Official Title: A Phase 2 Study of INCMGA00012 in Participants With Metastatic Merkel Cell Carcinoma (POD1UM-201)

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Clinical Study Protocol

INCMGA 0012-201

A Phase 2 Study of INCMGA00012 in Participants With Metastatic Merkel Cell Carcinoma (POD1UM-201)

Product:	**INCMGA00012**
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Phase of Study:	**2**
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INVESTIGATOR'S AGREEMENT

I have read the INCMGA 0012-201 Protocol Amendment 7 (Version 7 dated 16 DEC 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
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
CI	confidence interval
CNS	central nervous system
COVID-19	coronavirus disease 2019
CR	complete response according to RECIST v1.1
CRF	case report form
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCR	disease control rate
DMC	Data Monitoring Committee
[redacted]	[redacted]
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EOT	end of treatment
[redacted]	[redacted]
ESMO	European Society for Medical Oncology
[redacted]	[redacted]
FAS	full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
HDL	high-density lipoprotein
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
[redacted]	[redacted]

Abbreviations and Special Terms	Definition
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
[redacted]	[redacted]
[redacted]	[redacted]
ICR	Independent Central Radiographic Review
IEC	independent ethics committee
[redacted]	[redacted]
INR	international normalized ratio
[redacted]	[redacted]
irAE	immune-related adverse event
IRB	institutional review board
[redacted]	[redacted]
IRT	interactive response technology
[redacted]	[redacted]
[redacted]	[redacted]
IV	intravenous
LDL	low-density lipoprotein
MCC	Merkel cell carcinoma
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
mRNA	messenger RNA
MTD	maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NE	not evaluable
ORR	overall response rate
OS	overall survival
PD	progressive disease
PD-1	programmed cell death protein 1
PD-L1	programmed cell death ligand protein 1
PFS	progression-free survival
PK	pharmacokinetic(s)
PR	partial response according to RECIST1.1
[redacted]	[redacted]

Abbreviations and Special Terms	Definition
PT	prothrombin time
PTT	partial thromboplastin time
Q2W	once every 2 weeks
Q4W	once every 4 weeks
RECIST v1.1	Response Evaluation Criteria in Solid Tumors version 1.1
[redacted]	[redacted]
RNAseq	ribonucleic acid sequencing
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2 (a strain of the coronavirus family causing coronavirus disease 2019)
SD	stable disease
TCR	T-cell receptor
TEAE	treatment-emergent adverse event
TIL	tumor-infiltrating lymphocytes
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
UV	ultraviolet
WBC	white blood cell

1. PROTOCOL SUMMARY

Protocol Title: A Phase 2 Study of INCMGA00012 in Participants With Metastatic Merkel Cell Carcinoma (POD1UM-201)

Protocol Number: INCMGA 0012-201

Objectives and Endpoints:

Primary and secondary endpoints and objectives are presented in Table 1.

Table 1: Primary and Secondary Objectives and Endpoints

Objectives	Endpoints
Primary	
To determine the efficacy of INCMGA00012 in terms of the ORR in chemotherapy-naive participants with advanced/metastatic MCC.	ORR, defined as the percentage of participants having an objective response (CR or PR), according to RECIST v1.1, as determined by ICR.
Secondary	
To determine the DOR, DCR, PFS, and OS in the chemotherapy-naive population with advanced/metastatic MCC treated with INCMGA00012.	• DOR, defined as the time from an initial objective response (CR or PR) according to RECIST v1.1 until disease progression, or death due to any cause, as determined by ICR. • DCR, defined as the proportion of participants with either an objective response or SD lasting at least 6 months. • PFS, defined as the time from the start of therapy until disease progression, or death due to any cause, as determined by the ICR. • OS, defined as the time from the start of therapy until death due to any cause.
To evaluate the safety of INCMGA00012 in participants with advanced/metastatic MCC.	Safety, determined by the number, frequency, duration, and severity of AEs using CTCAE v5.0; laboratory tests; vital signs; and ECGs.
To determine the PK of INCMGA00012 administered to participants with advanced/metastatic MCC.	The PK of INCMGA00012 when given to participants with advanced/metastatic MCC, including C_{max}, t_{max}, C_{min}, and AUC_t, will be summarized.

Overall Design:

Key study design elements are presented in Table 2. Further study details are presented after the table.

Table 2: Key Study Design Elements

Study Phase	Phase 2
Clinical Indication	Advanced/Metastatic MCC
Population	Male and female participants at least 18 years of age who have been diagnosed with advanced/metastatic MCC. Participants must be chemotherapy-naive to be eligible. Participants who had received prior chemotherapy for MCC were enrolled up to Amendment 4.
Number of Participants	Approximately 100 chemotherapy-naive participants will be enrolled. The primary analysis is planned with approximately 60 chemotherapy-naive participants, while the additional participants will be enrolled to support confirmation of efficacy and provide additional information on safety.
Study Design	This is a Phase 2, open-label, single-arm, multicenter study.
Estimated Duration of Study Participation	Participants will participate in the study for up to approximately 3 years. 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 will go to follow-up until study completion (see Section 4.2).
DSMB/DMC	Yes (external)

Treatment Groups and Duration:

This study will enroll participants with advanced/metastatic MCC who are chemotherapy-naive. Participants with locally advanced disease are eligible only if they have had a recurrence following locoregional therapy and are not considered amenable to further curative therapy with surgery or radiation. The participants should not have received any prior therapy with PD-1/PD-L1 inhibitors. Participants will be required to provide a tumor biopsy (fresh or archival), at screening for central pathology review. Participants may be enrolled and initiate treatment before receiving results from the central pathology review. All enrolled participants will receive INCMGA00012 at the recommended Phase 2 dose of 500 mg IV Q4W. The primary endpoint is ORR in chemotherapy-naive participants as determined by ICR according to RECIST v1.1 (Eisenhauer et al 2009).

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

Treatment with study drug may continue 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.

Eligible participants will receive treatment with single-agent INCMGA00012 500 mg. Treatment will be administered by IV infusion over 60 minutes on Day 1 of each 28-day cycle. Subsequent treatment cycles should be delayed until the following criteria are met:

- Resolution of all immune-related toxicity to ≤ Grade 1 (with the exception of endocrinopathy that is controlled on hormonal replacement)
- Resolution of all non–immune-related toxicity to ≤ Grade 1 or baseline (with the exception of alopecia or non–transfusion-dependent anemia).
  Note: transient asymptomatic laboratory elevations ≤ Grade 3 do not require dose interruption if the participant is asymptomatic, and if the elevation is clinically insignificant and has been discussed with the medical monitor.

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 delays of > 12 weeks for logistical reasons (eg, travel restrictions due to COVID-19) may be acceptable but must be discussed with the medical monitor.

The follow-up period will begin once a participant has completed or prematurely discontinued the study treatment. Participants will be evaluated for AEs and other safety parameters for up to 90 days after the last dose of study treatment or until the start of new anticancer therapy, whichever occurs first. All participants entering follow-up will be assessed for survival until study completion. Participants who enter the follow-up period without experiencing disease progression will continue tumor assessments according to the schedule of activities until they experience disease progression, the start of a new anticancer treatment, withdrawal of consent, lost to follow-up, the end of the study, or death.

The complete study-specific schedule of activities required for participants in this clinical study is presented in Table 3. Details regarding the sample collection for PK [redacted] analyses are defined in Table 4. The analytes to be evaluated in the safety laboratory analyses are found in Table 22. Adherence to the study design requirements, including those specified in the schedule of activities, is essential and required for study conduct.

Table 3: Schedule of Activities

Visit Day (Range)	Screening	Treatment			EOT*	Follow-Up		Notes
	28 Days	Cycle 1 Day 1	Cycle ≥ 2 Day 1 (± 7 d)	Q8W (± 7 d)		Safety 28 Days After Last Dose (± 7 d)*	Survival Q12W (± 14 d)	*** If EOT visit is > 21 days after the last dose, the EOT visit will also serve as the 28-day follow-up visit, and all EOT and 28-day follow-up required assessments will be performed. If EOT is ≤ 21 days after the last dose, the 28-day follow-up visit is required.**
Administrative procedures								
Informed consent	X							
Interactive Response Technology	X	X	X		X			
Inclusion/exclusion criteria	X							
General and disease medical history	X							
Prior/concomitant medications	X	X	X		X	X*		* Concomitant Medications are collected from signing of the ICF until 90 days after the final dose of study drug or until the start of new anticancer therapy, whichever occurs first.
Administer INCMGA00012		X	X					Monitor participants for infusion reactions as per institutional guidelines.
Safety assessments								
AE assessments	X*	X	X		X	X*		* Adverse events are collected from signing of the ICF until 90 days after the final dose of study drug or until the start of new anticancer therapy, whichever occurs first.
Physical examination	X	X	X			X		A comprehensive examination is performed at screening and 28-day safety follow-up. All other scheduled examinations will be targeted.
Vital signs	X	X	X			X		
12-lead ECG	X	X	X*			X		* Performed every third cycle (C4, C7, C10, etc).
ECOG performance status	X	X	X			X		
Efficacy assessments								
Tumor imaging/response assessments	X			X			X*	Includes photography of skin disease (if target lesions). Response assessments are to be performed every 8 weeks for the first 12 months (including the Week 56 scan) and then every 12 weeks thereafter. * Scans during follow-up will only be performed for participants continuing to be followed for disease status.
[redacted]								

Table 3: Schedule of Activities (Continued)

Visit Day (Range)	Screening	Treatment			EOT*	Follow-Up		Notes
	28 Days	Cycle 1 Day 1	Cycle ≥ 2 Day 1 (± 7 d)	Q8W (± 7 d)		Safety 28 Days After Last Dose (± 7 d)*	Survival Q12W (± 14 d)	*** If EOT visit is > 21 days after the last dose, the EOT visit will also serve as the 28-day follow-up visit, and all EOT and 28-day follow-up required assessments will be performed. If EOT is ≤ 21 days after the last dose, the 28-day follow-up visit is required.**
Post study anticancer therapy status					X	X	X	
Survival status							X	Participants may be contacted for survival status at any time during the course of the study.
Clinical laboratory assessments								
Blood chemistries	X	X*	X			X		* Not necessary on C1D1 if performed during screening within 7 days on C1D1.
Hematology	X	X*	X			X		* Not necessary on C1D1 if performed during screening within 7 days on C1D1.
Fasting lipid panel	X		X*					Participants are expected to fast prior to sample collection for all lipid panel analyses. * Performed every third cycle (C4, C7, C10, etc).
Coagulation panel	X		X*					* Performed every third cycle (C4, C7, C10, etc).
Endocrine panel	X		X					
Urinalysis	X		X*					* Performed every third cycle (C4, C7, C10, etc).
Pregnancy testing	X	X*	X			X		Serum pregnancy test is performed at screening and 28 days after the last dose. For other cycles, either urine- or serum-based testing is acceptable. * Not necessary on C1D1 if performed during screening within 7 days on C1D1.
[redacted]								

Table 4: Pharmacokinetic [redacted] Sample Collections

Sample	Collection	Purpose/ Analysis	Screening	Treatment Period								EOT*	Notes
			28 Days	Cycle 1 Day 1	Cycle 2 Day 1 (± 7 d)	Cycle 4 Day 1 (± 7 d)	Cycle 6 Day 1 (± 7 d)	Cycle 7 Day 1 (± 7 d)	Cycle 8 Day 1 (± 7 d)	Cycle 10 Day 1 (± 7 d)	Cycle 12 Day 1 (± 7 d)		*** PK [redacted] samples are only collected at the EOT visit, including if the EOT visit also serves as the 28-day safety follow-up visit**
Whole blood	PK serum	PK		X*	X	X	X*	X					Samples will be collected preinfusion on Day 1 of Cycles 1, 2, 4, 6, and 7. * Samples are collected 10 minutes postinfusion (± 10 minutes) and 4 hours postinfusion (± 15 minutes) on Day 1 of Cycles 1 and 6.
[redacted]													

Table 4: Pharmacokinetic [redacted] Sample Collections (Continued)

Sample	Collection	Purpose/ Analysis	Screening	Treatment Period								EOT*	Notes
			28 Days	Cycle 1 Day 1	Cycle 2 Day 1 (± 7 d)	Cycle 4 Day 1 (± 7 d)	Cycle 6 Day 1 (± 7 d)	Cycle 7 Day 1 (± 7 d)	Cycle 8 Day 1 (± 7 d)	Cycle 10 Day 1 (± 7 d)	Cycle 12 Day 1 (± 7 d)		* PK [redacted] samples are only collected at the EOT visit, including if the EOT visit also serves as the 28-day safety follow-up visit
[redacted]													

2. INTRODUCTION

2.1. Background

The clinical study INCMGA 0012-201 is a Phase 2, open-label, multicenter study designed to assess the clinical activity and safety of INCMGA00012 in participants with advanced/metastatic MCC.

Merkel cell carcinoma is a rare, aggressive, cutaneous malignancy attributed to multiple factors, such as Merkel cell polyomavirus, UV irradiation, and immunosuppression. This disease typically is found in older adults with light skin types and has a poor prognosis with lower survival rates compared with other skin malignancies. Surgery and/or radiation therapy are indicated and potentially curative for local-regional disease, and relapse is common (Bhatia et al 2011).

The 5-year survival rates for patients with MCC are 75%, 59%, and 25% for primary localized tumors, tumors with regional lymph node metastases (or local recurrences), and tumors with distant metastases, respectively (Becker 2010). More than 30% of patients will develop distant metastatic disease (Voog et al 1999), and the 5-year survival rate for these patients is only approximately 10% (Allen et al 2005).

Historically, metastatic MCC has been treated with chemotherapy regimens similar to those used for small cell lung cancer (NCCN 2017). Platinum-based chemotherapy provides high initial response rates that are of short duration. No survival advantage has ever been demonstrated for chemotherapy in this disease (Cassler et al 2016, Hughes et al 2014, Lebbe et al 2015, NCCN 2017, Voog et al 1999). Management of patients with recurrent, locally advanced, unresectable MCC is also challenging (Becker et al 2017). Similar to distant metastatic disease, patients with recurrent unresectable MCC require systemic therapy to achieve disease control.

