Official Title:	A Phase 3 Global, Multicenter, Double-Blind Randomized Study of Carboplatin-Paclitaxel With INCMGA00012 or Placebo in Participants With Inoperable Locally Recurrent or Metastatic Squamous Cell Carcinoma of the Anal Canal Not Previously Treated With Systemic Chemotherapy (POD1UM-303/InterAACT 2)
NCT Number:	NCT04472429
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Clinical Study Protocol

INCMGA 0012-303

A Phase 3 Global, Multicenter, Double-Blind Randomized Study of Carboplatin-Paclitaxel With INCMGA00012 or Placebo in Participants With Inoperable Locally Recurrent or Metastatic Squamous Cell Carcinoma of the Anal Canal Not Previously Treated With Systemic Chemotherapy (POD1UM-303/InterAACT 2)

Product:	**INCMGA00012**
IND Number:	**139,333**
EudraCT Number:	**2020-000826-24**
EU CT Number:	**2024-512331-72-00**
Phase of Study:	**3**
Sponsor:	**Incyte Corporation 1801 Augustine Cut-Off Wilmington, DE 19803**
Original Protocol (Version 1):	**17 MAR 2020**
Original Protocol (Version 1-UK):	**01 SEP 2020**
Amendment 1 (Version 2):	**21 DEC 2021**
Amendment 2 (Version 3):	**25 MAY 2022**
Amendment 3 (Version 4)	**04 FEB 2025**

INVESTIGATOR'S AGREEMENT

I have read the INCMGA 0012-303 Protocol Amendment 3 (dated 04 FEB 2025) 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
ADA	antidrug antibody
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
anti–HBc	anti–hepatitis B core
anti–HCV	hepatitis C virus antibody
aPTT	activated partial thromboplastin time
ART/HAART	antiretroviral therapy/highly active antiretroviral therapy
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the curve
$AUC_{0-\infty}$	area under the single-dose plasma or serum concentration-time curve extrapolated to infinity
AUC_{0-t}	area under the plasma or serum concentration-time curve from time = 0 to the last measurable concentration at time = t
AUS	Australia
BCG	Bacillus Calmette–Guérin
BICR	blinded independent central radiographic review
BSA	body surface area
CFR	Code of Federal Regulations
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
C_{max}	maximum observed plasma or serum concentration
C_{min}	minimum observed plasma or serum concentration over the dose interval
$C_{min,ss}$	C_{min} at steady state
CNS	central nervous system
COVID-19	coronavirus disease 2019
CR	complete response
CrCl	creatinine clearance
CSF	colony stimulating factor
CSR	Clinical Study Report

Abbreviations and Special Terms	Definition
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCR	disease control rate
DDI	drug-drug interaction
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EEA	European Economic Area
EORTC-QLQ-C30	European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire
EOT	end of treatment
EQ VAS	EuroQol visual analogue scale
EQ-5D	EuroQol-5D
ESMO	European Society for Medical Oncology
EU	Europe Union
FAS	full analysis set
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
FT3	free triiodothyronine
FT4	free thyroxine
FU	fluorouracil
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
HAV	hepatitis A virus
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act of 1996

Abbreviations and Special Terms	Definition
HIV	human immunodeficiency virus
HPV	human papillomavirus
HR	hazard ratio
HR-PRO	health-related patient reported outcomes
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICD	immunogenic cell death
ICF	informed consent form
ICH	International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
iCPD	confirmed progressive disease per iRECIST
IEC	independent ethics committee
IgG	immunoglobulin G
IgG4	immunoglobulin G4
IgM	immunoglobulin M
IHC	immunohistochemistry
INR	international normalized ratio
irAE	immune-related adverse event
IRB	institutional review board
iRECIST	modified RECIST v1.1 for immune-based therapeutics
IRT	interactive response technology
ITT	intent-to-treat
iUPD	unconfirmed progressive disease per iRECIST
IV	intravenous(ly)
IVRS	interactive voice response system
IWRS	interactive web response system
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MSI	microsatellite instability status
NA	North America
NCI	National Cancer Institute
NSAID	nonsteroidal anti-inflammatory drug

