteroids at initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper, and initiate other hormonal replacements as clinically indicated. • Consult with endocrinologist as needed.

Table 10: Dose Modification and Toxicity Management Guidelines for Immune-Related Adverse Events (Continued)

Immune-Related Adverse Event	Toxicity Grade or Conditions (CTCAE v5.0)	Action Taken With INCMGA00012	AE Management With Corticosteroid and/or Other Supportive Care Therapies
Nephritis with renal dysfunction	Grade 1	No action.	None.
	Grade 2 or Grade 3 increased blood creatinine	Withhold until ≤Grade 1.	Administer corticosteroids per local practice followed by taper.
	Grade 4 increased blood creatinine	Permanently discontinue.	
Skin (eg, Stevens-Johnson syndrome, or toxic epidermal necrolysis)	Grade 1	No action.	None.
	Grade 2	No action.	Manage with topical steroids with or without drug interruption.
	Grade 3[b] or persistent Grade 2 (≥ 2 weeks) or suspected Stevens-Johnson syndrome[c]	Withhold until ≤ Grade 1 after corticosteroid taper to ≤ 10 mg/day prednisone or equivalent	• Administer corticosteroids per local practice followed by taper. Additionally, oral antihistamines such as diphenhydramine or famotidine (per institutional preference) may be utilized as needed. • Should refer to dermatology if no resolution with these measures.
	Grade 4 or confirmed Stevens-Johnson syndrome[b] or toxic epidermal necrolysis[d]	Permanently discontinue.	• Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper. • Refer to dermatology consult.
Myocarditis	Grade 2	Depending on severity of symptoms, withhold until symptoms fully resolve and management with corticosteroids is complete. Permanent discontinuation of INCMGA00012 may take place earlier at the investigator's discretion.	• Treatment with systemic corticosteroids should be initiated (initial dose of 1-2 mg/kg per day of prednisone or equivalent). Taper as appropriate. • Manage cardiac symptoms according to standard of care and with guidance from cardiology. Consider cardiac MRI and myocardial biopsy for diagnosis.
	Grades 3 or 4	Permanently discontinue.	
Important nervous system events (eg, Guillain-Barre syndrome, autoimmune encephalitis, myasthenia gravis, autonomic neuropathy, or transverse myelitis)	Grade 2	Withhold until ≤ Grade 1.	• Neurology consultation is recommended for all neurologic irAEs ≥ Grade 2. • Treatment with systemic corticosteroids should be initiated (initial dose of 1-2 mg/kg per day of prednisone or equivalent). Taper as appropriate. • For Grade 2 transverse myelitis consider permanent discontinuation. • Manage symptoms according to standard of care and with guidance from neurology.
	Grades 3 or 4	Permanently discontinue.	

Table 10: Dose Modification and Toxicity Management Guidelines for Immune-Related Adverse Events (Continued)

Immune-Related Adverse Event	Toxicity Grade or Conditions (CTCAE v5.0)	Action Taken With INCMGA00012	AE Management With Corticosteroid and/or Other Supportive Care Therapies
All other irAEs	Grade 2 or Grade 3 based on severity and type of reaction	Withhold until ≤ Grade 1.	Based on severity of AE, administer corticosteroids.
	Recurrent Grade 3 or Persistent Grade 2 and Grade 3	Permanently discontinue.	
	Grade 4 (excluding endocrinopathies)	Permanently discontinue.	

[a] If AST and ALT are less than or equal to ULN at baseline, withhold or permanently discontinue INCMGA00012 based on recommendations for hepatitis with no liver involvement.

[b] Participants with Grade 3 rash in the absence of desquamation, with no mucosal involvement, not requiring systemic steroids, and resolving or improving to ≤ Grade 1 within 14 days do not need INCMGA00012 interrupted. Permanent discontinuation of study drug may be necessary if there is recurrence of Grade 3 after resuming study drug.

[c] Grade 3 Stevens-Johnson syndrome is defined as skin sloughing covering < 10% BSA with associated signs (eg, erythema, purpura, epidermal detachment, mucous membrane detachment). Grade 4 Stevens-Johnson syndrome is defined as skin sloughing covering 10% to 30% BSA with associated signs (eg, erythema, purpura, epidermal detachment, mucous membrane detachment).