Chemotherapy is also associated with risk of severe toxicity and toxic death, particularly among older patients. Responses to second-line chemotherapy are anecdotal, and current guidelines recommend clinical studies in this setting. Other drug classes under early investigation for metastatic MCC include cytokines, adoptive T-cell therapy, toll-like receptor 4 agonists, and somatostatin analogues (Schadendorf et al 2017).

Immunotherapy is a promising new approach to treatment of advanced/metastatic MCC. Updated results from a study with the PD-L1 inhibitor, avelumab, showed an ORR of 39.7% in chemotherapy-naive participants (D'Angelo et al 2019) and 32% in participants with chemotherapy-refractory metastatic disease, most of which were durable (Kaufman et al 2016). Responses occurred in patients with both PD-L1+ and negative tumors and were independent of Merkel cell polyomavirus status. Recently, updated results from a study of pembrolizumab, a PD-1 inhibitor, in participants with advanced MCC were published. In this Phase 2 trial, the objective response rate was 56% in participants with distant metastatic or recurrent, locoregional MCC not amenable to definitive surgery or radiation therapy (Nghiem et al 2019). Based on these initial results, NCCN guidelines recommend pembrolizumab as a treatment option for patients with recurrent locally advanced disease (NCCN 2019).

2.2. Study Rationale

Though initial results with checkpoint inhibitors are encouraging, there still remains an unmet medical need in the treatment of advanced/metastatic MCC. In particular, safety, efficacy, and convenience of therapy could be improved by using alternative immunotherapies, either as monotherapy or as part of rational combination strategies. Clinical trials also provide an important means by which promising investigational therapies can be delivered, when access is otherwise limited (eg, by labeling restrictions or reimbursement).

The study drug, INCMGA00012, is a humanized, IgG4 monoclonal antibody that recognizes human PD-1. As of the data cutoff date of 23 SEP 2021, 660 unique patients had been exposed to INCMGA00012 as monotherapy at doses of 1 mg/kg Q2W, 3 mg/kg Q2W, 3 mg/kg Q4W, 10 mg/kg Q2W, 375 mg Q3W, 500 mg Q4W, or 750 mg Q4W. The most frequently reported TEAEs seen in patients who received INCMGA00012 monotherapy were asthenia (17.3%), fatigue (16.1%), and diarrhea (15.9%). Immune-related TEAEs occurred in 27.4% of patients. The most frequent irAE was hypothyroidism (9.2%) and the most frequent nonendocrine irAE was skin reactions (7.1%). Most irAEs were Grade 1 or 2 in severity. Grade ≥ 3 irAEs occurred in 6.7% of participants with most frequent being acute kidney injury and pneumonitis (0.9% each).

Further details are presented in the INCMGA00012 IB. INCMGA00012 has shown clinical activity as monotherapy against a variety of solid tumors, including chemotherapy-naïve and previously treated Merkel cell carcinoma, lung, urothelial, renal, squamous carcinoma of the anal canal, cervical, and endometrial carcinomas, as well as melanoma (Berton et al 2021, Grignani et al 2021, Maio et al 2021, Mehnert et al 2018, Mehnert et al 2019, Rao et al 2020).

INCMGA00012 offers potential advantages over other checkpoint inhibitors in the treatment of MCC. In particular, INCMGA00012 offers the convenience of Q4W flat dosing as opposed to the more frequent administration schedules for avelumab and pembrolizumab. Development of combination therapies with the sponsor's portfolio of immunomodulatory drugs using the INCMGA00012 backbone will also be explored in future studies.

2.2.1. Justification for Dose

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

The proposed flat dose regimen of 500 mg Q4W is based on modeling of clinical PK data from the ongoing first-in-human monotherapy study (NCT03059823) and benchmarking to pembrolizumab. This dose-escalation study of INCMGA00012 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 escalation from 1 mg/kg to 3 mg/kg, linear PK was shown from 3 mg/kg to 10 mg/kg. No dose-limiting toxicity was observed at any dose level, and an MTD was not reached.

A population PK analysis was performed on these participants to characterize the effect of body weight on the PK of INCMGA00012. The plasma concentrations of INCMGA00012 can be

adequately described by a 2-compartment model with first-order elimination. Higher clearance of INCMGA00012 was estimated for 1 mg/kg than the other dose groups. Body weight dependence of clearance was characterized by a power relationship with an exponent of 0.911.

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

Pharmacokinetic data were obtained from 15 participants who received INCMGA00012 500 mg Q4W in the Cohort Expansion Phase of Study INCMGA 0012-101. The observed AUC_{∞} for 500 mg Q4W is close to the steady state AUC_t based on the population PK analysis of weight-based dosing, as is the estimated clearance. The estimated $t_{½}$ (333 h) is slightly shorter than that from the previous estimate of 409 h. The mean trough plasma concentration on Cycle 2 was 17.1 µg/mL, and the mean projected plasma $C_{min,ss}$ is 23.1 µg/mL (which meets or slightly exceeds the targeted concentration based on pembrolizumab data) with a mean accumulation index of 1.50. Overall, the 500 mg Q4W dose had very similar PK properties to 3 mg/kg dosing, and has ~77% probability for steady state trough plasma concentration ≥ 10 µg/mL, which is associated with maximum target engagement and greatest probability of efficacy. Based on these observations, 500 mg Q4W was chosen as the dosing regimen for further development in the MCC indication.

2.3. Benefit/Risk Assessment

Treatment directed at the PD-1/PD-L1 axis is a promising approach to MCC. Phase 2 results with avelumab and pembrolizumab show efficacy in terms of durable tumor response with preservation of health-related quality of life (Kaufman et al 2018, Nghiem et al 2019). Safety of these agents has been well-characterized, and no unexpected safety findings have been reported in this population with either avelumab or pembrolizumab. Alternative treatments (eg, chemotherapy) are associated with both inferior activity and serious toxicities. Based on these observations, the benefit/risk for INCMGA00012 should also be favorable, provided efficacy objectives in the proposed study are met.

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

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

2.3.1. Benefit/Risk Assessment During the COVID-19 Pandemic

An ESMO multidisciplinary panel highlighted the importance of clinical cancer research to find better therapeutic options for participants even during the pandemic, including potential investigational therapies similar to immunotherapy with a known survival benefit (Curigliano

et al 2020). Data released based on real-world experience indicate that the use of immunotherapy does not appear to increase the risk of hospitalization upon COVID-19 infection (Horn et al 2020) or cause an increased risk of mortality (Lee et al 2020, Sharafeldin et al 2021). Real world experience has also shown that the risk of SAEs is higher in cancer patients who were SARS-CoV-2 positive; however, the incidence of SAEs is similar in patients treated with immunotherapy and chemotherapy. Reported SAEs were generally COVID-19 related rather than related to the cancer therapy (Mandala et al 2021).

Vaccines to SARS-CoV-2 are recommended for patients with cancer by oncology organizations such as NCCN, ASCO, and ESMO (NCCN 2021a, ASCO 2021, ESMO 2021). There has been no indication of increased risk of new or worsening irAEs in patients receiving immunotherapy within a month of SARS-CoV-2 vaccination (Malek et al 2021).

Participants will be monitored with safety procedures as described in Section 8 and with additional safety assessments as per standard of care. Additional information regarding the flexibility of assessments/visits scheduling, where possible and warranted, and strategy for participant management during the dynamic pandemic as applicable is described in Appendix D.

3. OBJECTIVES AND ENDPOINTS

The study objectives and endpoints are presented in Table 5.

Table 5: Objectives and Endpoints

Objectives	Endpoints
Primary	
To determine the efficacy of INCMGA00012 in terms of the ORR in chemotherapy-naive participants with advanced/metastatic MCC.	ORR, defined as the percentage of participants having an objective response (CR or PR), according to RECIST v1.1, as determined by ICR.
Secondary	
To determine the DOR, DCR, PFS, and OS in the chemotherapy-naive population with advanced/metastatic MCC treated with INCMGA00012.	• DOR, defined as the time from an initial objective response (CR or PR) according to RECIST v1.1 until disease progression, or death due to any cause, as determined by ICR. • DCR, defined as the proportion of participants with either an objective response or SD lasting at least 6 months. • PFS, defined as the time from the start of therapy until disease progression, or death due to any cause, as determined by the ICR. • OS, defined as the time from the start of therapy until death due to any cause.
To evaluate the safety of INCMGA00012 in participants with advanced/metastatic MCC.	Safety, determined by the number, frequency, duration, and severity of AEs using CTCAE v5.0; laboratory tests; vital signs; and ECGs.
To determine the PK of INCMGA00012 administered to participants with advanced/metastatic MCC.	The PK of INCMGA00012 when given to participants with advanced/metastatic MCC, including C_{max}, t_{max}, C_{min}, and AUC_t, will be summarized.

Table 5: Objectives and Endpoints (Continued)

Objectives	Endpoints
Exploratory	
[redacted]	
To determine the efficacy of INCMGA00012 in terms of the ORR, DOR, DCR, PFS, and OS in the full study population (chemotherapy-naive and chemotherapy-refractory) with advanced/metastatic MCC. Note: Chemotherapy-refractory participants enrolled before implementation of Amendment 5 will be included in these analyses.	• ORR, defined as the percentage of participants having an objective response (CR or PR), according to RECIST v1.1, as determined by ICR. • DOR, defined as the time from an initial objective response (CR or PR) according to RECIST v1.1 until disease progression, or death due to any cause, as determined by ICR. • DCR, defined as the proportion of participants with either an objective response or SD lasting at least 6 months. • PFS, defined as the time from the start of therapy until disease progression, or death due to any cause, as determined by the ICR. • OS, defined as the time from the start of therapy until death due to any cause.

4. STUDY DESIGN

4.1. Overall Design

The clinical study INCMGA 0012-201 is a Phase 2, open-label, single-arm, multicenter study designed to assess the clinical activity and safety of INCMGA00012 in participants with advanced/metastatic MCC. This study will enroll participants with advanced/metastatic MCC who are chemotherapy-naive. Participants with locally advanced disease are eligible only if they have had a recurrence following locoregional therapy and are not considered amenable to further curative therapy with surgery or radiation. The participants should not have received any prior therapy with PD-1/PD-L1 inhibitors. All participants must submit tissue samples (fresh or archival) for central pathology review. Participants who do not have MCC confirmed by pathology may remain on study treatment but may be replaced for efficacy analysis (see Section 5.5).

All participants who meet the eligibility criteria during screening will receive treatment with INCMGA00012. The primary endpoint is ORR in chemotherapy-naive participants as determined by ICR according to RECIST v1.1.

Approximately 100 chemotherapy-naive participants will be enrolled. The primary analysis is planned with approximately 60 chemotherapy-naive participants, while the additional participants will be enrolled to support confirmation of efficacy and provide additional information on safety. The primary analysis will occur after 60 chemotherapy-naive participants have been enrolled and followed for at least 6 months after confirmed response. If the study meets the predefined efficacy threshold at the primary analysis (see Section 10.1), the final analysis will occur after all 100 participants have been enrolled and followed for survival for a minimum of 2 years. Study enrollment may stop if the predefined efficacy threshold is not met at the time of primary analysis.

Study treatment will consist of monotherapy INCMGA00012 administered at the recommended Phase 2 dose of 500 mg by IV infusion once every 28 days. Treatment with study drug may continue 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 listed in Section 7.1.

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

Eligible participants will receive treatment with single-agent INCMGA00012 500 mg administered by IV infusion over 60 minutes on Day 1 of each 28-day cycle. Subsequent treatment cycles should be delayed until the following criteria are met:

- Resolution of all immune-related toxicity to ≤ Grade 1 (with the exception of endocrinopathy that is controlled on hormonal replacement)
- Resolution of all non–immune-related toxicity to ≤ Grade 1 or baseline (with the exception of alopecia or non–transfusion-dependent anemia)

  Note: Transient asymptomatic laboratory elevations ≤ Grade 3 do not require dose interruption if the participant is asymptomatic, and if the elevation is clinically insignificant and has been discussed with the medical monitor.

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 (see Section 6.5.2.8). Treatment delays of > 12 weeks for logistical reasons (eg, travel restrictions due to COVID-19) may be acceptable but must be discussed with the medical monitor.

The follow-up period will begin once a participant has completed treatment or prematurely discontinued the study treatment. Participants will be evaluated for AEs and other safety parameters for up to 90 days after the last dose of study treatment or until the start of new anticancer therapy, whichever occurs first.

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

The complete study-specific assessment schedule required for participants in this clinical study is presented in Table 3. The analytes to be evaluated in the safety laboratory analyses are found in Table 22. 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. Participants may receive study treatment for up to 2 years, unless prematurely discontinued. Participants discontinuing treatment will enter the follow-up period after their last dose of study treatment. The study ends once every participant receiving active treatment has been followed for at least 6 months after confirmed response or until all participants have been followed for survival for a minimum of 2 years. Participants remaining on active therapy at study conclusion may be eligible for continued treatment up to 2 years from first dose if, in the assessment of the investigator, they are tolerating therapy and receiving benefit.

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 or upon advice of the DMC. If the study is terminated prematurely, the sponsor will notify the investigators, the IRBs and IECs, and regulatory bodies of the decision and reason for termination of the study.

4.3.1. Data Monitoring Committee

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

Preplanned analyses of safety will be provided to an independent DMC as specified in the DMC charter. In addition, the DMC will make recommendations to the sponsor at a planned interim analysis (see Section 10.5). In terms of efficacy, the DMC will use the guidelines provided for recommendation of either continuation or early termination of the study at the interim analysis. Additionally, the DMC will review safety data of the ongoing study at regular intervals as specified in the DMC Charter. The process by which the DMC will make recommendations and decisions will be documented in the DMC Charter.

As of Protocol Amendment 6, the DMC has reviewed the data for the interim analysis. The preliminary efficacy based on the ORR assessed by ICR exceeded the futility threshold, and the DMC recommended the study to proceed as planned.