Abbreviations and Special Terms	Definition
NSCLC	non–small cell lung cancer
ORR	overall response rate
ORR-CO	overall response rate – Crossover Period
OS	overall survival
PCR	polymerase chain reaction
PD	progressive disease
PD-1	programmed cell death protein 1
PD-L1	programmed cell death-ligand 1
PD-L2	programmed cell death-ligand 2
PET	positron emission tomography
PFS	progression-free survival
PFS2	progression-free survival 2
PK	pharmacokinetic(s)
PMDA	Pharmaceuticals and Medical Devices Agency
PO	oral
PR	partial response
PRO	patient-reported outcome
PT	prothrombin time
PTT	partial thromboplastin time
Q12W	every 12 weeks
Q2W	every 2 weeks
Q4W	every 4 weeks
Q8W	every 8 weeks
QLG	Quality of Life Group
QLQ-ANL27	Quality of Life Questionnaire for Anal Cancer
QoL	quality of life
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
ROW	rest of world
RSI	Reference Safety Information
RT-PCR	reverse transcription-polymerase chain reaction
SAE	serious adverse event

Abbreviations and Special Terms	Definition
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SCAC	squamous cell carcinoma of the anal canal
SD	stable disease
SJS	Stevens-Johnson syndrome
SoA	schedule of activities
SOC	standard of care
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
TEN	toxic epidermal necrolysis
T3	triiodothyronine
T4	thyroxine
TEAE	treatment-emergent adverse event
t_{max}	time to maximum concentration
TSH	thyroid-stimulating hormone
UK	United Kingdom
ULN	upper limit of normal
WOCBP	women of childbearing potential
WBC	white blood cell

1. PROTOCOL SUMMARY

Protocol Title: A Phase 3 Global, Multicenter, Double-Blind Randomized Study of Carboplatin-Paclitaxel With INCMGA00012 or Placebo in Participants With Inoperable Locally Recurrent or Metastatic Squamous Cell Carcinoma of the Anal Canal Not Previously Treated With Systemic Chemotherapy (POD1UM-303/InterAACT 2)

Protocol Number: INCMGA 0012-303

Objectives and Endpoints:

Table 1 presents the primary and major/key secondary objectives and endpoints.

Table 1: Primary and Key Secondary Objectives and Endpoints

Objectives	Endpoints
Primary	
To compare the efficacy of carboplatin-paclitaxel with INCMGA00012 versus carboplatin-paclitaxel with placebo in participants with inoperable locally advanced or metastatic SCAC not previously treated with systemic chemotherapy.	PFS, defined as the time from the date of randomization until disease progression according to RECIST v1.1 by BICR or death due to any cause.
Key Secondary	
To compare the efficacy of carboplatin-paclitaxel with INCMGA00012 versus carboplatin-paclitaxel with placebo in participants with inoperable locally advanced or metastatic SCAC not previously treated with systemic chemotherapy.	OS, defined as the time from the date of randomization until death due to any cause.

Overall Design:

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

Table 2: Key Study Design Elements

Study Phase	Phase 3
Clinical Indication	Squamous Cell Carcinoma of the Anal Canal
Population	Male and female participants at least 18 years of age who have inoperable locally recurrent or metastatic SCAC not previously treated with systemic chemotherapy.
Number of Participants	Approximately [redacted] evaluable participants will be randomized 1:1 to 1 of 2 Groups.
Study Design	This study is a Phase 3 global, multicenter, placebo-controlled double-blind, randomized study that will enroll participants with inoperable locally recurrent or metastatic SCAC not previously treated with systemic chemotherapy. Participants with well-controlled HIV infection will be eligible. Randomization will be stratified by PD-L1 expression (< 1%, ≥ 1%), region (AUS/EU/NA/UK vs ROW), and extent of disease (locally recurrent, metastatic). For the stratification category of PD-L1 status, participants with tumor results of PD-L1 negative and nonevaluable are grouped in the PD-L1 < 1% stratum. Participants with nonevaluable tumors for PD-L1 status will be capped at 10% of total population. The primary endpoint of the study is PFS. The key secondary endpoint is OS. Other secondary endpoints include ORR, DOR, DCR, safety, and PK. The study consists of 4 periods: Screening, Study Drug Administration, Crossover, and Follow-Up. The date of Cycle 1 Day 1 is the date of administration of the first dose of INCMGA00012 or placebo. During Study Drug Administration, participants will receive up to [redacted] induction cycles ([redacted] weeks) of carboplatin ([redacted] on Day 1) and paclitaxel ([redacted] mg/m^2 on Days [redacted] every [redacted] weeks as per standard of care, concurrently with INCMGA00012 or placebo. INCMGA00012 or placebo will be administered by IV infusion of [redacted] minutes (-5/+15 minutes) up to [redacted] cycles ([redacted]). The initial safety experience will be reviewed by the DMC after approximately 30 participants have been enrolled and have completed at least 1 cycle of study drug(s) and at regular intervals throughout the duration of the study. No interim analyses for efficacy are planned. In the event that chemotherapy must be discontinued for toxicity, INCMGA00012 or placebo should be continued if the participant is able to tolerate INCMGA00012 or placebo. Similarly, chemotherapy should be continued, if able, when INCMGA00012 or placebo is stopped for immune-related unacceptable toxicity. Crossover will be allowed for participants who received placebo in combination with chemotherapy upon verification of RECIST v1.1 progression by BICR. Once participants complete or discontinue administration of all assigned study drugs in the Study Drug Administration Period, they enter the Crossover or Follow-Up Period as applicable and continue disease assessments until second disease progression. Upon second disease progression, participants will be followed for safety and/or survival as applicable until withdrawal of consent, lost to follow-up, the end of the study, or death.