[d] Toxic epidermal necrolysis is Grade 4 by definition and is defined as skin sloughing covering ≥ 30% BSA with associated symptoms (eg, erythema, purpura, epidermal detachment).

6.5.3. 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 treatment-related 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

Recommended supportive measures for specific toxicities are described in Section 6.5. Growth factors, bisphosphonates, anticoagulants, and transfusional support will also be permitted per standard institutional practice.

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

6.6.2. Prohibited Medications and Procedures

- Other anticancer therapies, including investigational treatments within 21 days before the first administration of study drug, 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.

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:

- Disease progression (see Section 4.1).
- Unacceptable toxicity as noted in Section 6.5.3.

- 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).
- 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 may be solicited from or collected on the participant.
- 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:

- 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 final safety visit. These visits are described in Table 3 and Table 4. 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 safety and AEs per Sections 8.8 and 9. The 90-day safety visit may be conducted via phone call.

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. However, if a participant actively withdraws consent for collection of follow-up data (safety follow-up), then no additional data collection should occur.

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 and withdrawn from the study if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

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.
- 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.

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.

Some study procedures may be conducted by phone call, where appropriate, or as per institutional guidelines during the COVID-19 pandemic. This information will be described in detail in the ICF. Some tests such as ECG or CT scan assessments may require longer time-windows due to the COVID-19 pandemic and thus may be done outside the regularly scheduled visits or may be conducted at the next scheduled visit. These delays will not be considered protocol deviations if they are due to administrative difficulties or travel restrictions during the COVID-19 pandemic and are documented accordingly. Details may be found in the eCRF guidelines or study monitoring plan, as applicable.

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. Efficacy assessments of response should be performed according to schedule found in Table 3. Scans should follow calendar days 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.

Participants who discontinue study treatment will not require further disease assessments.

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. 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. 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. After completion of the primary efficacy analysis, scans may be performed per the institutional standard of care. Only the overall assessment (eg, response category) by the investigator to support continuation of study drug will be collected in the EDC.

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.

8.2.2. iRECIST

iRECIST is not used to determine efficacy of INCMGA00012 in this study but may be used for patient management with the decision to treat beyond conventional RECIST progression documented in the study file.

Immunotherapeutic agents may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents and can manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions. iRECIST was developed to ensure a consistent methodology for assessing response to immunotherapy (Seymour et al 2017). The use of iRECIST accounts for potentially different response patterns of immunotherapies and includes a requirement for the confirmation of progression to rule out or confirm pseudoprogression, which should be performed between 4 and 8 weeks after the initial determination of iUPD.

8.2.3. Health Economics

Not applicable.

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. Immune-related AEs will be collected until 90 days after the last dose of study drug. The 90-day visit may be conducted via phone call. 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, the participant reaches the end of the study, or the participant is lost to follow-up before the safety follow-up visit (as defined in Section 7.3).

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, weight, 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 11.

Table 11: 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 12. 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.

Abnormal laboratory findings associated with AEs and not associated with the underlying disease are considered clinically significant. All abnormal laboratory assessments considered

clinically significant up to 28 days after the last dose of study treatment should be repeated until the values are no longer considered clinically significant by the investigator.

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.

For participants who are known to be HIV-positive, laboratory checks of HIV viral load and CD4+ cell count will be performed every 8 weeks during the first year of study drug treatment. Frequency of HIV management testing may be reduced to every 3 months during the second year of treatment.

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 12: Required Laboratory Analytes

<table>
<tr><th>Serum Chemistries</th><th>Hematology</th><th>Urinalysis With Microscopic Examination</th><th>Coagulation</th><th>Pregnancy Testing</th></tr>
<tr><td rowspan="2">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</td><td rowspan="2">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</td><td>Color and appearance
pH and specific gravity
Bilirubin
Glucose
Ketones
Leukocytes
Nitrite
Occult blood
Protein</td><td>PT
PTT or aPTT
INR</td><td rowspan="2">Women of childbearing potential</td></tr>
<tr><td>Lipid Panel (Fasting)</td><td>Endocrine Function</td><td>HIV Management</td></tr>
<tr><td></td><td></td><td>Total cholesterol
Triglycerides
LDL
HDL</td><td>Thyroid-stimulating hormone (TSH)
Thyroxine (T4/FT4)[a]
Triiodothyronine (T3/FT3)[a]</td><td>Only applicable for participants known to be HIV-positive
HIV viral load
CD4+ cell count</td></tr>
</table>

Note: Additional tests may be required, as agreed by investigator and sponsor, based on emerging safety data.
[a] If considered standard by the region.