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. Signed informed consent.
2. Men and women, aged 18 or older (or as applicable per local country requirements).
3. Diagnosis of MCC with distant metastatic disease or recurrent, advanced locoregional disease not amenable to surgery or radiation.
4. ECOG performance status of 0 to 1 (see Table 21).
5. Measurable disease according to RECIST v1.1. Tumor lesions that are located in a previously irradiated area or in an area subjected to other locoregional therapy should only be selected as target lesions if progression has been demonstrated in such lesions.
6. Availability of tumor tissue (fresh or archival) for central pathology review.
7. 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 treatment 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 before the first dose on Day 1 and must agree to take appropriate precautions to avoid pregnancy (with at least 99% certainty) from screening through 120 days after the last dose of study treatment. 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. Prior systemic therapy for MCC, including chemotherapy and prior PD-1– or PD-L1–directed therapy.
2. Treatment with anticancer drugs or participation in another interventional clinical study within 21 days before the first administration of study drug.

3. Participant has not recovered to ≤ Grade 1 or baseline from toxic effects of prior therapy (with the exceptions for anemia not requiring transfusion support and any grade of alopecia) and/or complications from prior surgical intervention within 7 days before starting study treatment.
4. Radiation therapy administered within 2 weeks of first dose of study treatment or radiation therapy to the thoracic region that is > 30 Gy within 6 months of the first dose of study treatment.
5. Known CNS metastases and/or carcinomatous meningitis.

   Note: Participants with previously treated brain metastases may participate provided that 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.
6. Any known additional malignancy that is progressing or requires active treatment, or history of other malignancy within 3 years of study entry with the exception of cured basal cell or squamous cell carcinoma of the skin, superficial bladder cancer, prostate intraepithelial neoplasm, carcinoma in situ of the cervix, or other noninvasive or indolent malignancy, or cancers from which the participant has been disease-free for > 1 year, after treatment with curative intent.
7. Participants with laboratory values at screening defined in Table 6.

Table 6: 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 OR > 5 × ULN for participants with liver metastases
E	AST	> 2.5 × ULN OR > 5 × ULN for participants with liver metastases
F	Bilirubin/total bilirubin	≥ 1.5 × ULN unless conjugated bilirubin is ≤ ULN (conjugated bilirubin only needs to be tested if total bilirubin exceeds the 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
I	aPTT	> 1.5 × ULN

8. Evidence of interstitial lung disease or active, noninfectious pneumonitis.
9. Participants with impaired cardiac function or clinically significant cardiac disease:
    a. New York Heart Association Class III or IV cardiac disease, including preexisting clinically significant ventricular arrhythmia, congestive heart failure, or cardiomyopathy.
    b. Unstable angina pectoris ≤ 6 months before study participation.
    c. Acute myocardial infarction ≤ 6 months before study participation.
    d. Other clinically significant heart disease (ie, uncontrolled ≥ Grade 3 hypertension, history of labile hypertension, or poor compliance with an antihypertensive regimen). Must have recovered (to baseline or ≤ Grade 1) from toxicity associated with prior treatment.
10. Active autoimmune disease requiring systemic immunosuppression in excess of physiologic maintenance doses of corticosteroids.
11. Chronic or current active infectious disease requiring systemic antibiotics, antifungal, or antiviral treatment.
12. Known active hepatitis A, B, or C or active infections requiring systemic antibiotics.
13. Has received a live vaccine within 28 days of planned start of study therapy.

    Note: Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox/zoster, yellow fever, rabies, Bacillus Calmette–Guérin, 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.
14. Current use of prohibited medication as described in Section 6.6.2.
15. Known hypersensitivity to another monoclonal antibody, which cannot be controlled with standard measures (eg, antihistamines and corticosteroids).
16. Participant lacks the ability or is unlikely, in the opinion of the investigator, to comply with the Protocol requirements.
17. Participant who is pregnant or breastfeeding
18. Any condition that would, in the investigator's judgment, interfere with full participation in the study, including administration of study drug/treatment and attending required study visits; pose a significant risk to the participant; or interfere with interpretation of study data.
19. History of organ transplant, including allogeneic stem cell transplantation.
20. Known allergy or hypersensitivity to any component of the study drug formulation.
21. Participants who are known to be HIV-positive, unless all of the following criteria are met:
    a. CD4+ count ≥ 300 µL.
    b. Undetectable viral load.
    c. Receiving highly active antiretroviral therapy.

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 do not meet all the eligibility criteria as defined in Sections 5.1 and 5.2.

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

5.5. Replacement of Participants

Participants who do not meet the eligibility requirements or fail to have a MCC diagnosis by central pathology review, but initiated study treatment will be removed from study unless, in the judgment of the investigator, the participant is benefiting from treatment and there is no evidence of disease progression or unacceptable toxicity. The sponsor's medical monitor and the investigator will jointly evaluate such cases and make a decision regarding continued therapy on a case-by-case basis. However, these participants may not be included in the efficacy analysis population (see Section 10.2) and may be replaced by further enrollment for the efficacy analysis.

6. STUDY TREATMENT

6.1. Study Treatment Administered

The study treatment information is presented in Table 7.

Table 7: Study Treatment Information

Study treatment name:	INCMGA00012
Dosage formulation:	Liquid formulation supplied as 250 mg vials
Unit dose strength/dosage level:	500 mg Q4W
Route of administration:	IV
Administration instructions:	Administered IV over 60 minutes (+ 15 minutes) through a filter. Participants should be monitored for infusion reactions during the infusion as per institutional guidelines.
Packaging and labeling:	INCMGA00012 will be provided in a 250 mg vial. Each vial will be labeled as required per country requirement.
Storage:	Upright under refrigeration at 2°C-8°C (36°F-46°F) protected from light.

6.2. Preparation, Handling, and Accountability

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

Only participants enrolled in the study may receive study treatment, and only authorized site staff may supply or administer study treatment. All study treatment 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 treatment 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.
- Participant use of the study drug including vial counts from each supply dispensed.
- Lot numbers and/or vial numbers of study drug used to prepare the infusion solution.

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 standard operating procedures. 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 Standard Operating Procedures.

Further guidance and information for the final disposition of unused study treatments 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 administration will be calculated by the sponsor based on study treatment infusion records documented by the site staff and monitored by the sponsor/designee.

6.5. Dose Modifications

Dose interruptions of INCMGA00012 are allowed for AEs as outlined in the following subsections and tables located throughout Section 6.5. No dose reductions or other modifications of INCMGA00012 are allowed for the management of toxicities for individual participants. Doses of INCMGA00012 may be delayed up to 12 weeks for toxicity management.

Before the start of each treatment cycle, the participant must meet the treatment continuation criteria noted in (see Section 4.1) before administration of INCMGA00012. If the criteria are not met at the beginning of a treatment cycle, INCMGA00012 infusion may be delayed up to 12 weeks to allow for resolution of any abnormal laboratory results or AEs. Participants should be withdrawn from the active treatment portion of the study if re-treatment criteria are not met within 12 weeks of the scheduled start of a cycle. Upon resolution, participants may resume treatment if no medical condition or other circumstance exists that, in the opinion of the investigator, would make the participant unsuitable for further participation in the study. If INCMGA00012 must be discontinued due to unacceptable toxicity, then the participant should be withdrawn from active treatment and enter the follow-up period of the study.

6.5.1. Management of Suspected Infusion Reactions

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

Guidelines for management of suspected infusion reactions are provided in Table 8. Grade 3 or Grade 4 infusion reactions should be reported within 24 hours to the study medical monitor regardless of whether criteria for reporting as a SAE are met.

Table 8: 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, or as per institutional guidelines.
2	Requires infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, analgesic/antipyretic, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hours.	**First occurrence:** Stop infusion and initiate appropriate medical measures (eg, IV fluids, antihistamines, analgesic/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 (despite recommended prophylaxis):** Permanently discontinue treatment.	Premedicate at least 30 minutes before infusion with antihistamines (eg, diphenhydramine 50 mg PO or comparable dose of antihistamine) and acetaminophen/ paracetamol (500-1000 mg PO or equivalent dose of analgesic/antipyretic). Additional supportive measures may be acceptable (per institutional preference) but should be discussed with medical monitor. Next infusion should start at 50% of the original infusion rate. If no reaction, the 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%.

Table 8: Guidelines for Management of Suspected Infusion Reactions (Continued)

Grade	Description[a]	Treatment	Subsequent Infusions
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 or rechallenge; 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 analgesic/antipyretic, narcotics, oxygen, pressors, epinephrine, corticosteroids, per institutional preferences). Monitor vital signs frequently until medically stable. Hospitalization may be indicated.	Discontinue study treatment. **Note:** NCI CTCAE Grade 3 infusion related reaction (NCI CTCAE v5): if rapidly responsive to symptomatic medication and/or to brief interruption of infusion, study treatment does not need to be permanently discontinued.

[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. Procedures for Participants Exhibiting Immune-Related Adverse Events

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

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

Recommendations for management of specific irAEs known to be associated with INCMGA00012 and other PD-1 inhibitors (eg, pembrolizumab, nivolumab) are detailed in the sections below.

Algorithms for evaluation of selected immune toxicities that have previously been attributed to PD-1 inhibitors and management guidance for irAEs not detailed elsewhere in the Protocol should follow the American Society of Clinical Oncology or European Society for Medical Oncology Clinical Practice Guidelines or NCCN Guidelines (Brahmer et al 2018, Haanen et al 2017, NCCN 2021b.

6.5.2.1. Immune-Mediated Pneumonitis

Participants with symptomatic pneumonitis should immediately stop receiving study treatment and have an evaluation. The evaluation may include bronchoscopy and pulmonary function tests to rule out other causes such as infection. Recommendations for management of study drug-associated pneumonitis are detailed in Table 9.

Table 9: Recommended Approach to Handling Pneumonitis

Study Drug–Associated Pneumonitis	Withhold/Discontinue Study Treatment	Supportive Care
Grade 1 (asymptomatic)	No action.	Intervention not indicated.
Grade 2	Withhold study treatment. May return to treatment if condition improves to ≤ Grade 1. Permanently discontinue if toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to ≤ 10 mg per day prednisone or equivalent within 12 weeks.	• Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment. • Administer systemic corticosteroids per local practice followed by taper. • Add prophylactic antibiotics for opportunistic infections.
Grades 3 and 4 or recurrent Grade 2	Permanently discontinue study treatment.	

6.5.2.2. Immune-Mediated Colitis/Enterocolitis/Diarrhea

Participants should be carefully monitored for signs and symptoms of colitis (eg, diarrhea, abdominal pain, mucus, or blood in stool, with or without fever). In symptomatic participants, infectious etiologies should be ruled out, and endoscopic evaluation should be considered for persistent or severe symptoms. Recommendations for management of enterocolitis are shown in Table 10.

Table 10: Recommended Approach for Handling Colitis/Enterocolitis/Diarrhea

Study Drug–Associated Colitis/Enterocolitis/ Diarrhea	Withhold/Discontinue Study Treatment	Supportive Care
Grade 1	No action.	None.
Grade 2 or 3	Withhold study treatment until ≤ Grade 1.	• Consider prompt initiation of standard anti-diarrheal agents or 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. • Consider stool sample evaluation to rule out Clostridium difficile (C. diff) and infectious etiologies.
Grade 4 or recurrent Grade 3	Permanently discontinue study treatment.	

6.5.2.3. Immune-Mediated Hepatitis

Liver chemistry testing (hepatic transaminase and bilirubin levels) should be monitored and participants assessed for signs and symptoms of hepatotoxicity before each dose of INCMGA00012. In participants with hepatotoxicity, infectious or malignant causes should be ruled out, and frequency of liver chemistry monitoring increased until resolution. Recommendations for management of hepatitis are shown in Table 11.

Table 11: Recommended Approach for Handling Hepatitis

Study Drug–Associated Hepatitis	Withhold/Discontinue Study Treatment	Supportive Care
Grade 1	No action.	Increase frequency of liver chemistry monitoring to twice per week until liver chemistry tests return to baseline[a].
Grade 2	Withhold study treatment.	Systemic corticosteroids are indicated (initial dose of 0.5-1 mg/kg per day of prednisone or equivalent). Taper as appropriate.
Grades 3 and 4 OR In case of liver metastasis with baseline Grade 2 elevation of ALT or AST, hepatitis with ALT or AST increases ≥ 50% and lasts ≥ 1 week	Permanently discontinue study treatment.	Treatment with systemic corticosteroids should be initiated (initial dose of 1-2 mg/kg per day of prednisone or equivalent). Taper as appropriate.

[a] In addition to ALT and AST, consider monitoring total bilirubin, direct bilirubin, and alkaline phosphatase at an increased frequency.

6.5.2.4. Immune-Mediated Endocrinopathies

6.5.2.4.1. Hypophysitis

Monitor for signs and symptoms of hypophysitis (including hypopituitarism). Recommendations for management of hypophysitis are shown in Table 12.

Table 12: Recommended Approach for Handling Hypophysitis

Study Drug–Associated Hypophysitis	Withhold/Discontinue Study Treatment	Supportive Care
Grade 1	No action.	None.
Grades 2 (asymptomatic)	Withhold until ≤ Grade 1. May restart INCMGA00012 treatment after controlled by hormone replacement therapy.	Administer hormonal replacement as clinically indicated.
Grade 2 (symptomatic, e.g. headaches, visual disturbances)	Withhold until ≤ Grade 1. May restart INCMGA00012 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.
Grades 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.

6.5.2.4.2. Thyroid Disorders

Monitor participants for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders. Recommendations for management of thyroid disorders are shown in Table 13.

Table 13: Recommended Approach for Handling Thyroid Disorders

Study Drug–Associated Thyroid Disorders	Withhold/Discontinue Study Treatment	Supportive Care
Hypothyroidism		
Grades 1 and 2	No action.	None.
Grades 3 and 4	Withhold until ≤ Grade 1 or is otherwise clinically stable.	Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care.
Hyperthyroidism		
Grades 1 and 2	No action.	None.
Grades 3 and 4	Withhold until ≤ Grade 1 or is otherwise clinically stable.	Initiate symptomatic management.

6.5.2.4.3. New Onset Type 1 Diabetes Mellitus/Hyperglycemia

Monitor participants for hyperglycemia or other signs and symptoms of diabetes mellitus. Recommendations for management of diabetes mellitus are shown in Table 14.