Table 2: Key Study Design Elements (Continued)

Estimated Duration of Study Participation	Up to 28 days for screening, study drug administration in consecutive 28-day cycles up to [redacted] cycles) as long as participants are receiving benefit and have not met any criteria for study drug discontinuation, INCMGA00012 administration in consecutive 28-day cycles up to [redacted] cycles) during the Crossover Period for eligible participants, 28-day Safety Follow-Up, at least every [redacted] months during Disease Follow-Up, and at least every [redacted] weeks thereafter for Survival Follow-Up. Follow-Up may occur through a phone call, email, or visit by the participant, as applicable. Participants will be followed until all participants have completed at least [redacted] cycles) of INCMGA00012 or placebo or have discontinued all assigned study drugs or have reached second disease progression.
DMC	Yes (external)
Coordinating Principal Investigator	[redacted]

Treatment Groups and Duration:

Approximately [redacted] participants will be enrolled worldwide, and randomized 1:1 to a blinded study drug administration group (Group).

Enrolled participants in each Group of this study will receive chemotherapy to up to [redacted] weeks ([redacted] cycles) of carboplatin [redacted] IV on Day 1 of each 28-day cycle and paclitaxel [redacted] mg/m^2 IV on Days [redacted] of each 28-day cycle.

INCMGA00012 [redacted] mg or placebo will be administered via IV on Day 1 of each 28-day cycle (+/− 3 days) for up to [redacted] cycles) in the absence of unacceptable toxicity, disease progression, withdrawal of consent, loss to follow-up, or premature discontinuation for any other reason.

Study periods will include Screening, Study Drug Administration, Crossover, and Follow-Up. The date of Cycle 1 Day 1 is the date of administration of the first dose of INCMGA00012 or placebo. Enrolled participants will be assigned to Group A or Group B as summarized in Table 3.

Table 3: Randomization Assignment

Group	Carboplatin-Paclitaxel	INCMGA00012 or Placebo
Group A	Carboplatin [redacted] IV: Day 1 Paclitaxel [redacted] mg/m^2, IV: Days [redacted] Each cycle = 28 days Up to [redacted] months/[redacted] weeks ([redacted] cycles)	Placebo IV: Q4W Up to [redacted] cycles)
Group B	Carboplatin [redacted] IV: Day 1 Paclitaxel [redacted] mg/m^2, IV: Days [redacted] Each cycle = 28 days Up to [redacted] months/[redacted] weeks ([redacted] cycles)	INCMGA00012 [redacted] mg IV: Q4W Up to [redacted] cycles)

Figure 1 presents the study design schema. Table 4 and Table 5 present the SoAs. Adherence to the study design requirements, including those specified in the SoAs, is essential and required for study conduct.