8.4. Pharmacokinetic Assessments

Assessment of PK is an important objective of this study, representing the first clinical experience with administration of INCMGA00012 as a 30-minute infusion. Blood samples for PK [redacted] analysis will be obtained at the visits and timepoints indicated in Table 4.

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

8.5.1. Description of Analyses

Additional optional specimens may be collected at any time during study to assess changes associated with safety, efficacy, or resistance to treatment. [redacted]

Analyses will be conducted by Incyte Corporation (Wilmington, DE) or Incyte's designee. The collection schedule is found in Table 4. [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. 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.

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.

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 or until the participant begins a new anticancer therapy, whichever occurs first. 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 the new anticancer therapy is started.

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 <u>Meeting</u> 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 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 or the start of a new anticancer therapy, whichever occurs first. 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, the participant completes study, 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. Suspected unexpected serious adverse reactions 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 suspected unexpected serious adverse reactions 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 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

Adverse events that are potentially immune-related will be assessed as AEs of special interest. Examples of these (including diagnostic algorithms to be followed) are provided in the Study Procedures Manual.

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

This study is planned as a signal-finding study for efficacy in tumor types of interest for future development. Approximately 30 participants are planned to be enrolled in each disease-specific cohort to provide a preliminary assessment of efficacy, safety, and PK. The response rate and 95% CI for each disease cohort based on 30 participants are provided in Table 13. The relevant benchmarks are provided in Table 5.

Table 13: Response Rate and 95% Confidence Interval

Sample Size	Number of Responses	Response Rate (%)	95% CI (%)
30	3	10.0	2.1, 26.5
30	5	16.7	5.6, 34.7
30	7	23.3	9.9, 42.3
30	9	30.0	14.7, 49.4
30	11	36.7	19.9, 56.1
30	12	40.0	22.7, 59.4

10.2. Populations for Analysis

Table 14 presents the populations for analysis.

Table 14: Populations for Analysis

Population	Description
Full analysis set	The FAS includes all study participants who have received at least 1 dose of study drug. Participants will be analyzed based on disease-specific diagnosis. The FAS will be used for demographics, baseline characteristics, and all efficacy analysis.
Safety evaluable	The safety evaluable population includes all participants who received at least one dose of study drug. All safety analyses will be conducted using the safety evaluable population. In this study, the FAS and safety evaluable population are identical.
PK evaluable	The PK evaluable population will include all participants who received at least 1 dose of study drug and have provided a baseline and at least 1 postdose PK sample.

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

All efficacy analyses will be performed independently for each disease cohort.

10.4.1.1. Overall Response Rate

The primary endpoint of the study is ORR, defined as the proportion of participants with an objective response (CR or PR), according to RECIST v1.1 (Eisenhauer et al 2009) as determined by the investigator. The primary analysis of ORR will be based on the FAS population as defined in Table 14 and will be performed once all participants on study treatment have been followed for at least 6 months from the start of treatment or prematurely discontinued study treatment. Overall response rate and its exact 95% CI will be presented. Overall response rate will not be recalculated after the primary analysis is performed.

10.4.1.2. Handling of Missing Data in Primary Analysis

A response assessment of CR or PR reported before any additional anticancer therapy will be considered as a response in the calculation of ORR irrespective of the number of missed assessments before response. Participants with subsequent missing assessments that prevent the evaluation of the primary endpoint will be considered as nonresponders. No data imputation will be applied.

10.4.2. Secondary Analysis

10.4.2.1. Duration of Response

Duration of response is defined as the time from first objective response (CR or PR) to the time of first documented disease progression according to RECIST v1.1 or death due to any cause. If a participant does not have disease progression or death, the DOR will be censored at the date of the last adequate tumor assessment before data cutoff or new anticancer therapy. The Kaplan-Meier estimate of the distribution function will be constructed for DOR. The estimated median along with 95% CI will be reported.