Table 14: Recommended Approach for Handling New Onset Type 1 Diabetes Mellitus/Hyperglycemia

Study Drug–Associated Diabetes Mellitus	Withhold/Discontinue Study Treatment	Supportive Care
Grades 1 and 2	No action.	Intervention not indicated.
Grades 3 and 4 Type 1 diabetes mellitus (or hyperglycemia)	Withhold study drug until ≤ Grade 1 or is otherwise clinically stable.	Initiate treatment with antihyperglycemics or insulin as clinically indicated.

6.5.2.4.4. Adrenal Insufficiency

Monitor for signs and symptoms of adrenal insufficiency. Recommendations for management of adrenal insufficiency are shown in Table 15.

Table 15: Recommended Approach for Handling Adrenal Insufficiency

Study Drug-Associated Adrenal Insufficiency	Withhold/Discontinue Study Treatment	Supportive Care
Grade 1	No action.	Intervention not indicated.
Grade 2	Withhold study drug until ≤ Grade 1 or is otherwise clinically stable.	Initiate treatment with hormone replacement as clinically indicated.
Grades 3 and 4	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.

6.5.2.5. Immune-Mediated Nephritis and Renal Dysfunction

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

Table 16: Recommended Approach for Handling Nephritis and Renal Dysfunction

Study Drug–Associated Nephritis and Renal Dysfunction	Withhold/Discontinue Study Treatment	Supportive Care
Grade 1	No action.	Intervention not indicated.
Grade 2 or Grade 3 increased blood creatinine	Withhold study treatment until ≤ Grade 1.	Administer corticosteroids per local practice followed by taper.
Grade 4 increased blood creatinine	Permanently discontinue study treatment.	

6.5.2.6. Immune-Mediated Skin Reactions

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

Table 17: Recommended Approach for Handling Skin Reactions

Study Drug–Associated Skin Reactions	Withhold/Discontinue Study Treatment	Supportive Care
Grade 1	No action.	Intervention not indicated.
Grade 2	No action.	Manage with topical steroids with or without study treatment interruption.
Grade 3[a] or persistent Grade 2 (≥ 2 weeks) OR Suspected Stevens-Johnson syndrome[b]	Withhold study treatment until ≤ Grade 1 after corticosteroid taper to ≤10mg/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. Refer to dermatology if no resolution with these measures. • Refer to dermatology if SJS or TEN is suspected.
Grade 4 OR Confirmed Stevens-Johnson syndrome or toxic epidermal necrolysis[c]	Permanently discontinue study treatment.	• Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper. • Refer to dermatology consult.

[a] 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 have to interrupt INCMGA00012. Permanent discontinuation of study treatment may be necessary if there is recurrence of Grade 3 after resuming the study treatment.

[b] 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 10-30% BSA with associated signs (eg, erythema, purpura, epidermal detachment, mucous membrane detachment).

[c] 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)

6.5.2.7. Immune-Mediated Myocarditis

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

Table 18: Recommended Approach for Handling Myocarditis

Study Drug–Associated Myocarditis	Withhold/Discontinue Study Treatment	Supportive Care
Grade 2, 3, and 4	Permanently discontinue study treatment.	• 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. • Timely cardiology referral.

6.5.2.8. Immune-Mediated Nervous System Events

Immune-mediated nervous system events, including Guillain-Barre syndrome, autoimmune enceophalitis, myasthenia gravis, autonomic neuropathy, and transverse myelitis, can occur. Monitor participants for these immune-mediated nervous system events and exclude other causes. Recommendations for the management of immune-mediated nervous system events are shown in Table 19.

Table 19: Recommended Approach for Handling Immune-Mediated Nervous System Events

Study Drug–Associated Nervous System Events	Withhold/Discontinue Study Treatment	Supportive Care
Grade 1	No action.	Intervention not indicated.
Grade 2	Withhold study treatment 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.
Grade 3 or 4	Permanently discontinue study treatment.	

6.5.2.9. Other Immune-Mediated Adverse Events

Recommendations for management of immune-mediated adverse events not specified above are shown in Table 20.

Table 20: Recommended Approach to Handling Other Immune-Mediated Adverse Events

Study Drug-Associated Immune-Mediated Adverse Events	Withhold/Discontinue Study Treatment	Supportive Care
Grade 1	No action.	None
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 study treatment.	
Grade 4 (excluding endocrinopathies)		

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 AE requiring a delay of therapy for more than 12 weeks.
- Any AE defined in the dose modifications management guidelines (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) and medical procedures must be recorded in the eCRF. Any medication or procedure received from signing the ICF to 90 days after the last dose of study treatment, 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 should be recorded regardless of when they are provided. Concomitant medications and/or procedures administered to a participant for management of a 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

Highly active antiretroviral therapy should be continued for participants who are known to be HIV-positive. Recommended supportive measures for specific toxicities are described above. Growth factors, bisphosphonates, anticoagulants, and transfusional support will also be permitted at any point in the study.

Premedication with an antipyretic (eg, acetaminophen/paracetamol) and a histamine blocker should be considered for participants who have had previous systemic reactions to protein product infusions or when recommended according to institutional policy.

6.6.2. Prohibited Medications and Procedures

- Other anticancer therapies, including investigational treatments.
- Immunosuppression in excess of physiologic maintenance corticosteroid doses (with the exception of acute treatment for an AE). The use of corticosteroids should be limited to the extent possible. Chronic doses of corticosteroids in excess of 10 mg daily of prednisone or equivalent are prohibited other than for the management of drug-related adverse experiences. Steroids may be employed in the treatment of suspected INCMGA00012-associated immune-inflammatory or autoimmune AEs in consultation with the sponsor.

- Live vaccines within 28 days prior to first administration of study drug, throughout the treatment phase 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, Bacillus Calmette–Guérin, 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.

- Probiotic dietary supplements

6.7. Treatment After the End of the Study

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

7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Treatment

7.1.1. Reasons for Discontinuation

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

- Disease progression.
- Unacceptable toxicity as noted in Section 6.5.2.8.
- Consent is withdrawn.

  Note: Consent withdrawn means that the participant has explicitly indicated that they do not want to be followed any longer; in this case no further data, except data in public domain, may be solicited from or collected on the participant. Participants may choose to discontinue study treatment and remain in the study to be followed for progression and survival.
- Further participation would be, based on the medical judgment of the investigator, injurious to the health or well-being of the participant.
- The study is terminated by the sponsor.
- The study is terminated by the local health authority, IRB, or IEC.
- The participant becomes pregnant (see Section 9.7).

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

- If a participant is noncompliant with study procedures or treatment administration, and in the judgment of the investigator the participant is not receiving a clinical benefit. When possible, the sponsor should be informed and/or consulted.
- The participant achieves a confirmed CR after at least 6 months of treatment. Participants may continue on study treatment after confirmation of CR per the discretion of the investigator if they feel the participant may gain additional benefit. Note: The participant should be continue to be followed for disease status and survival after discontinuation of treatment.

7.1.2. Discontinuation Procedures

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

If a participant is discontinued from study treatment:

- The study monitor or sponsor must be notified.
- The reason(s) for withdrawal must be documented in the participant's medical record and the primary reason for withdrawal must be included in the eCRF.

- The EOT visit should be performed.
- The date of the EOT visit should be recorded in the IRT.
- Participants must be followed for safety for 90 days after the last study treatment, or until study treatment–related toxicities resolve, return to baseline, or are deemed irreversible, whichever is longest.

If the participant discontinues study treatment and actively withdraws consent for collection of follow-up data (safety follow-up or disease assessment), then no additional data collection should occur; however, participants will have the option of withdrawing consent for study treatment and further assessments but allowing survival follow-up.

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 consent 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 discontinuation and follow-up and for any further evaluations that need to be completed.

7.3. Lost to Follow-Up

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

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

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

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Administrative and General Procedures

8.1.1. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
  - Informed consent must be obtained before any study-related procedures are conducted, unless otherwise specified by the Protocol.
  - Informed consent must be obtained using the IRB/IEC-approved version in a language that is native and understandable to the participant. A template will be provided by the sponsor or its designee. The sponsor or its designee must review and acknowledge the site-specific changes to the ICF template. The ICF must include a statement that the sponsor or its designee and regulatory authorities have direct access to participant records.
  - The ICF must contain all required elements and describe the nature, scope, and possible consequences of the study in a form understandable to the study participant.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the applicable requirements and regulations for the countries in which the study is being conducted as well as the IRB/IEC or study center.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection laws. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must provide consent to the most current version of the ICF(s) during their participation in the study.
- 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 enrollment in the study (Cycle 1 Day 1). Screening may not exceed 28 days. Assessments required to demonstrate eligibility will be performed during the screening period.

Procedures conducted as part of the participant's routine clinical management (such as laboratory analyses) before signing the ICF may be used for screening or baseline purposes, provided the procedure meets the Protocol-defined criteria and has been performed within 28 days of Cycle 1 Day 1.

Tests with results that fail eligibility requirements may be repeated once during screening if the investigator believes the results to be in error. 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. Site staff should contact the IRT to obtain the participant ID number during screening upon determination of the final eligibility status of the participant, as well as once the participant prematurely discontinues or completes treatment. Additionally, the IRT will be used throughout the study to dispense study drug to the site for each infusion and to maintain the site inventory and update the study drug supply as needed. Details regarding the use of IRT will be provided in a separate document.

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 and time of the next visit and will also inform the participant about visit-specific procedures.

8.1.5. Demography and Medical History

8.1.5.1. Demographics and General Medical History

Demographic data and general medical history will be collected at screening by the investigator or qualified designee and will include date of birth, race, ethnicity, medical and surgical history, and current illnesses. Medical history will include relevant medical or surgical treatment considered to be clinically significant by the investigator.

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) by the ICR. Participants should be actively monitored for RECIST response up until they start new anticancer therapy or have PD. [redacted] The disease response assessments according to RECIST v1.1 [redacted] by investigators will be entered into the eCRF.

Efficacy assessments of response should be performed according to schedule found in Table 3. **Scans should follow calendar days and remain on the 8-week schedule (± 7 days), established on Cycle 1 Day 1, and should not be delayed for treatment holds or interruptions**. Disease status will be assessed every 8 weeks for the first 12 months and then every 12 weeks thereafter (ie, the schedule should switch to every 12 weeks after the Week 56 scan). For participants who discontinue study treatment for reasons other than disease progression, every effort should be made to continue monitoring their disease status by radiographic imaging according to the follow-up schedule.

Participants who continue study participation in the follow-up period without experiencing disease progression will continue to have efficacy assessments every 12 weeks (± 7 days) from the previous scan until they complete participation in the study, start a new anticancer therapy, experience disease progression, or death.

8.2.1. Tumor Imaging

Disease assessment and tumor response to study drug will be evaluated according to RECIST v1.1 guidelines (Eisenhauer et al 2009) as described in Appendix B. All imaging must be submitted to the central imaging vendor for independent review. 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 treatment. Scans performed as part of routine clinical management are acceptable for use as the screening scan if they are of diagnostic quality and performed within 28 days before the first dose of study treatment. Tumor lesions that are located in a previously irradiated area or in an area subjected to other locoregional therapy should only be selected as target lesions if progression has been demonstrated in such lesions. Additionally, it is recommended that tumor lesions selected for biopsy not be selected as target lesions. Images of the chest, abdomen, and pelvis are required for all subjects. Additional imaging of anatomical sites (ie, head, neck, and extremities) should be performed as applicable if participant has suspected disease in those areas. Computed tomography or MRI scan of the brain

will be performed at screening if there are signs or symptoms suggesting that the participant has disease involvement in the CNS.

8.2.2. Photographic Analysis of Skin Lesions

Photographic imaging of skin tumors that are being followed as target lesions is required and should follow the schedule of events for clinical tumor assessment. Instructions are provided in the Photography User Manual.

[redacted]

8.2.4. Health Economics

Not applicable.

[redacted]

[redacted]

8.3. Safety Assessments

See Section 6.5 and refer to the American Society of Clinical Oncology and European Society for Medical Oncology Clinical Practice Guidelines (Brahmer et al 2018, Haanen et al 2017) for management guidelines regarding of known or potential AEs and toxicities.

Safety will be monitored by ongoing review of AEs by the sponsor's study physician and pharmacovigilance physician. Regularly scheduled meetings/teleconferences will be held for review of AEs by the sponsor's study physician and pharmacovigilance physician with participating investigators.

8.3.1. Adverse Events

Adverse events will be monitored from the time the participant signs the ICF until at least 90 days after the last dose of study treatment or until the start of new anticancer therapy, whichever occurs first. 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 treatment(s). 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. The severity of AEs will be determined using CTCAE v5.0.

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 treatment/procedures, or that caused the participant to discontinue the study treatment. Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant, such as "How are you feeling?" is the preferred method to inquire about AE occurrences. Adverse events may also be detected when they are volunteered by the participant during the screening process or between visits, or through physical examinations, laboratory tests, or other assessments. The definition, reporting, and recording requirements for AEs are described in Section 9.

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

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

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 signing the ICF constitute an AE if they are considered clinically meaningful, induce clinical signs or symptoms, require concomitant therapy, or require changes in study treatment (with the exception of abnormalities associated with clinical disease progression). Investigators should pay special attention to clinical signs related to previous serious illnesses.

At the screening visit, a comprehensive physical examination should be conducted. The comprehensive physical examination will include height (only at screening), weight, and assessment(s) 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. 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 including blood pressure, O2 saturation, pulse, respiratory rate, and body temperature should to be taken prior to the blood collection for laboratory analyses. Blood pressure and pulse will be taken with the participant in the recumbent, semirecumbent, or sitting position after 5 minutes of rest. If vital signs cannot be taken before blood collection for laboratory tests, there must be a minimum of 30 minutes from the completion of the blood collection procedures to the beginning of the vital signs collection. Abnormal vital signs identified after the first dose of study treatment constitute an AE if they are considered clinically meaningful, induce clinical signs or symptoms, require concomitant therapy, or require changes in study treatment.

8.3.4. Eastern Cooperative Oncology Group Performance Status

The ECOG performance status score will be assessed according to the criteria in Table 21.

Table 21: Eastern Cooperative Group Performance Status Scoring

Grade	ECOG 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. ECGs only need to be performed in triplicate if there has been a QTc prolongation on study or the ECG shows a clinically significant abnormality not present at baseline. 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.