Figure 1: Study Design Schema

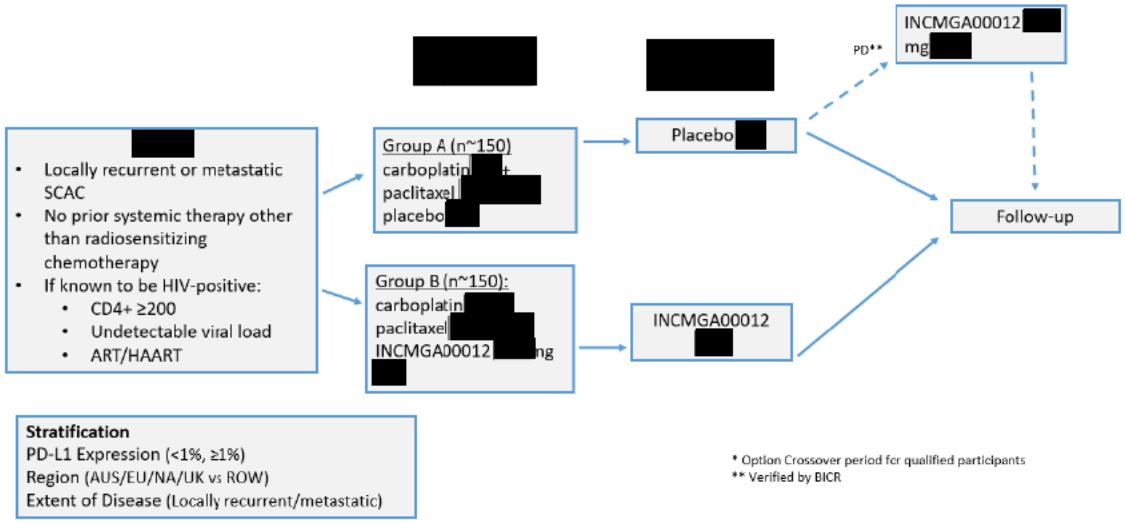

Table 4: Schedule of Activities

Visit Day (Range)	Screening 28 Days	Study Drug Administration: Induction Cycles [redacted] Day 1[a]	[redacted] (± 1 d)	[redacted] (± 1 d)	Postinduction Cycles [redacted] Day 1 (± 3 d)	[redacted] (± 7 d)	EOT[b] If Not Continuing in Crossover (+ 7 d)	Follow-Up (If Not Continuing in Crossover): Safety Follow-Up[b] (+ 28 d)	Disease Follow-Up	Survival Follow-Up	Notes
Administrative procedures											
Informed consent	X										
IRT	X	X			X		X				
Inclusion/ exclusion criteria	X	X*									*C1D1 only
General and disease medical history	X										
Prior/concomitant medications	X	X	X	X	X		X	X			
Distribution of participant identification card	X										
ECOG performance status	X	X*			X		X				*Does not have to be done at C1D1 if screening ECOG was performed within 3 days before first dose of any study drug.
Administer INCMGA00012 or placebo		X			X						Premedication with an antipyretic (eg, acetaminophen/ paracetamol or equivalent) and a histamine blocker (eg, diphenhydramine or equivalent) should be considered for participants who have had previous systemic reactions to protein product infusions or when recommended by institutional policy.

Table 4: Schedule of Activities (Continued)

Visit Day (Range)	Screening 28 Days	Study Drug Administration: Induction Cycles [redacted] Day 1[a]	Induction Cycles [redacted] (± 1 d)	Induction Cycles [redacted] (± 1 d)	Postinduction Cycles [redacted] Day 1 (± 3 d)	[redacted] (± 7 d)	EOT[b] If Not Continuing in Crossover (+ 7 d)	Follow-Up (If Not Continuing in Crossover): Safety Follow-Up[b] (+ 28 d)	Disease Follow-Up	Survival Follow-Up	Notes
Administrative procedures (continued)											
Administer paclitaxel		X	X	X							All participants should be premedicated with oral or IV steroid and antihistamines according to the approved label and/or standard practice. Additional premedications should be administered as per standard practice. For participants known to be HIV-positive, consultations should occur prior to dosing and throughout the study to determine any potential DDIs and modification to anti-HIV medications, in particular protease inhibitors.
Administer carboplatin		X									Before administration of carboplatin, participants should receive appropriate premedications based on institutional guidelines, investigator practice, local prescribing information, or standards of care. For participants known to be HIV-positive, consultations should occur prior to dosing and throughout the study to determine any potential DDIs and modification to anti-HIV medications, in particular protease inhibitors.

Table 4: Schedule of Activities (Continued)