10.4.2.2. Disease Control Rate

Disease control rate is defined as the proportion of participants with either an objective response (CR or PR) or SD, according to RECIST v1.1.

10.4.2.3. Progression-Free Survival

Progression-free survival, defined as the time from first dose of study drug 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 an event is not observed, PFS will be censored at the 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 drug to the date of death due to any cause. Kaplan-Meier estimate of OS will be provided, including median and its 95% CI. Participants still alive at time of analysis will be censored at the date last confirmed to be 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 evaluable population. Adverse events will be coded by the MedDRA dictionary, and TEAE (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. 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.

10.4.3.3. Vital Signs

Descriptive statistics and mean change from baseline will be determined for vital signs (blood pressure, pulse, respiratory rate, weight, 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.

10.4.3.4. Electrocardiograms

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

10.4.3.5. Dose Intensity

Measures of exposure (eg, days of exposure, dose intensity) 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.

[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.

The sponsor (or designee) will be responsible for:

- The data management of this study including quality checking of the data.
- 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.

The investigator will be responsible for:

- Ensuring participant data relating to the study is recorded in the eCRF unless transmitted to the sponsor or designee electronically (eg, laboratory data, diary data) or as otherwise specified in the Protocol. The investigator is responsible for 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.
  - 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 reported on the CRF or 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 medical records must be available.
- 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. The sponsor reserves the right to review radiology studies that were used in determining response to study drug at any point during conduct of the study.

- 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. 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 subject 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 from screening 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 from screening 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:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[a]
  - oral
  - intravaginal
  - transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation[a]
  - oral
  - injectable
  - implantable[b]
- Intrauterine device[b]
- Intrauterine hormone-releasing system[b]
- Bilateral tubal occlusion[b]
- Vasectomized partner[bc]
- Sexual abstinence[d]

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[e]
- Cap, diaphragm, or sponge with spermicide[e]
- Tubal ligation

[a] Hormonal contraception may be susceptible to interaction with the investigational medicinal product, which may reduce the efficacy of the contraception method.

[b] Contraception methods that in the context of this guidance are considered to have low user dependency.

[c] Vasectomized partner is a highly effective method of avoiding pregnancy provided that partner is the sole sexual partner of the woman of childbearing potential study participant and that the vasectomized partner has received medical assessment of the surgical success.

[d] 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 treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the participant.

[e] 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: Clinical Trial Facilitation Group 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:	17 JAN 2019
Amendment (Version) 1-FR:	11 JUN 2019
Amendment (Version) 2:	09 AUG 2019
Amendment (Version) 3:	10 DEC 2019
Amendment (Version) 4:	25 NOV 2020
Amendment (Version) 5:	23 JUN 2021

Amendment 5 (23 JUN 2021)

Overall Rationale for the Amendment: The purpose of this amendment is to update the guidelines for management of suspected immune related events.

1. **Section 1, Protocol Summary (Table 2: Key Study Design Elements)**

   Description of change: Under the estimated study duration of study participation section, the sentence about participants participating in the study for up to approximately 3 years was removed.

   Rationale for change: This sentence is no longer relevant. Starting with Protocol Amendment 4, survival follow-up is not required for participants who have discontinued active treatment after the primary efficacy analysis is completed. Participants will be followed for irAEs for 90 days after the last dose of study drug or until the participant begins a new anticancer therapy, whichever occurs first and will complete the study at the end of this period.

2. **Section 6.5.1, Management of Suspected Infusion Reactions (Table 9: Guidelines for Management of Suspected Infusion Reactions)**

   Description of change: The guidance for Grade 1infusion reaction in Table 9 was revised from interruption is not indicated to interrupt or slow the rate of infusion.

   Rationale for change: To align with guidance regarding Grade 1 infusion reaction to reflect the most recent information available with INCMGA00012 and other PD-1 inhibitors (eg, pembrolizumab, nivolumab).

3. **Section 6.5.2, Management of Suspected Immune-Related Adverse Events (Table 10: Dose Modification and Toxicity Management Guidelines for Immune-Related Adverse Events)**

   Description of change: Guidance was updated for management of diarrhea/colitis, hepatitis, endocrinopathies, nephritis, skin, myocarditis, and all other irAEs.