Electrocardiograms should be performed before study drug infusion and will be interpreted by the investigator at the site to be used for immediate participant management. Additional 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 treatment 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, fasting lipid panel, 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. Participants are expected to fast prior to blood collection during visits that include lipid panel analysis. The laboratory analytes to be evaluated are found in Table 22. Additional testing may be required by the sponsor based on emerging safety data. Additional tests may also be performed if clinically indicated.

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

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

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

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 labs should only be performed at the EOT visit if the EOT visit is also serving as the 28-day safety visit.

[redacted]

8.3.6.1. Pregnancy Testing

Serum pregnancy tests are required for all women of childbearing potential during screening and either EOT or the safety follow-up visit 28 days after the last dose. Pregnancy testing 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.

A positive urine pregnancy should be confirmed with a serum pregnancy test. Section 9.7 provides reporting requirements in the case of confirmation by a serum pregnancy test.

Table 22: Required Laboratory Analytes

Blood Chemistries	Hematology	Urinalysis With Microscopic Examination	Coagulation	Pregnancy Testing
Albumin Alkaline phosphatase ALT AST Amylase Bicarbonate or CO_2 Blood urea nitrogen or urea Calcium Chloride Creatinine Glucose Lactate dehydrogenase Lipase Phosphate Potassium Sodium Total bilirubin Direct bilirubin (if total bilirubin is elevated above ULN) Total protein Uric acid	Complete blood count, including: • Hemoglobin • Hematocrit • Platelet count • Red blood cell count • WBC count Differential count, including: • Basophils • Eosinophils • Lymphocytes • Monocytes • Neutrophils Absolute values must be provided for: • WBC differential laboratory results	Color and appearance pH and specific gravity Bilirubin Glucose Ketones Leukocytes Nitrite Occult blood Protein	PT PTT or aPTT INR	Female participants of childbearing potential require a serum pregnancy test at screening and EOT, or 28 days after the last dose. Either a serum or urine pregnancy test will be acceptable prior to receiving study treatment on Day 1 of each treatment cycle.
		Lipid Panel[a]	**Endocrine Function**	[redacted]
		Total cholesterol Triglycerides LDL HDL	TSH T4/FT4 T3/FT3	[redacted]
			SARS-CoV-2	
			SARS-CoV-2 testing during the COVID-19 pandemic, as per country, local, institution's requirements	

Note: Additional tests may be required, as agreed upon by the investigator and sponsor, based on emerging safety data.
[a] Participants are required to fast prior to blood collection for lipid panel analysis.

8.4. Pharmacokinetic Assessments

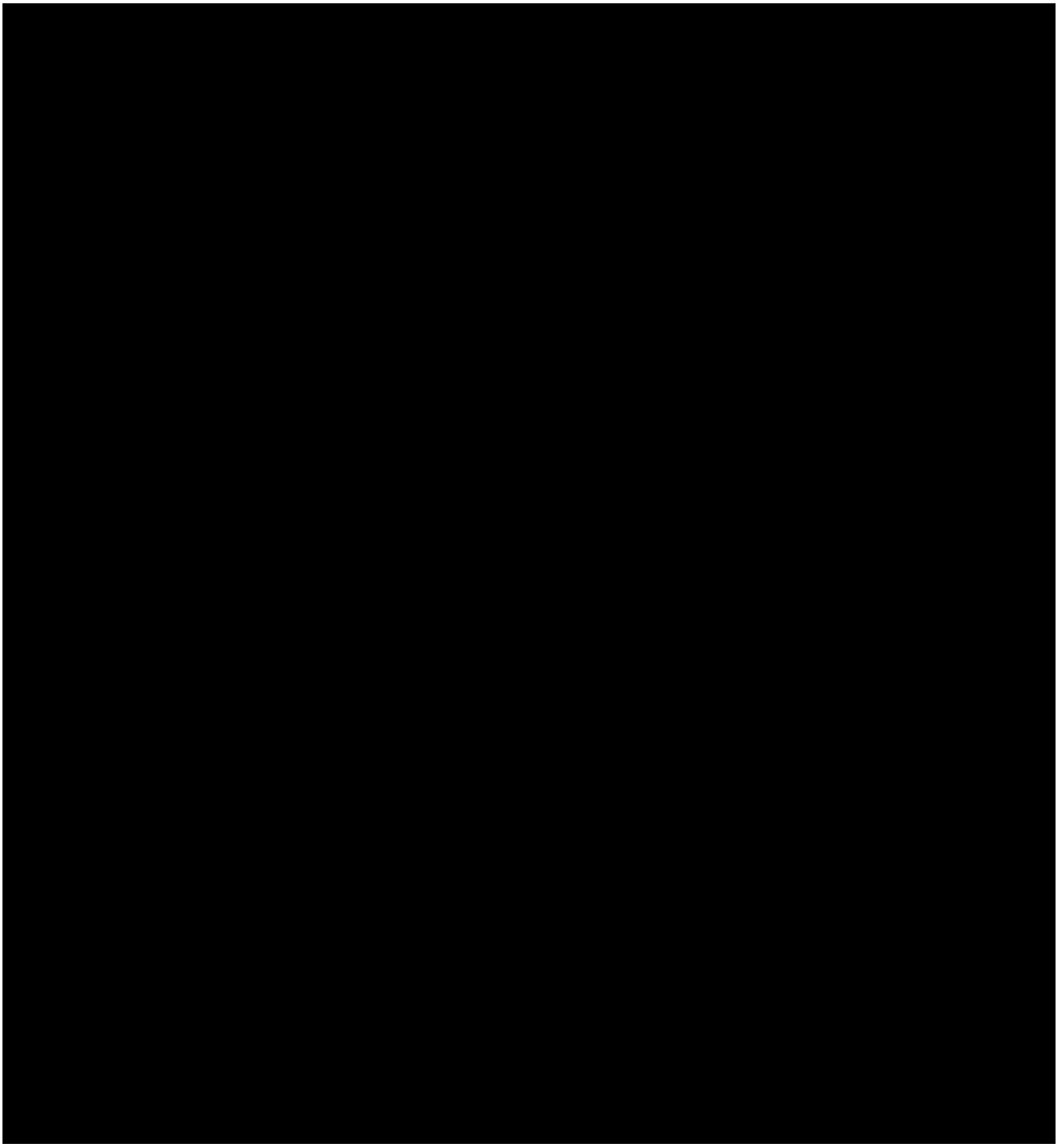
Blood samples for PK [redacted] analysis will be obtained at the visits and timepoints indicated in Table 4 and Table 23. After the preinfusion PK sample is drawn, participants will begin the study drug infusion. Adjustments to the timing of blood sampling may be made based on emerging PK data. The exact 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.

Table 23: Pharmacokinetic and Antidrug Antibody Serum Blood Sample Timing

Study Visit	Assessment	Timing of Sample
Cycle 1 Day 1	PK [redacted]	Preinfusion
	PK	10 minutes post INCMGA00012 infusion (± 10 minutes) 4 hours post INCMGA00012 infusion (± 15 minutes)
Cycle 2 Day 1	PK [redacted]	Preinfusion
Cycle 4 Day 1	PK [redacted]	Preinfusion
Cycle 6 Day 1	PK [redacted]	Preinfusion
	PK	10 minutes post INCMGA00012 infusion (± 10 minutes) 4 hours post INCMGA00012 infusion (± 15 minutes)
Cycle 7 Day 1	PK	Preinfusion

[redacted]

[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 and all assessments for the EOT and 28-day follow-up visits will be performed.

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, except for those who have actively withdrawn consent for any further participation in the study, should be encouraged to participate in the follow-up period.

8.8.1. Safety Follow-Up

The safety follow-up period starts once the participant discontinues study treatment. Approximately 28 (± 7) days after the final dose of study drug, participants are to attend a clinical visit for a safety evaluation. During this visit, blood will be collected for safety laboratory analysis, and other safety assessments, such as a physical examination and recording AEs and concomitant medications, will be performed as described in Table 3. Participants will be followed for AEs up to 90 days after the last dose of study drug or until the start of a new anticancer therapy, whichever occurs first. Reasonable efforts should be made to align the first

12-week follow up visit with the end of the 90-day AE reporting period. However, if necessary, contact by phone or other methods of communication are acceptable in order for the participant to report any AEs that may occur during this period.

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

8.8.2. Post-Treatment Disease Follow-Up

Participants who discontinue study treatment for a reason other than disease progression will move into the disease status follow-up period and should be assessed according to the schedule of events until:

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

8.8.3. Survival Follow-Up

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

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

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

9.1. Definition of Adverse Event

Adverse Event Definition
• An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related. • An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study treatment.
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 treatment 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 treatment 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. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an AE or SAE if they fulfill the definition of an AE or SAE.

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 v5.0 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 treatment 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 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 Nondrug 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 study treatment 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 treatment 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 treatment or study procedure[s]), all SAEs occurring after the participant has signed the ICF through 90 days after the last dose of study treatment ***or*** until the participant starts a new anticancer therapy, whichever occurs earlier must be reported to the sponsor (or designee) within **24 hours** of learning of its occurrence, unless otherwise specified by the Protocol. 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 treatment or study participation, the investigator must notify the sponsor (or designee) within 24 hours of becoming aware of the event.

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

Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment 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 treatment 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 the PhV/designee. The contact information of the sponsor's study-specific representatives is listed in the Investigator Site Binder 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 study drug because of the SAE (eg, dose reduced, interrupted, or discontinued), or participant disposition (eg, continued or withdrew from study participation). Each recurrence, complication, or progression of the original event should be reported as follow-up to that event, regardless of when it occurs.
- In rare circumstances and in the absence of facsimile or computer equipment, notification by telephone is acceptable with a copy of the Incyte Serious Adverse Event Report Form sent by overnight mail or courier service. Initial notification via telephone does not replace the need for the investigator to complete and sign the Serious Adverse Event Report Form within the designated reporting time frames.
- Contacts for SAE reporting can be found in the Investigator Site Binder.

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 American Society of Clinical Oncology and European Society for Medical Oncology Clinical Practice Guidelines (Brahmer et al 2018, Haanen et al 2017). Guidance for the management of irAEs are provided in Section 6.5.2.

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 discontinued 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 treatment 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 the study treatment, derived from safety information collected by the sponsor or its designee, are presented in in the INCMGA00012 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 drugs 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.

9.10. Treatment of Overdose

In the event of an overdose of more than 25%, the investigator should:

- Contact the medical monitor immediately.
- Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

10. STATISTICS

10.1. Sample Size Determination

A pilot study of avelumab in participants with chemotherapy-naive metastatic MCC shows a confirmed ORR of 39.7% with lower 95% CI of 30.7% (D'Angelo et al 2019). A pilot study of pembrolizumab in the same population showed an ORR of 56% with lower 95% CI of 35% (Nghiem et al 2016, Nghiem et al 2019).

Based on the results from studies of avelumab and pembrolizumab, it is reasonable to target a response rate of approximately 48%. Approximately 60 chemotherapy-naive participants will be enrolled for the primary analysis. Based on a target ORR of 48% and a sample size of approximately 60, this study has over 80% power to exclude the lower 95% confidence limit of 30% with $\alpha = 0.025$ (1-sided) in the chemotherapy-naive population.

Approximately 100 chemotherapy-naive participants will be enrolled for the final analysis. This sample size ensures that half of the 95% CI will be approximately 10% for an ORR ranging from 40% to 60%. This sample size also ensures 99% power to detect any AE with an underlying event rate as low as 0.5%.

Note: Participants who had received prior chemotherapy for MCC were enrolled up to Amendment 4.

10.2. Populations for Analysis

Table 25: Populations for Analysis

Population	Description
FAS	The FAS includes all participants enrolled in the study who received at least 1 dose of study drug and will include the first 60 chemotherapy-naive participants. The FAS will be used for the summary of demographics, baseline characteristics, participant disposition, and efficacy. Note: this analysis population will be used in the interim CSR.
Efficacy evaluable population	The efficacy evaluable population includes all participants from the FAS with a centrally confirmed diagnosis of MCC who are evaluable according to RECIST v1.1 and have received at least 1 dose of study drug.
Safety evaluable population	The safety evaluable population includes all enrolled participants who received at least 1 dose of study drug. The safety evaluable population will be used to support the safety analysis at the primary analysis and to support all analyses including efficacy at the final analysis.
PK evaluable population	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.

The primary analysis will occur after 60 chemotherapy-naive participants have been enrolled and followed for at least 6 months after confirmed response. If the study meets the predefined efficacy threshold at the primary analysis (see Section 10.1), the final analysis will occur after all 100 participants have been enrolled and followed for survival for a minimum of 2 years.

10.4.1. Primary Analysis

10.4.1.1. Overall Response Rate

The primary endpoint of the study is ORR in the chemotherapy-naive population, 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 an ICR. The primary analysis of ORR will be based on the chemotherapy-naive subset of the FAS, as defined in Table 25. Overall response rate and its exact 95% CI will be presented. The analysis will be assessed using the efficacy evaluable population as a sensitivity analysis. The ORR will be assessed again at the final analysis using the safety evaluable population.

10.4.1.2. Handling of Missing Data in Primary Analysis

The efficacy evaluable population must have measurable disease at baseline per RECIST v1.1. Participants with subsequent missing assessments that prevent the evaluation of the primary endpoint will be considered as nonresponders. No data imputation will be applied.

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.

10.4.2. Secondary Analysis

10.4.2.1. Duration of Response

Duration of response is defined as the time from first documented 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. Duration of response will be assessed for chemotherapy-naive participants. The Kaplan-Meier estimate of the distribution function will be constructed for DOR. The estimated median along with 95% CI will be reported. Duration of response will be analyzed using the FAS at the primary analysis and may be assessed using the safety evaluable population at the final analysis.

10.4.2.2. Disease Control Rate

Disease control rate is defined as the proportion of participants with either an objective response (CR and PR) or SD lasting at least 6 months, according to RECIST v1.1. Disease control rate

will be assessed for chemotherapy-naive participants using the FAS at the primary analysis and may be assessed using the safety evaluable population at the final analysis.