Visit Day (Range)	Screening 28 Days	Study Drug Administration: Induction Cycles [redacted] Day 1[a]	Induction Cycles [redacted] (± 1 d)	Induction Cycles [redacted] (± 1 d)	Postinduction Cycles [redacted] Day 1 (± 3 d)	[redacted] (± 7 d)	EOT[b] If Not Continuing in Crossover (+ 7 d)	Follow-Up (If Not Continuing in Crossover): Safety Follow-Up[b] (+ 28 d)	Disease Follow-Up	Survival Follow-Up	Notes
Safety assessments											
AE assessments	X	X	X	X	X		X	X	X*		*Immune-related AEs to be collected for 90 days after the last dose of study drug, regardless of continuation of chemotherapy during induction cycles or start of a new anticancer therapy. Reasonable efforts should be made to align the first 12-week follow-up visit with the end of the 90-day irAE reporting period when appropriate.
Physical examination	X	X	X	X	X		X	X			A comprehensive examination is performed at screening and at EOT. All other scheduled examinations will be targeted.
Vital signs/body weight/height	X	X	X	X	X		X	X			Height at screening only.
12-lead ECG	X	X*			X*		X**	X**			*Not necessary if screening assessment performed within 7 days of Cycle 1 Day 1, unless clinical signs or symptoms are present; then at every fourth cycle (eg, screening/Day 1, [redacted]). **Only at EOT if EOT and safety visit are performed separately.

Table 4: Schedule of Activities (Continued)

Visit Day (Range)	Screening 28 Days	Study Drug Administration: Induction Cycles [redacted] Day 1[a]	Induction Cycles [redacted] (± 1 d)	Induction Cycles [redacted] (± 1 d)	Postinduction Cycles [redacted] Day 1 (± 3 d)	[redacted] (± 7 d)	EOT[b] If Not Continuing in Crossover (+ 7 d)	Follow-Up (If Not Continuing in Crossover): Safety Follow-Up[b] (+ 28 d)	Disease Follow-Up	Survival Follow-Up	Notes
Efficacy assessments											
Tumor imaging/response assessments	X					X*			X*†		*Imaging and response assessment should be performed every 8 weeks (56 days ± 7 days) during Study Drug Administration, Crossover, and/or Disease Follow-up regardless of any treatment delays, until second disease progression. Complete response or PR should be confirmed by imaging at least 4 weeks after initial documentation. †Upon implementation of Amendment 3, imaging may be performed at intervals according to local institution standard practice (eg, every 3-4 months) but at least every 6 months.
HR-QoL assessments (HR-PRO assessments)		X*				X*	X*	X*			When scheduled, participants are to complete the PRO assessments before meeting with medical professionals at site/imaging visits and before any study procedures are performed. *HR-PRO assessments will be performed at Cycle 1 and Cycle 2, then in alignment with imaging assessments, and at EOT or safety follow-up if EOT and safety follow-up visits are combined.
New anticancer therapy status							X	X	X	X	
Survival status							X	X	X	X*	*During survival follow-up, participants should be contacted by telephone, email, or visit at least every 12 weeks.

Table 4: Schedule of Activities (Continued)

Visit Day (Range)	Screening 28 Days	Study Drug Administration: Induction Cycles [redacted] Day 1[a]	Induction Cycles [redacted] (± 1 d)	Induction Cycles [redacted] (± 1 d)	Postinduction Cycles [redacted] Day 1 (± 3 d)	[redacted] (± 7 d)	EOT[b] If Not Continuing in Crossover (+ 7 d)	Follow-Up (If Not Continuing in Crossover): Safety Follow-Up[b] (+ 28 d)	Disease Follow-Up	Survival Follow-Up	Notes
Clinical laboratory assessments											
Blood chemistries	X	X*			X		X	X			*Not necessary on Cycle 1 Day 1 if performed during screening within 7 days on Cycle 1 Day 1.
Hematology	X	X*	X	X	X		X	X			*Not necessary on Cycle 1 Day 1 if performed during screening within 7 days on Cycle 1 Day 1.
Coagulation panel	X						X*	X*			*Only at EOT if EOT and safety visits are combined.
Endocrine panel	X	X*			X*		X	X			*Every third cycle (ie, Cycles [redacted]).
Urinalysis	X						X*	X*			*At EOT if EOT and safety visits are combined.
HIV management testing* (HIV viral load, CD4+ cell count)	X					X	X	X	X		*Only participants who are known to be HIV-positive. HIV management testing will occur Q8W during the study drug administration period. Frequency of HIV management testing may be reduced to every 6 months during safety and disease follow-up.