   Rationale for change: To align with updated information available for immune-related AEs known to be associated with INCMGA00012 and other PD-1 inhibitors (eg, pembrolizumab, nivolumab). Guidance regarding hypophysitis was updated in response to the request received from the regulatory agency in France.

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 4 (25 NOV 2020)

Overall Rationale for the Amendment: The main purpose of this amendment is to minimize the burden of data collection for ongoing participants after the primary objective of the study has been achieved.

1. **Section 1, Protocol Summary (Table 2: Key Study Design Elements)**

   Description of change: The coordinating principal investigator for the study was added.

   Rationale for change: To identify the study's coordinating principal investigator.

2. **Section 1, Protocol Summary (Table 3: Schedule of Activities)**

   Description of change: Lipid panel, coagulation panel, and urinalysis assessments have been updated to only be required at screening.

   Rationale for change: Based on the safety information from the 2020 IB (23 SEP 2020 data-cut), there are no safety issues with the study drug that warrant continuation of these tests at routine intervals.

3. **Section 1, Protocol Summary (Table 2: Key Study Design Elements; Table 3: Schedule of Activities); Section 4.1, Overall Design; Section 4.2, Overall Study Duration; Section 6.7, Treatment After the End of the Study; Section 7.1.1, Reasons for Discontinuation; Section 7.1.2, Discontinuation Procedures; Section 7.3, Lost to Follow-Up; Section 8.2, Efficacy Assessments; Section 8.2.1 Tumor Imaging; Section 8.3.1 Adverse Events; Section 8.3.6, Laboratory Assessments; Section 8.8.2, Post-Treatment Disease Follow-Up; Section 8.8.3, Survival Follow-Up**

   Description of change: Added clarification that disease follow-up and survival follow-up are not required after the primary efficacy analysis is completed. Relevant text requiring disease follow-up and survival follow-up visits and associated assessments was removed.

   Rationale for change: Per Section 10.4.1.1, the primary efficacy analysis will be performed once all participants have been followed for at least 6 months from the start of treatment or discontinued prematurely. The last participant was enrolled in the study in APR 2020, and all participants have been followed for at least 6 months or discontinued. For this type of benchmark study, it is sufficient for the secondary endpoint of OS to be estimated from the available participant information from the start of study treatment to the time of efficacy analysis. Additional data from disease follow-up and survival follow-up are no longer required.

4. **Section 1, Protocol Summary (Table 3: Schedule of Activities); Section 4.1 Overall Design; Section 4.2, Overall Study Duration; Section 7.1.2, Discontinuation Procedures; Section 8.3.1 Adverse Events; Section 8.8.1 Safety Follow-Up; Section 9.4, Reporting of Serious Adverse Events**

   Description of change: Provided clarification that all AEs and SAEs will be collected for 28 days after the last dose of study drug, whereas irAEs will be collected until 90 days after the last dose of study drug or until the start of a new anticancer therapy, whichever occurs first. A 90-day visit can be performed by phone.

Rationale for change: Unconfounded safety assessments will no longer be possible once a new therapy has begun, and delaying treatment with other anticancer therapies is not an option for participants with progressive cancer.

5. **Section 1, Protocol Summary, Section 8.1.4 Distribution of Reminder Cards**

   Description of change: Added clarification that some procedures may be conducted by phone call, where appropriate, or as per institutional guidelines during the COVID-19 pandemic. Due to COVID-19 pandemic, some tests may be done outside the regularly scheduled visits or may be conducted at the next scheduled visit. Details may be found in the eCRF guidelines or study monitoring plan, as applicable.

   Rationale for change: To provide flexibility with study visits for the safety of participants during the COVID-19 pandemic.

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

   Description of change: [redacted]

   Rationale for change: [redacted]

7. **Section 4.2, Overall Study Duration**

   Description of change: No participant will be followed for longer than 27 months (ie, 2 years of study treatment followed by 90 days of observation for irAEs in the event the participant does not discontinue treatment prematurely or start a new anticancer therapy).

   Rationale for change: To clarify the duration of study participation and to specify that the study will end when the last participant completes 90 days of safety follow-up for irAEs.