10.4.2.3. Progression-Free Survival

Progression-free survival, defined as the time from first dose of study treatment to the date of the first documented progression per RECIST v1.1 by ICR 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. Progression-free survival will be assessed for chemotherapy-naive participants using the FAS at the primary analysis and may be assessed using the safety evaluable population at the final analysis.

10.4.2.4. Overall Survival

Overall survival is defined as the time from first dose of study treatment to the date of death due to any cause. 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. Overall survival will be assessed for chemotherapy-naive participants using the FAS at the primary analysis and may be assessed using safety evaluable population at the final analysis.

10.4.3. Safety Analyses

The clinical safety data (eg, vital signs, ECGs, routine laboratory tests, physical examinations, and AEs) will be summarized using descriptive statistics (eg, mean, frequency) using the safety evaluable population. The safety analysis will be performed separately for chemotherapy-naive participants and the full study population.

Summary tables may be replaced with listings when appropriate. For instance, an AE frequency table may be replaced with a listing if it only contains a few unique preferred terms reported on relatively few participants.

10.4.3.1. Adverse Events

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

10.4.3.2. Adverse Events of Special Interest

Adverse events of special interest will include irAEs.

10.4.3.3. Clinical Laboratory Tests

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

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

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

10.4.3.4. Vital Signs

Descriptive statistics and mean change from baseline will be determined for vital signs (blood pressure, O2 saturation, pulse, respiratory rate, and body temperature) at each assessment time. Vital sign results will be reviewed for clinically notable abnormalities, and participants exhibiting clinically notable vital sign abnormalities will be listed.

10.4.3.5. Electrocardiograms

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

10.4.3.6. Dose Intensity

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

10.4.4. Pharmacokinetics

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

10.4.5. Exploratory Analyses

[redacted]

10.4.5.6. Efficacy Endpoints for Full Study Population

Efficacy will be determined for the full study population, including participants who are chemotherapy-naive and those participants who received prior chemotherapy who enrolled before Amendment 5.

The ORR in the full study population, comprised of chemotherapy-naive and chemotherapy-refractory participants, will be evaluated as an exploratory endpoint. The ORR and its exact 95% CI will be presented. The ORR in chemotherapy-refractory participants will be provided as a subgroup analysis. The ORR in the full study population will be analyzed using the FAS at the primary analysis.

Duration of response, DCR, PFS, and OS will be analyzed using the methods described in Sections 10.4.2.1, 10.4.2.2, 10.4.2.3, and 10.4.2.4. These endpoints will be assessed separately for chemotherapy-naive participants and the full study population.

10.5. Futility Analysis

An analysis is planned after approximately 20 chemotherapy-naive participants are assessable for response. The primary intent of this analysis is to minimize unnecessary exposure of participants to INCMGA00012 in the event of futility. The futility analysis will be based on conditional power/probability of success to achieve the primary endpoint of target ORR. Enrollment will continue while the analysis is being conducted. This futility analysis will be reviewed by an independent DMC as specified in the DMC charter. The process by which the DMC will review data and make recommendations and decisions will be documented in the DMC charter. This futility analysis will be described in greater detail in the Statistical Analysis Plan.

As of Protocol Amendment 6, the DMC has reviewed the data for the interim analysis. The preliminary efficacy based on the ORR assessed by ICR exceeded the futility threshold, and the DMC recommended the study to proceed as planned.

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 health authorities or regulatory agencies and 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. Data from external vendors may also be integrated into the clinical database. 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.

- 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 (including but not limited to HIPAA and GDPR) as applicable. Appropriate consent for collection, use, and disclosure and/or transfer (if applicable) of personal information must be obtained in accordance with local data protection laws.

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 appropriate technical and organizational measures as required by 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 otherwise. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

11.4. Financial Disclosure

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

Any new clinical investigators added to the covered clinical study during its conduct must also submit a completed Investigator Financial Disclosure Form. During a covered clinical study,

any changes to the financial information previously reported by a clinical investigator must be reported to the sponsor or its designee. At the conclusion of the covered clinical study, the clinical investigators will be reminded of their obligations. In the event that the clinical investigator is not reminded, they nevertheless will remain obligated to report to the sponsor or its designee any changes to the financial information previously reported, as well as any changes in their financial information for a period of 1 year after completion of the covered clinical study.

11.5. Publication Policy

By signing the study Protocol, the investigator and his/her institution agree that the results of the study may be used by the sponsor, Incyte Corporation, 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 treatment development.

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APPENDIX A. INFORMATION REGARDING EFFECTIVENESS OF CONTRACEPTIVE METHODS

For male participants in the study:

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

For female participants in the study:

The following methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods:

- 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

General principles of RECIST v1.1 are provided below. For full details, refer to Eisenhauer et al 2009.

Evaluation of Target Lesions

CR	Disappearance of all target lesions. Any pathological lymph nodes (whether target or nontarget must have reduction in short axis to < 10 mm).
PR	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
PD	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study), 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 diameters while on study.

CR = complete response; 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. All lymph nodes must be nonpathological in size (< 10 mm short axis).
Non-CR/ Non-PD	Persistence of 1 or more nontarget lesion(s) and/or maintenance of tumor marker level above the normal limits.
PD	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 New Lesions

PD	The appearance of new malignant lesions denotes disease progression. The finding of a new lesions should be unequivocal.

Evaluation of Best Overall Response

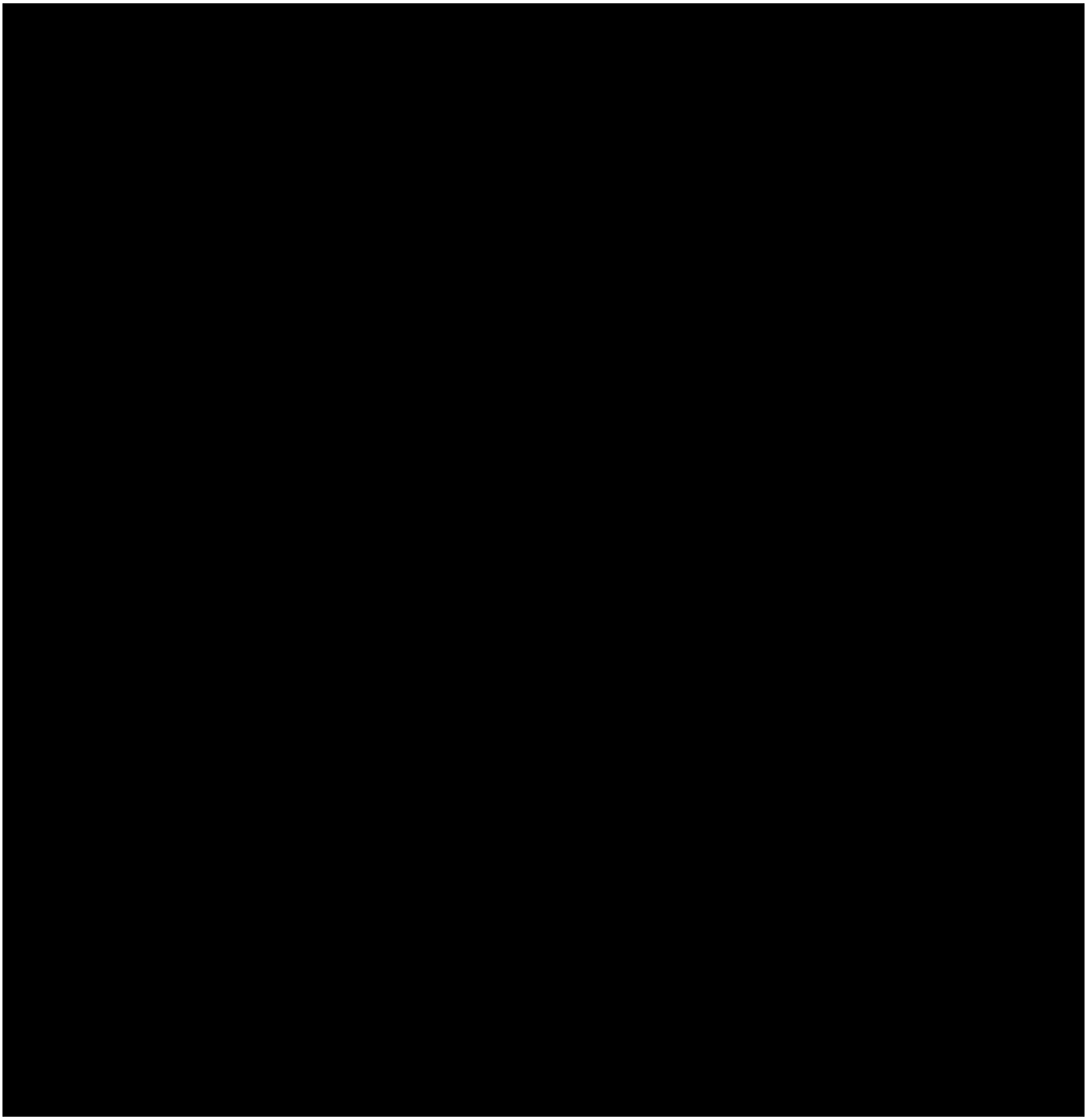
- The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the participant's best response assignment will depend on the achievement of both measurement and confirmation criteria.

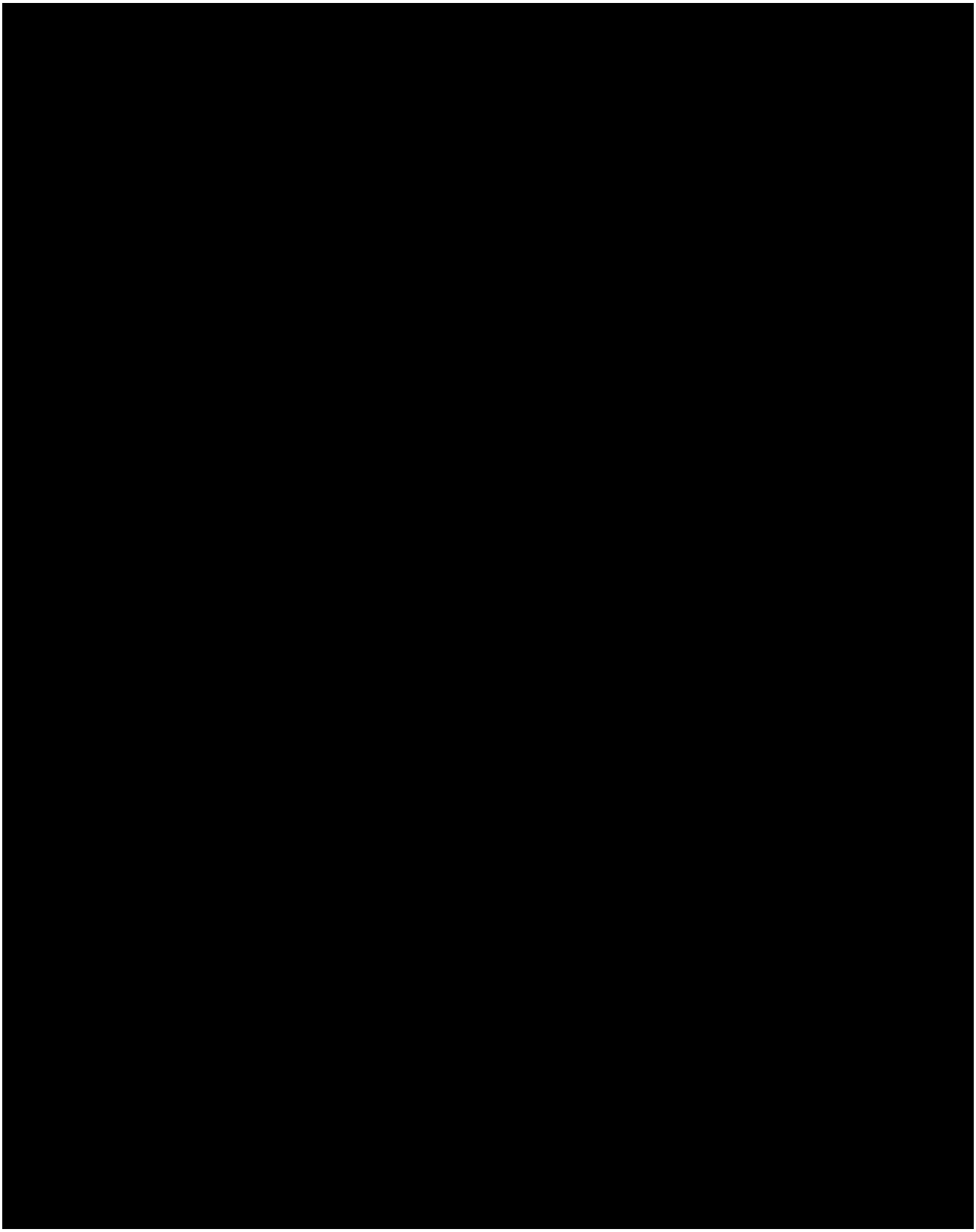
Target lesions	Nontarget Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or Not all evaluated	No	PR
SD	Non-PD or Not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

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 "clinical progression." 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 D. COVID-19 PANDEMIC MITIGATION STRATEGIES AND INSTRUCTIONS

The COVID-19 global pandemic presents challenges to the ongoing conduct of clinical trials. In line with regulatory guidance regarding clinical study execution during the pandemic, the sponsor has issued the following protocol considerations to ensure participant safety is maintained and adequate benefit/risk analyses are applied relative to participation in the study, the completion of study procedures, and objectives.

Recognizing the dynamic nature and flexibility required to manage the impact of the pandemic on this clinical study, additional details will be incorporated into respective study manuals and site-specific monitoring plans as applicable, with institutional requirements as warranted, and communicated and discussed with investigative sites as needed. Relevant test results will be documented in the eCRF, and applicable changes to the ICF will be made and monitored.

SARS-CoV2 Infection and Participation in the Study

Benefit/risk assessment in the context of the COVID-19 pandemic is provided in Section 2.3.1. During the COVID-19 pandemic, additional risks to participants exist either related to going to a healthcare facility or as a result of study-related activities. It is at the investigator's discretion to balance the risk/benefit while considering the participant's safety, existing comorbidities, and current malignancy. In addition, country-specific requirements are to be followed with regard to COVID-19 testing.