Table 4: Schedule of Activities (Continued)

Visit Day (Range)	Screening 28 Days	Study Drug Administration: Induction Cycles [redacted] Day 1[a]	Induction Cycles [redacted] (± 1 d)	Induction Cycles [redacted] (± 1 d)	Postinduction Cycles [redacted] Day 1 (± 3 d)	(± 7 d)	EOT[b] If Not Continuing in Crossover (+ 7 d)	Follow-Up (If Not Continuing in Crossover): Safety Follow-Up[b] (+ 28 d)	Disease Follow-Up	Survival Follow-Up	Notes
Clinical laboratory assessments (continued)											
Pregnancy testing	X	X*			X		X**	X**			For WOCBP serum pregnancy test is performed at screening and safety follow-up; at other visits urine pregnancy testing is acceptable. *Not necessary if performed during screening within 7 days of C1D1. **Can be performed at either EOT or safety follow-up visit through 120 days after the last dose of study drug or through 180 days after the last dose of chemotherapeutic agents, whichever occurs later (additional testing may be performed during the post-treatment follow-up period if recommended by the investigator, or required by local regulation, or local practice). Timing and type of testing may be adjusted based on country-specific requirements. Telephone/telehealth/video visits can be utilized to check pregnancy status (via testing, including home pregnancy tests) during the same period when contraception is mandatory. Sites in Germany: This must be a serum test and performed on Day 1 of all cycles before administration of study treatment. Required 1 time at 12 weeks post EOT for those in follow-up attending clinic visits.

Table 4: Schedule of Activities (Continued)

Visit Day (Range)	Screening 28 Days	Study Drug Administration: Induction Cycles [redacted] Day 1[a]	Induction Cycles [redacted] (± 1 d)	Induction Cycles [redacted] (± 1 d)	Postinduction Cycles [redacted] Day 1 (± 3 d)	[redacted] (± 7 d)	EOT[b] If Not Continuing in Crossover (+ 7 d)	Follow-Up (If Not Continuing in Crossover): Safety Follow-Up[b] (+ 28 d)	Disease Follow-Up	Survival Follow-Up	Notes
Pharmacokinetic and translational laboratory assessments (central testing)											
PK		X			X						Samples will be collected preinfusion on Day 1 of Cycles [redacted] Samples are collected immediately after infusion (+ 10 min) on Day 1 of Cycles [redacted] There is a 2-hour window for the preinfusion collection at Cycle 1 Day 1 and a 24-hour window at the other visits. Detailed PK sampling is provided in Table 15.
ADA		X			X						Samples will be collected preinfusion on Day 1 of Cycles [redacted] There is a 2-hour window for the preinfusion collection at Cycle 1 Day 1 and a 24-hour window at the other visits. Detailed ADA sampling is provided in Table 15.
Tumor sampling											
Tumor tissue sample collection	X										Fresh or archival sample is mandatory for stratification/randomization. Biopsy for archival samples should have occurred within 9 months before randomization.

Table 4: Schedule of Activities (Continued)

Visit Day (Range)	Screening	Study Drug Administration						Follow-Up (If Not Continuing in Crossover)			Notes
		Induction Cycles			Postinduction Cycles						
	28 Days	Day 1[a]	[redacted] (± 1 d)	(± 1 d)	Day 1 (± 3 d)	[redacted] (± 7 d)	EOT[b] If Not Continuing in Crossover (+ 7 d)	Safety Follow-Up[b] (+ 28 d)	Disease Follow-Up	Survival Follow-Up	
Blood sampling											
Whole blood	X										Collected at screening only.
Plasma 1 (plasma correlative)		X*									*Collected at [redacted]
Plasma 2 (plasma biomarker EDTA)		X*					X*				*Collected at [redacted] for all participants and at [redacted] for participants with disease progression.
Plasma 3 (plasma cfDNA)		X*					X*				*Collected at [redacted] for all participants and at [redacted] for participants with disease progression.
Stool sampling											
Stool sample	X*	X*									*Stool sample [redacted] days before study treatment. May be collected predose on [redacted]

[a] Cycle 1 Day 1 is the date when the first dose of study treatment is administered. Cycle 1 Day 1 should occur within 3 days of the date of randomization.
[b] The EOT and 28-day safety follow-up visit may be combined if necessary provided all assessments for both visits are completed.