8. **Section 6.5.2, Management of Suspected Immune-Related Adverse Events (Table 10: Dose Modification and Toxicity Management Guidelines for Immune-Related Adverse Events)**

   Description of change: Action taken with INCMGA00012 for Grade 2 myocarditis was updated from withhold until ≤ Grade 1 to withhold until symptoms resolve and management with corticosteroids is complete.

   Rational for change: Adverse event toxicity assessment is done per NCI CTCAE v5.0 in this study, and Grade 1 myocarditis is not included in this version.

9. **Section 8.3.6, Laboratory Assessments**

   Description of change: All abnormal laboratory values associated with AEs are considered clinically significant and will be followed for up to 28 days instead of 90 days after the last dose of study treatment.

Rationale for change: Based on the safety information from the 2020 IB (23 SEP 2020 data-cut), 90-day follow-up is not required, which negates the rationale for extended safety assessments following completion of study drug.

10. **Section 8.3.6, Laboratory Assessments (Table 12: Required Laboratory Analytes)**

    Description of change: Added FT4 so that sites can use either a total T4 or free T4 test.

    Rationale for change: The FT4 test a standard practice at several participating sites.

11. **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 (10 DEC 2019)

Overall Rationale for the Amendment: The main purpose of this amendment is to adjust the overall study enrolment and statistical analysis, remove interim analysis and update the guidance for suspected immune related AEs based on the data from ongoing studies with INCMGA00012 and recent IB update.

1. **Section 1, Protocol Summary; Section 10.1, Sample Size Determination; Section 10.5, Interim Analysis**

   Description of change: Enrollment for each disease-specific cohort was reduced from approximately 40 participants per cohort to approximately 30 participants per cohort, and overall study enrollment was reduced from approximately 160 participants to approximately 120 participants. Statistical analysis assumptions were revised based on the revised enrollment numbers, and the interim analysis was removed.

   Rationale for change: This study is planned as a signal-finding study for efficacy in tumor types of interest for future development. Approximately 30 participants in each disease-specific cohort is sufficient to provide a preliminary assessment of efficacy, safety, and PK. Based on the revised enrollment numbers, the response rate and 95% CIs were updated and an interim analysis was no longer needed.

2. **Section 1, Protocol Summary (Table 3: Schedule of Activities); Section 10.4.3.4, Electrocardiograms**

   Description of change: On-study ECG assessments were removed. Participants are now required to have ECG assessments at screening and at the safety follow-up visit. Additional ECGs may be performed as clinically indicated to manage participant safety.

   Rationale for change: INCMGA00012 does not demonstrate a large effect on the QTc interval (ie, > 20 milliseconds) based on extensive assessment in Study INCMGA 0012-101 (refer to the IB).

3. **Section 1, Protocol Summary (Table 3: Schedule of Activities)**

   Description of change: Frequency of urinalysis was changed from every 3 cycles to every 6 cycles.

   Rationale for change: Based on data from ongoing INCMGA0012 studies, there are no safety signals to indicate frequent urinalysis assessments are required.

4. **Section 3, Objectives and Endpoints (Table 6: Objectives and Endpoints); Section 8.2, Efficacy Assessments; Section 8.2.2, iRECIST; Section 10.4.5.3, Immune-Based RECIST Assessments**

   Description of change: [redacted] Section 8.2.2 was updated to indicate iRECIST is not used to determine efficacy of INCMGA00012 but may be used for patient management.

   Rationale for change: Historical ORRs were assessed using RECIST (Table 5: Activity of Other PD-1 Inhibitors), and this is the relevant methodology for benchmarking comparisons.

5. **Section 1, Protocol Summary; Section 4.2, Overall Study Duration**

   Description of change: Revised to specify how long participants will be followed for survival.

   Rationale for change: For the purpose of clarification.

6. **Section 5.2, Exclusion Criteria**

   Description of change: Criterion 2 was updated to indicate prior adjuvant therapy completed ≥ 12 months before study entry may be allowed but should be discussed with the medical monitor.

   Rationale for change: Received investigator feedback that these patients should be allowed to participate in the study.