Study Site Visits

If local travel restrictions, isolation requirements, or the investigator's benefit/risk assessment determines it to be unsafe for participants to attend study visits at the investigational site, the site staff may elect to pursue the following:

- In order to minimize participant risk, some study procedures may be conducted via telemedicine modalities (phone or video), where appropriate, or as per institutional guidelines during the COVID-19 pandemic. At a minimum, a review of AEs and concomitant medications must be completed. On-site visits should be conducted whenever feasible and **are required for administration of study treatment**. The participant may also be asked to undergo additional safety laboratory assessments.
- **During COVID-19 restrictions only,** scans for disease assessments may be delayed by an additional 7 days from the time allowed in the protocol (see Table 3). If necessary, scans may be done at a different hospital only if the quality and methodology is the same as the participating study site and the images can be transferred to the study site. It is the investigator's responsibility to confirm that the external facility meets these requirements before any scans are performed at that location.

Study Treatment Administration:

- Treatment delays of > 12 weeks for logistical reasons (eg, travel restrictions due to COVID-19) may be acceptable but must be discussed with the medical monitor.

Study Treatment Management in the Event of SARS-CoV-2 Infection

If a participant develops a SARS-CoV2 infection, the event should be reported as an AE or SAE (if it meets the SAE definition requirements according to Section 9.2) and appropriate medical intervention provided. COVID-19 testing should follow country-specific requirements depending on the extent of COVID-19 pandemic, local institutional guidance, or investigator's clinical judgment. For participants who are diagnosed with COVID-19 during the study (positive COVID-19 test) or presumed affected by SARS-CoV-2 infection (test pending/clinical suspicion), study treatment should be delayed until COVID-19 test normalization and clinical recovery. Safety monitoring following COVID-19 infection should be implemented as per institutional guidance or clinical judgment (eg, coagulation factors). Concomitant medication administered for treatment of SARS-CoV-2 infection should be carefully considered for potential drug-drug interactions and medications should be recorded in the eCRFs.

COVID-19 Vaccination During Participation in the Study

Participants may receive the COVID-19 vaccine as long as it is not a live vaccine.

- It is recommended that COVID vaccine is not administered on the day of INCMGA00012 infusion. Administration of study treatment may be delayed by 3 days to ensure vaccination is completed and acute AEs (if any) are managed.
- The COVID-19 vaccination must be entered in the EDC as a concomitant medication.
- Any AEs resulting from the vaccination and medications for treating the AEs must be entered in eCRFs.

Clinical Study Monitoring

Study monitoring visits could be postponed; however, the site monitor and sponsor will continue to employ off-site monitoring practices such as routine communication methods (eg, phone calls, emails, video visits, remote visits with source data monitoring where allowed) with the sites to get information on study progress, participant status, and information on issue resolution. The study monitor may remotely review data entered into the EDC for accuracy and completeness if allowed by the national regulatory body, investigational site, and/or in compliance with local authorities.

Reimbursement of Additional Expenses

The sponsor will reimburse for any extraordinary expenses, keeping appropriate documentation as evidence (eg, travel expenses for the local laboratory visit[s], the costs of local [proximate] laboratory tests).

APPENDIX E. PROTOCOL AMENDMENT SUMMARY OF CHANGES

Document	Date
Amendment (Version) 1:	27 JUN 2018
Amendment (Version) 2:	04 OCT 2018
Amendment (Version) 3:	05 DEC 2018
Amendment (Version) 4:	16 AUG 2019
Amendment (Version) 5:	09 APR 2020
Amendment (Version) 6:	22 OCT 2020
Amendment (Version) 7:	16 DEC 2021

Amendment 7 (16 DEC 2021)

Overall Rationale for the Amendment: The primary purpose of this amendment is to update irAE management guidelines to reflect updated published guidance and to provide guidance on the management of participants during the COVID-19 pandemic. Additional changes are summarized below.

1. **Section 2.2, Study Rationale**

   Description of change: Background information on safety and efficacy of INCMGA00012 was updated to reflect more recent data.

   Rationale for change: To provide investigators with the most recent safety and efficacy data for their knowledge.

2. **Section 2.3.1, Benefit/Risk Assessment During the COVID-19 Pandemic; Section 8.3.6, Laboratory Assessments (Table 22: Required Laboratory Analytes); Appendix D, COVID-19 Pandemic Mitigation Strategies and Instructions**

   Description of change: Information regarding the COVID-19 pandemic including a risk/benefit assessment and instructions for changes to protocol-required procedures have been added to the protocol.

   Rationale for change: To provide additional information regarding COVID-19.

3. **Section 6.5.1, Management of Suspected Infusion Reactions (Table 8: Guidelines for Management of Suspected Infusion Reactions)**

   Description of change: Minor updates to guidance for infusion reactions.

   Rationale for change: Updates reflect evolving guidance in published recommendations.

4. **Section 6.5.2, Procedures for Participants Exhibiting Immune-Related Adverse Events; Section 9.5, Adverse Events of Special Interest**

   Description of change: Updated and/or added irAEs. The added irAEs are included in Section 6.5.2.4.4, Section 6.5.2.8, and Section 6.5.2.9.

   Rational for change: Updates and/or additions reflect evolving guidance in published recommendations.

5. **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 6 (22 OCT 2020)

Overall Rationale for the Amendment: The primary purpose of this amendment is to increase the sample size of the study to allow for more robust characterization of the primary and secondary endpoints.

1. **Section 1, Protocol Summary (Table 2: Key Study Design Elements); Section 4.1, Overall Design; Section 4.2, Overall Study Duration; Section 10.1, Sample Size Determination; Section 10.2, Populations for Analysis (Table 22: Populations for Analysis); Section 10.4, Statistical Analyses; Section 10.4.1.1, Overall Response Rate; Section 10.4.2.1, Duration of Response; Section 10.4.2.2, Disease Control Rate; Section 10.4.2.3, Progression-Free Survival; Section 10.4.2.4, Overall Survival; Section 10.4.5.6, Efficacy Endpoints for Full Study Population**

   Description of change: The number of participants to be enrolled was increased to 100 chemotherapy-naive participants. Based on this change, the study duration section was updated to clarify that the study will end once every participant receiving active treatment has been followed for at least 6 months after confirmed response or until all participants have been followed for survival for a minimum of 2 years. The statistical section was also updated to clarify how the populations will be analyzed for the primary and final analyses.

   Rationale for change: Guidance from a regulatory authority indicated that additional participants should be enrolled for more robust characterization of durability of response and OS. As of Protocol Amendment 6, approximately 60 chemotherapy-naive participants have been enrolled in this study. An independent, external DMC has reviewed the preliminary safety and efficacy data as part of the futility analysis. The safety profile was as expected for agents of this class, and efficacy exceeded the futility threshold. The DMC has recommended that the study proceed as planned. Therefore, the benefit/risk profile of INCMGA00012 remains favorable in this population.

   The study will continue until all participants receiving active treatment have been followed for at least 6 months after confirmed response or until all participants have been followed for survival for a minimum of 2 years. Following participants on active treatment for at least 6 months after confirmed response allows for robust characterization of durability of response. Survival follow-up for a minimum of 2 years is likely to provide a durable estimate of OS. The median OS for patients with metastatic MCC treated with avelumab was 20.3 months (D'Angelo et al 2019). The median OS in patients treated with pembrolizumab was not reached at the time of publication (Nghiem et al 2019). Based on these results, it is reasonable to assume that a minimum of 2 years of follow-up will provide a reliable estimate of OS.

2. **Section 2.1, Background; Section 10.1, Sample Size Determination**

   Description of change: Information about avelumab in MCC was updated to reflect a recent publication of more mature data.

   Rationale for change: To provide updated information to investigators. Preliminary data from the JAVELIN Merkel 200 study of avelumab in 29 first-line MCC patients showed an ORR of 62.1% (D'Angelo et al 2018). Updated data, presented in 2019, with a larger sample size (n = 116) and follow-up of ≥ 15 months show an ORR of 39.7% (D'Angelo et al 2019). As the sample size and power for Study INCMGA 0012-201 are based on the preliminary data from the JAVELIN 200 study and published data on pembrolizumab, the updated data needed to be taken into account.

3. **Section 4.3.1, Data Monitoring Committee; Section 10.5, Futility Analysis**

   Description of change: An update on the futility analysis has been provided.

   Rationale for change: This information was included to provide information to reviewers and investigators regarding the futility analysis.

[redacted]

5. **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 5 (09 APR 2020)

Overall Rationale for the Amendment: The primary purpose of this amendment is to clarify the definition of target lesions for participants who have progression in areas previously treated with locoregional therapy.

1. **Section 1, Protocol Summary (Table 1, Primary and Secondary Objectives and Endpoints; Table 2, Key Study Design Elements); Section 3, Objectives and Endpoints (Table 5: Objectives and Endpoints); Section 4.1, Overall Design; Section 5.1, Inclusion Criteria (Criterion 3); Section 5.2, Exclusion Criteria (Criterion 1); Section 10.1, Sample Size Determination; Section 10.4.2, Secondary Analyses; Section 10.4.5.6, Efficacy Endpoints for Full Study Population**

   Description of change: The study design and eligibility criteria were adjusted to exclude participants who have received prior systemic therapy for treatment of MCC. All relevant sections were updated accordingly.

   Rationale for change: The treatment landscape for patients with advanced/metastatic MCC has changed with the availability of anti–PD-(L)1 therapies. These therapies are increasingly available and reimbursed in many regions, and it is rare for patients to receive systemic chemotherapy before treatment with an anti–PD-(L)1 agent. The primary endpoint of this study is ORR in chemotherapy-naive participants with advanced/metastatic MCC. Chemotherapy-refractory patients are becomingly increasingly uncommon as demonstrated by slow recruitment in this study. Only 5 chemotherapy-refractory participants were enrolled in this study in 18 months. Chemotherapy-refractory participants are hence excluded from future enrollment in this study.

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

   Description of change: Updated to indicate that treatment delays of > 12 weeks for logistical reasons (eg, travel restrictions due to COVID-19) may be acceptable but must be discussed with the medical monitor.

   Rationale for change: To allow for continued participation in the study if there are treatment delays longer than 12 weeks for certain logistical reasons.

3. **Section 2.2, Study Rationale**

   Description of change: Removed redundant text in the second paragraph.

   Rationale for change: The information is included elsewhere in the section.

4. **Section 5.1, Inclusion Criteria (Criterion 5); Section 8.2.1, Tumor Imaging**

   Description of change: Protocol language was updated to clarify that tumor lesions located in areas that have received prior locoregional therapy may be selected as target lesions if progression has been demonstrated in these lesions.

   Rationale for change: In Amendment 4, the Protocol was revised to allow participants with recurrent, advanced locoregional MCC to enroll in the study. Protocol language regarding the selection of target lesions in areas subjected to locoregional therapy needed to be updated to reflect this change.

5. **Section 5.2, Exclusion Criteria (Table 6, Exclusionary Laboratory Values)**

   Description of change: Adjusted creatinine clearance value considered exclusionary was changed to < 30 mL/min.

   Rationale for change: Monoclonal antibodies are not filtered by the kidney; therefore, the PK of INCMGA00012 should not be impacted by allowing participants with more limited renal function to be enrolled. No significant drug-related renal toxicity has been observed in more than 300 participants treated with INCMGA00012 monotherapy. Additionally, nephritis is an uncommon drug-related AE seen with other drugs of this class that have used a creatinine clearance of 30 mL/min as threshold for administration.

6. **Section 8.3.6, Laboratory Assessments (Table 19, Required Laboratory Analytes)**

   Description of change: Added free T4 to the list of acceptable analytes.

   Rationale for change: Either free T4 or total T4 is acceptable for monitoring thyroid hormone levels.

7. **Appendix B, Response Evaluation Criteria for Solid Tumors Version 1.1**

   Description of change: Language was updated to reflect RECIST v1.1 terminology.

   Rationale for change: Language in the appendix was not consistent with RECIST v1.1 guidance.

8. **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 (16 AUG 2019)

Overall Rationale for the Amendment:

The primary purpose of this amendment is to expand the eligibility criteria to include participants with recurrent locoregional advanced disease in addition to participants with distant metastatic MCC.

1. **Section 1, Protocol Summary; Section 2.1, Background; Section 2.2, Study Rationale; Section 3, Objectives and Endpoints; Section 4.1, Overall Design; Section 5.1, Inclusion Criteria (Criterion 3)**

   Description of change: Updated to allow participants with recurrent, advanced locoregional MCC to enroll in the trial.

   Rationale for change: Approximately half of patients with locally advanced MCC experience disease recurrence within 2 years from diagnosis. Management of patients with recurrent locally advanced unresectable MCC is challenging (Becker JC, Stang A, DeCaprio JA, et al. Merkel cell carcinoma. Nat Rev Dis Primers 2017;3:17077.). Similar to distant metastatic disease, patients with recurrent unresectable MCC require systemic therapy to achieve disease control. While MCC is responsive to chemotherapy, the responses are short lived. Durable responses have been achieved with anti-PD-(L)1 antibodies in patients with metastatic as well as recurrent locally advanced MCC (Nghiem P, Bhatia S, Lipson EJ, et al. Durable tumor regression and overall survival in patients with advanced Merkel cell carcinoma receiving pembrolizumab as first-line therapy. J Clin Oncol 2019;37:693-702.; D'Angelo SP, Russell J, Lebbé C, et al. Efficacy and safety of first-line avelumab treatment in patients with Stage IV metastatic Merkel cell carcinoma: a preplanned interim analysis of a clinical trial [published online ahead of print March 22, 2018]. JAMA Oncol doi:10.1001/jamaoncol.2018.0077.; Kaufman HL, Russell J, Hamid O, et al. Avelumab in patient with chemotherapy-refractory metastatic Merkel cell carcinoma: a multicenter, single-group, open-label, phase 2 trail. Lancet Oncol 2016;17:1374-1385.). A 2019 update to the NCCN guidelines also indicate that pembrolizumab may be considered as a treatment option for patients with recurrent locally advanced disease (National Comprehensive Cancer Network. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology: Merkel Cell Carcinoma Version 2.2019. 2019. https://www.nccn.org/professionals/physician_gls/pdf/mcc.pdf.).