Table 5: Crossover Period Schedule of Activities

Visit Day (Range)	Crossover Period Screening	Study Drug Administration					Follow-Up			Notes
	28 Days	Cycle 1 Day 1[a]	Cycles 2-[redacted] Day 1 (± 3 d)	[redacted] (± 7 d)	[redacted] (± 7 d)	EOT[b] (+ 7 d)	Safety (+ 28 d) Follow-Up[b]	Disease Follow-Up	Survival Follow-Up	
Administrative procedures										
IRT	X	X	X			X				
Inclusion/exclusion criteria	X	X								
Prior/concomitant medications	X	X	X			X	X			
ECOG performance status	X*	X**	X			X				*ECOG for screening is to be performed within 10 days before the first dose of study drug. **Does not have to be done at crossover C1D1 if screening ECOG was performed within 3 days before this visit.
Administer INCMGA00012		X	X							Premedication with an antipyretic (eg, acetaminophen/ paracetamol or equivalent) and a histamine blocker (eg, diphenhydramine or equivalent) should be considered for participants who have had previous systemic reactions to protein product infusions or when recommended by institutional policy.
Safety assessments										
AE assessments	X	X	X		X	X	X	X*		*Immune-related AEs to be collected for 90 days after the last dose of INCMGA00012 regardless of start of a new anticancer therapy. Reasonable efforts should be made to align the first 12-week follow-up visit with the end of the 90-day irAE reporting period when appropriate.
Physical examination	X	X	X			X	X			A comprehensive examination is performed at crossover period screening and at EOT. All other scheduled examinations will be targeted.
Vital signs/body weight	X	X	X			X	X			Height is not required to be collected during Crossover.

Table 5: Crossover Period Schedule of Activities (Continued)

Visit Day (Range)	Crossover Period Screening	Study Drug Administration					Follow-Up			Notes
	28 Days	Cycle 1 Day 1[a]	Cycles 2-[redacted] Day 1 (± 3 d)	[redacted] (± 7 d)	[redacted] (± 7 d)	EOT[b] (+ 7 d)	Safety (+ 28 d) Follow-Up[b]	Disease Follow-Up	Survival Follow-Up	
Safety assessments (continued)										
12-lead ECG	X	X*	X*			X**	X**			*Not necessary if crossover screening assessment is performed within 28 days of Cycle 1 Day 1 of the crossover period, unless clinical signs or symptoms are present; then at every fourth cycle (eg, screening/Day 1, [redacted]). **Only at EOT if EOT and safety visit are performed separately.
Efficacy assessments										
Tumor imaging/response assessments	X*			X**				X**†		*Imaging must be performed within 28 days before starting treatment with the first cycle of INCMGA00012 monotherapy in the crossover period. There must not be more than 12 weeks (+ 7 days) between the last imaging assessment during the main study that confirmed PD as verified by central imaging vendor and first scan in the crossover period. **Once INCMGA00012 is received in the crossover period, tumor response by the investigator's assessment is required every 8 weeks (56 days ± 7 days) regardless of any treatment delays, until second disease progression (see Section 8.2.1.3). Imaging will be rebaselined prior to the participant beginning another anticancer therapy, including INCMGA00012 in the Crossover period. †Upon implementation of Amendment 3, imaging may be performed at intervals according to local institution standard practice (eg, every 3-4 months) but at least every 6 months. (see Section 8.2.1.4).

Table 5: Crossover Period Schedule of Activities (Continued)

Visit Day (Range)	Crossover Period Screening	Study Drug Administration					Follow-Up			Notes
	28 Days	Cycle 1 Day 1[a]	Cycles 2-[redacted] Day 1 (± 3 d)	[redacted] (± 7 d)	[redacted] (± 7 d)	EOT[b] (+ 7 d)	Safety (+ 28 d) Follow-Up[b]	Disease Follow-Up	Survival Follow-Up	
Efficacy assessments (continued)										
Post study anticancer therapy status						X	X	X	X	
Survival status	X	X	X		X	X	X	X	X*	*During survival follow-up, participants should be contacted by telephone, email, or visit at least every 12 weeks.
Clinical laboratory assessments										
Blood chemistries	X*		X				X			*To be performed within 10 days before the first dose of INCMGA00012 in the crossover period.
Hematology	X*		X				X			*To be performed within 10 days before the first dose of INCMGA00012 in the crossover period.
Coagulation panel	X									*To be repeated as clinically indicated.
Endocrine panel	X	X	X*				X			*Every third cycle (ie, Cycles [redacted]).
Urinalysis	X					X*	X*			*At EOT if EOT and safety visits are combined.
HIV management testing (HIV viral load, CD4+ cell count)	X*		X*			X	X**	X**		Only participants who are known to be HIV-positive. *HIV management testing will occur Q8W during the crossover period. Does not need to be performed during crossover screening visit if performed in the prior 8 weeks. **Frequency of HIV management testing may be reduced to every 6 months during safety and disease follow-up.