7. **Section 6.5.2, Management of Suspected Immune-Related Adverse Events (Table 10: Dose Modification and Toxicity Management Guidelines for Immune-Related Adverse Events)**

   Description of change: Guidelines for management of nervous system–related events were added.

   Rationale for change: Guidelines were updated based on the data from the ongoing studies with INCMGA00012 and recent IB update.

8. **Section 8.3.3, Vital Signs; Section 10.4.3.3 Vital Signs**

   Description of change: Weight was added to vital signs data collection.

   Rationale for change: For the purpose of clarification.

9. **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 (09 AUG 2019)

Overall Rationale for the Amendment: The main purpose of this amendment is to update the Protocol based on the information from the ongoing Phase 1 study, INCMGA 0012-101, and to update the PK sample collection schedule.

1. **Incorporate changes from Amendment 1-FR (11 JUN 2019)**

   Description of change: Changes as listed in Amendment 1-FR (11 JUN 2019).

   Rationale for change: To align Protocol Amendment 2 as appropriate for all regions.

2. **Section 1, Protocol Summary; Section 4.1, Overall Design**

   Description of change: Criteria for treatment delays due to toxicity were removed and replaced with a cross-reference to Section 6.5 (Dose Modifications) and Table 10.

   Rationale for change: Guidelines for dose modification and toxicity management are provided in Section 6.5, Table 10.

3. **Section 1, Protocol Summary (Table 3: Schedule of Activities)**

   Description of change: Added text that for ECG tests, either Fridericia or Bazett method of correction is acceptable for QT.

   Rationale for change: For clarification.

4. **Section 2.1.1, INCMGA00012**

   Description of change: Provided updated data from the ongoing Phase 1 study, INCMGA 0012-101.

   Rationale for change: To include recent safety information.

5. **Section 2.2, Rationale for Study Design**

   Description of change: Additional rationale for the study design provided.

   Rationale for change: To provide additional information and clarification.

6. **Section 2.2.2, Dose and Schedule**

   Description of change: Revised the PK data based on the updates from the ongoing Phase 1 study, INCMGA 0012-101.

   Rationale for change: To include recent PK information.

7. **Section 2.3 Benefit/Risk Assessment**

   Description of change: Provided additional justification for expecting efficacy in this study based on recent publications.

   Rationale for change: New information from recent data.

8. **Section 4.1, Overall Design; Section 5.1, Inclusion Criteria (Criterion 3b)**

   Description of change: Added the text to indicate that cisplatin ineligibility in participants with UC will be determined by the investigator.

   Rationale for change: For clarification.

9. **Section 5.2, Exclusion Criteria**

   a. **Description of change:** Exclusion criterion 3 was updated to include a caveat for palliative radiation therapy: that participants must have recovered from all radiation-related toxicities, not require corticosteroids for this purpose, and not have had radiation pneumonitis.

   Rationale for change: To clarify when prior palliative radiation therapy is allowed.

   b. **Description of change:** Exclusion criterion 7 was updated to include more specific information regarding additional malignancies that are excluded (ie, additional malignancy that is progressing or requires active treatment, or history of other malignancy within 3 years of study entry with exceptions noted).

   Rationale for change: To provide clarification regarding exclusion of additional malignancies.

   c. Description of change: Exclusion criterion 8 was updated to include additional guidance on active autoimmune disease requiring systemic immunosuppression.

   Rationale for change: To provide clarification and to be consistent with Incyte's standard protocol text for INCMGA0012 studies.

   d. **Description of change:** In exclusion criterion 15 (cardiac function and disease), 15b (unstable angina pectoris) was updated to remove the time frame of ≤ 6 months before study participation, and 15d (other clinically significant heart disease) was updated to only include ≥ Grade 3 uncontrolled hypertension as an example.

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

10. **Section 5.2, Exclusion Criteria (Criterion 13c); Section 6.6.1, Permitted Medications and Procedures**

    Description of change: Highly active antiretroviral therapy was changed to antiretroviral therapy.

    Rationale for change: These terms are now considered synonymous.

11. **Section 6.1, Study Treatments Administered (Table 8: Study Drug Information)**

    Description of change: An infusion time range of -5/+ 15 minutes was added to the INCMGA00012 administration instructions.