   Patients with recurrent locally advanced disease who are not amenable to definitive surgery or radiation are likely to benefit from treatment with anti–PD-1 therapy and hence will be eligible for this trial.

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

   Description of change: Laboratory requirements for subsequent study treatment cycles were removed from the Protocol.

   Rationale for change: Laboratory abnormalities are addressed in other criteria and do not need to be specifically listed as these abnormalities are not expected to worsen with immunotherapy.

[redacted]

4. **Section 1, Protocol Summary (Table 4, Pharmacokinetic [redacted] Sample Collections); Section 8.4, Pharmacokinetic Assessments (Table 20, Pharmacokinetic [redacted] Serum Blood Sample Timing); [redacted]**

   Description of change: Added tables to detail the timing of PK, [redacted]

   Rationale for change: To provide clarity to the investigational sites and to remove unnecessary blood sampling for study participants.

5. **Section 1, Protocol Summary; Section 10.1, Sample Size Determination; Section 10.2, Populations for Analysis; Section 10.4.2.1, Overall Response Rate**

   Description of change: The FAS population was updated to include all participants who received a dose of study drug.

   Rationale for change: To address regulatory feedback from the United States Food and Drug Administration.

[redacted]

7. **Section 6.5.1, Management of Suspected Infusion Reactions (Table 8, Guidelines for Management of Suspected Infusion Reactions)**

   Description of change: Updated instruction for subsequent infusions for participants who have experienced a Grade 1 infusion reaction.

   Rationale for change: Premedication is no longer required per Amendment 2, so guidelines for management of suspected infusion reactions were updated to instruct sites to consider premedication in participants who experienced Grade 1 infusion reactions.

8. **Section 6.5.2.4, Immune-Mediated Endocrinopathies; Section 6.5.2.6, Immune-Mediated Skin Reactions**

   Description of change: Updates were made to irAE guidance in regard to restarting study treatment.

   Rationale for change: To make guidance consistent with ASCO clinical practice guidelines.

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

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

   Rationale for change: Updated based on emerging evidence that indicates the use of probiotic supplements may be associated with lower chance of responding to immunotherapy.

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

Amendment 3 (05 DEC 2018)

Overall Rationale for the Amendment:

The primary purpose of this amendment is to address comments received from Health Canada. Additional clarifications and administrative changes were also made.

1. **Section 1, Protocol Summary; Section 4.1, Overall Design; Section 7.1.1, Reasons for Discontinuation**

   Description of change: Clarified that participants should be discontinued from study treatment for disease progression.

   Rationale for change: Prior version of the Protocol required participants to discontinue from treatment for clinical disease progression; however, in general participants should also be removed from study treatment after radiographic disease progression.

2. **Section 1, Protocol Summary (Table 3, Schedule of Activities); Section 8.3.6, Laboratory Assessments (Table 19, Required Laboratory Analytes)**

   Description of change: Blood chemistry safety panel no longer specifies that it must be from serum.

   Rationale for change: To allow convenience for sites who typically use plasma for blood chemistry panel.

3. **Section 1, Protocol Summary (Table 3, Schedule of Activities); Section 5.2, Exclusion Criteria; Section 6.6.1, Permitted Medications and Procedures; Section 8.3.6, Laboratory Assessments (including Table 19, Required Laboratory Analytes)**

   Description of change: Participants who are HIV-positive may be enrolled into the study provided they meet the criteria specified in exclusion criterion 21. For those HIV-positive participants who do enroll, HIV management testing will be required and is now detailed in the Protocol.

   Rationale for change: To allow inclusion of participants with well-controlled HIV in this study since preliminary experience with immunotherapy in HIV-associated malignancy is promising.

[redacted]

5. **Section 1, Protocol Summary (Table 3, Schedule of Activities); Section 4.1, Overall Design; Section 8.8.1, Safety Follow-Up**

   Description of change: Clarified that AEs and concomitant medications are to be collected for 90 days after the last dose of study drug or until the participants start a new anticancer therapy.

   Rationale for change: Editorial change to ensure consistency with Sections 6.6, 8.3, and 9.4 in the Protocol.

[redacted]

7. **Section 1, Protocol Summary (Table 1); Section 3, Objectives and Endpoints (Table 5); Section 6.5.1, Management of Suspected Infusion Reactions (Table 8); Section 8.3.1, Adverse Events; Section 9.3, Recording and Follow-Up of Adverse Events and/or Serious Adverse Events**

   Description of change: Updated Protocol to indicate that CTCAE v5.0 will be used to assess the severity of AE.

   Rationale for change: To use the most recent version of CTCAE.

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

   Description of change: Added note indicating that survival status may be requested at any point during the study.

   Rationale for change: To allow flexibility for collecting updated survival data for analysis if required.

9. **Section 1, Protocol Summary (Table 3, Schedule of Activities; Table 4, Pharmacokinetic [redacted] Sample Collections)**

   Description of change: Adjusted the window for subsequent cycle visits to 7 days.

   Rationale for change: To allow flexibility for participant scheduling.

10. **Section 2.2, Study Rationale**

    Description of change: Results from the first-in-human monotherapy study (INCMGA 0012-101) were updated.

    Rationale for change: Provide updated information to investigators.

11. **Section 5.2, Exclusion Criteria**

    Description of change: The ALT and AST exclusionary laboratory values were adjusted to allow for the possibility of participants with liver metastases to enroll if their ALT or AST are ≤ 5 × ULN.

    Rationale for change: Language in prior versions of the Protocol had strict exclusion criterion for ALT and AST that may have excluded participants with liver metastases that were otherwise good candidates for the study.

12. **Section 6.1, Study Treatment Administered (Table 7, Study Treatment Information); Section 6.5.1, Management of Suspected Infusion Reactions; Section 6.6.1, Permitted Medications and Procedures**

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

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

13. **Section 6.5.1, Management of Suspected Infusion Reactions (Table 8, Guidelines for Management of Suspected Infusion Reactions)**

    Description of change: Additional guidance on the rate of infusion after a suspected infusion reaction was provided.

    Rationale for change: To provide clarification to sites.

14. **Section 7.1.1, Reasons for Discontinuation**

    Description of change: Added language that allows participants to discontinue study treatment if they achieve a confirmed CR and have received at least 6 months of study treatment.

    Rationale for change: This change will allow flexibility for the investigator to decide if it is in the participant's best interest to discontinue study treatment after achieving a CR.

[redacted]

16. **Section 8.3.3, Vital Signs**

    Description of change: Language was added to provide guidance on timing of vital signs in regards to blood collection when it is not feasible for vital signs to be taken before the blood collection.

    Rationale for change: This language was added to allow flexibility for sites in scheduling procedures.

17. **Section 8.3.5, Electrocardiograms**

    Description of change: Additional information was provided regarding the timing of ECGs and the need for triplicate ECGs.

    Rationale for change: To provide additional information to the sites.

18. **Section 9.7, Pregnancy**

    Description of change: Updated the time frame for restarting study treatment to 12 weeks.

    Rationale for change: To make the time frame consistent with treatment interruptions for other reasons.

19. **Incorporation of administrative changes:** Other minor administrative changes have been incorporated throughout the Protocol and are noted in the redline version of the document.

Amendment 2 (04 OCT 2018)

Overall Rationale for the Amendment:

The primary purpose of this amendment is to address comments received from the European Competent Authorities during the VHP.

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

   Description of change: Prior to receiving infusion of INCMGA00012, participants must have a hemoglobin level of ≥ 9 g/dL.

   Rationale for change: This requirement was changed based on feedback from the European Competent Authorities during the VHP and is consistent with the eligibility criterion for the study regarding hemoglobin.

2. **Section 1, Protocol Summary; Section 4.1, Overall Design; Section 6.5, Dose Modifications**

   Description of change: Edits were made to clarify that study treatment doses will not be modified, but dosing can be interrupted up to 12 weeks prior to restarting.

   Rationale for change: Provide additional clarity to clinical sites.

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

   Description of change: An independent data monitoring committee will be formed.

   Rationale for change: To provide independent review of safety and efficacy data during the study.

4. **Section 1, Protocol Summary (Table 3, Schedule of Activities); Section 6.1, Study Treatment Administered (Table 7, Study Treatment Information)**

   Description of change: A note was added to Table 3 and Table 7 to remind sites to monitor for reactions during the infusion of INCMGA00012.

   Rationale for change: To make it clear in the Protocol that sites should be monitoring participants for infusion reactions per their institutional guidelines during the infusion period.

5. **Section 2.2, Study Rationale**

   Description of change: Background information for INCMGA00012 was added to the Protocol.

   Rationale for change: This language will provide updated safety information regarding the study treatment to investigators.

6. **Section 5.1, Inclusion Criteria; Section 5.2, Exclusion Criteria; Section 6.6.2, Prohibited Medications and Procedures**

   Description of changes:

   - Inclusion Criterion 7b: The duration of contraception for females was changed to 120 days after the last dose of study treatment.
   - Exclusion Criterion 13: The criterion was edited to exclude participants who have received a live virus vaccine within 28 days of the start of study therapy. The protocol previously used a 90-day timeframe prior to the start of study therapy. This timeframe was updated in the prohibited medications and procedures section as well for consistency.
   - Exclusion Criterion 19: This new criterion was added to exclude anyone with a history of organ transplant, including allogeneic stem cell transplantation.
   - Exclusion Criterion 20: This new criterion was added to exclude anyone with a known allergy or hypersensitivity to any component of the study drug formulation.

   Rationale for changes: Inclusion/exclusion criteria were updated to address inconsistencies and address comments from European Competent Authorities during the VHP.

7. **Section 5.5, Replacement of Participants**

   Description of change: Additional clarity was provided on how participants may be replaced if they do not meet eligibility criteria.

   Rationale for change: Provide additional clarification to clinical sites.

8. **Section 6.5.1, Management of Suspected Infusion Reactions (Table 8: Guidelines for Management of Suspected Infusion Reactions)**

   Description of change: Table 8 was updated to indicate that study treatment must be discontinued for any ≥ Grade 3 infusion-related reaction. The definition of a Grade 3 infusion reaction was also edited to match CTCAE guidance.

   Rationale for change: Guidance for infusion-related reactions was edited to provide additional clarity to clinical sites.

9. **Section 6.5.2.7, Immune-Mediated Myocarditis**

   Description of change: Guidance for the management of immune-mediated myocarditis was added.

   Rationale for change: These events can be serious, and therefore, it is prudent to provide guidance to the Investigators.

10. **Section 7.1.1, Reasons for Discontinuation**

    Description of change: Pregnancy was listed as a reason for discontinuation from study treatment.

    Rationale for change: Provide additional clarification to clinical sites.

11. **Section 8.2, Efficacy Assessments; Section 8.2.1, Tumor Imaging**

Description of change: Language was added to specify that disease status will be evaluated by independent central radiographic review (ICR).

Rationale for change: The Protocol was not clear that the response assessments will be performed by an ICR for the primary endpoint.

Amendment 1 (27 JUN 2018)

Overall Rationale for the Amendment:

The primary purpose of this amendment is to address comments received from the US FDA.

1. **Section 1, Protocol Summary (Table 1: Primary and Secondary Objectives and Endpoints); Section 3, Objectives and Endpoints (Table 5: Objectives and Endpoints), Section 4.1, Overall Design**

   Description of changes:

   - Assessment of the primary endpoint of ORR will be limited to the chemotherapy-naive study population. The ORR in the full study population, comprised of both chemotherapy-naive and chemotherapy-refractory participants, will be assessed as a secondary endpoint.
   - Multiple secondary endpoints have been added and/or revised to specify that the analysis will be performed on the chemotherapy-naive population and the full study population, comprised of both chemotherapy-naive and chemotherapy-refractory participants.

   Rationale for changes:

   - The primary efficacy assessment should be performed in a homogeneous population (per guidance from the FDA), since a higher ORR is expected in the chemotherapy-naive population based on emerging data.
   - The primary endpoint of the study has been revised and is now based only on the chemotherapy-naive population. Therefore, the secondary efficacy analysis has been revised and will include analysis of the full study population.

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

   Description of changes:

   - The following language was added to the description of study participants: "The participants should not have received any prior therapy with PD-1/PD-L1 inhibitors."
   - The criteria for eligibility for subsequent treatment cycles was updated to address the maximum allowable length of time for delaying study drug treatment.

   Rationale for changes:

   - The added language regarding prior therapy with PD-1/PD-L1 inhibitors is intended to provide clarification of the study population.
   - The revised language regarding criteria for eligibility for subsequent treatment cycles provides further definition and clarification of the treatment criteria for subsequent cycles and the maximum length of time a participant can be on a drug hold before being permanently discontinued from study treatment.

3. **Section 5.1, Inclusion Criteria**

   Description of change: Eligibility criterion #3 was modified to clarify that that the study population will be limited to participants with distant, metastatic disease.

   Rationale for change: This language is intended to clarify, as this study excludes participants with locoregional disease.

4. **Section 1, Protocol Summary; Section 10.1, Sample Size Determination; Section 10.4, Statistical Analyses**

   Description of change: Assumptions and sample size were revised in accordance with literature estimates for ORR in both the primary efficacy population (chemotherapy-naive) and the full study population of chemotherapy-naive and chemotherapy-refractory patients. Final sample size also reflects allowance for attrition during the course of the study. Statistical analyses were updated to align with the revised primary and secondary efficacy endpoints.

   Rationale for change: Alignment with revised primary and secondary efficacy objectives and endpoints.

   The recent availability of avelumab, in many countries for frontline treatment of metastatic MCC, has impacted practice patterns. While both chemotherapy and checkpoint inhibitor therapy may be appropriate for initial treatment based on practice guidelines (as per the NCCN) and local reimbursement policies, it is expected that, over the duration of the study, an increasing majority of participants will be offered checkpoint inhibitors as frontline therapy. Therefore, a small excess of chemotherapy-naive participants (55%) has been assumed for the projected enrollment in calculating the expected ORR for the full study population.

5. **Section 10.5, Futility Analysis**

   Description of change: Language was revised to indicate that the futility analysis will be based on responses in the chemotherapy-naive population. The number of participants assessable for response needed for the analysis was updated from 25 to 20.

   Rationale for change: Alignment with revised primary objective and endpoint.

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

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