    Rationale for change: Updated based on supportive CMC information.

12. **Section 1, Protocol Summary (Table 3: Schedule of Activities); Section 6.5.1, Management of Suspected Infusion Reactions (including Table 9: Guidelines for Management of Suspected Infusion Reactions)**

    Description of change: Removed the requirement for premedication prophylaxis before the first dose of INCMGA00012 and added guidance to Table 9 for infusion rate for subsequent infusions.

    Rationale for change: Updated for consistency with the INCMGA00012 IB and to provide additional guidance to investigators.

13. **Sections 6.5.1, Management of Suspected Infusion Reactions (Table 9: Guidelines for Management of Suspected Infusion Reactions); Section 9.3, Recording and Follow-Up of Adverse Events and/or Serious Adverse Events**

    Description of change: NCI CTCAE v4.3 was updated to NCI CTCAE v5.0.

    Rationale for change: Updated version **(**NCI CTCAE v5.0) will be used for grading AEs.

14. **Section 6.5.2, Management of Suspected Immune-Related Adverse Events**

    Description of change: This section was updated with revised Table 10 (Dose Modification and Toxicity Management Guidelines for Immune-Related Adverse Events). Previous Sections 6.5.2.1 to 6.5.2.6 have been removed as the information is now presented in Table 10.

    Rationale for change: Guidelines were updated based on recent information from other checkpoint inhibitors and ASCO guidelines. Sections were consolidated to present the guidelines for all irAEs in 1 table.

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

    Description of change: Added probiotic dietary supplements to the list of prohibited medications and procedures.

    Rationale for change: Updated based on emerging epidemiologic evidence.

[redacted]

17. **Section 1, Protocol Summary (Table 4: Pharmacokinetic [redacted] Sample Collections); Section 8.4, Pharmacokinetic Assessments**

    Description of change: The PK sample collection schedule was updated. An additional PK sample was added on Cycle 4 Day 1 at 10 minutes (±10 minutes) postinfusion. Collection of some PK samples at selected centers was revised; PK samples will be collected at all sites.

    Rationale for change: To collect adequate PK data from this study.

18. **Section 10.1, Sample Size Determination**

    Description of change: Provided information about statistical power used for sample calculations.

    Rationale for change: For clarification.

19. **Section 10.4.1.2, Handling of Missing Data in Primary Analysis**

    Description of change: Information regarding the handling of missing data for the primary endpoint was added.

    Rationale for change: This information was not previously included in the Protocol.

20. **Section 8.3.6, Laboratory Assessments (Table 12: Required Laboratory Analytes)**

    Description of change: Additional names were added for thyroid analytes.

    Rationale for change: For clarification.

21. **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 1-FR (11 JUN 2019)

Overall Rationale for the Amendment: The purpose of this amendment is to add the country-specific information as requested by the ethics committee in France.

1. **Section 5.2, Exclusion Criteria (Exclusion Criterion #21)**

   Description of change: Added Exclusion Criterion #21:

   The following patients are excluded in France: vulnerable populations according to article L.1121-6 of the French Public Health code and adults under legal protection or who are unable to express their consent per article L.1121-8 of the French Public Health code.

   Rationale for change: Provide clarification about patient populations that are excluded per French Public Health code.

2. **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 1 (17 JAN 2019)

Overall Rationale for the Amendment: The primary purpose of this amendment is to address comments regarding the design of the study.

1. **Section 5.2, Exclusion Criteria (Exclusion Criterion #11)**

   Description of change: Added known active HAV infection to Exclusion Criterion #11:

   > Known active HAV~~HBA~~, 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).

   Rationale for change: To add consistency to Exclusion Criterion #11.

2. **Section 5.2, Exclusion Criteria (Exclusion Criterion #20)**

   Description of change: Added Exclusion Criterion #20:

   > History of organ transplant, including allogeneic stem cell transplantation.

   Rationale for change: To clarify the exclusion of allogeneic organ or hematopoietic stem cell transplant patients.

3. **Section 10.5, Interim Analysis**

   Description of change: Added details to the interim analysis.

   > The study will be stopped for futility if less than 4 out of 20 subjects responded at the time of the interim analysis.

   Rationale for change: To include information regarding the interim analysis.

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.