Table 5: Crossover Period Schedule of Activities (Continued)

Visit Day (Range)	Crossover Period Screening	Study Drug Administration					Follow-Up			Notes
	28 Days	Cycle 1 Day 1[a]	Cycles 2-[redacted] Day 1 (± 3 d)	[redacted] (± 7 d)	[redacted] (± 7 d)	EOT[b] (+ 7 d)	Safety (+ 28 d) Follow-Up[b]	Disease Follow-Up	Survival Follow-Up	
Clinical laboratory assessments (continued)										
Pregnancy testing	X	X*	X			X**	X**			*Not necessary on crossover period if performed during crossover period screening within 7 days on crossover period C1D1. **Can be performed at either EOT visit or safety follow-up visit through 120 days after the last dose of study drug or through 180 days after the last dose of chemotherapeutic agents, whichever occurs later (additional testing may be performed during the post-treatment follow-up period if recommended by the investigator, or required by local regulation, or local practice). Timing and type of testing may be adjusted based on country-specific requirements. Telephone/telehealth/video visits can be utilized to check pregnancy status (via testing, including home pregnancy tests) during the same period when contraception is mandatory. Sites in Germany: This must be a serum test and performed on Day 1 of all cycles before administration of study drug. Required 1 time at 12 weeks post EOT for those in follow-up attending clinic visits.

[a] Cycle 1 Day 1 of the crossover period is the date when the first dose of INCMGA00012 is administered during the Crossover Period.
[b] The EOT and 28-day safety follow-up visit may be combined if necessary provided all assessments for both visits are completed.

2. INTRODUCTION

2.1. Background and Study Rationale

Squamous cell carcinoma of the anal canal accounts for almost 3% of digestive system cancers and is increasing in frequency due to its association with HPV and HIV infection (Ghosn et al 2015). Although most patients have localized disease, systemic metastases will develop in approximately 25% of patients, and 5-year survival is poor in these individuals. The InterAACT study (NCT02051868, NCCN 2019a) has established carboplatin with weekly paclitaxel as the cytotoxic platform for future combination trials. Compared to the old standard of 5-FU with platinum, carboplatin with weekly paclitaxel demonstrated less toxicity while improving OS (median OS 20 months vs 12.3 months; Rao et al 2018).

Immunotherapy is a promising new approach to treatment of metastatic SCAC. Pembrolizumab has recently been shown to have activity in a cohort of participants with progression or intolerance to prior therapy for unresectable or metastatic disease (Marabelle et al 2020). The RECIST response rate in this trial was 10.7% (14.7% in participants with PD-L1+ tumors). These responses were durable (range 6.0+ to 33.9+ months), which should predict for important clinical benefit, as has previously been noted with immunotherapy for other HPV-associated malignancies (ie, cervical or squamous head and neck cancer). In a smaller study of nivolumab, the ORR in treatment-refractory SCAC was 24% (95% CI: 15, 33; Morris et al 2017). Among the 37 participants enrolled, there were 2 complete responses and seven partial responses, and most of these responses were durable. A pilot study of pembrolizumab in PD-L1+ SCAC (N = 24) also showed a similar ORR of 17% (Ott et al 2017).

Participants with well-controlled HIV infection were included on the nivolumab study, and no unexpected safety issues were reported. Anecdotal reports suggest that PD-1 inhibitor treatment may actually improve the outcome of chronic HIV infection through multiple mechanisms, including restoration of HIV-specific CD8 T-cell function (Guihot et al 2018).

INCMGA00012 is a humanized, hinge-stabilized, IgG4κ monoclonal antibody that recognizes human PD-1. INCMGA00012 contains a human IgG4 Fc domain to limit effector function while retaining neonatal Fc receptor binding to extend circulating half-life. INCMGA00012 is designed to target PD-1–expressing cells, including T cells, and to sustain/restore their effector function by blocking checkpoint inhibitory interactions between PD-1 and its 2 ligands, PD-L1 and PD-L2. INCMGA00012 is being studied in patients with advanced cancer. As of 23 SEP 2019, 382 participants have been treated with INCMGA00012 in clinical studies. Recommended phase 2 doses have been established for both Q3W and Q4W flat dosing schedules. The clinical pharmacology and safety profile are as expected for the PD-(L)1 inhibitor class, and preliminary efficacy has been demonstrated against a variety of solid tumor types (Chen et al 2019, Condamine et al 2019, Lakhani et al 2017, Mehnert et al 2018, Mehnert et al 2019). INCMGA00012 is currently being studied as monotherapy in the setting of locally advanced or metastatic SCAC following progression on platinum-based chemotherapy (POD1UM-202; NCT03597295). Preliminary safety and efficacy are promising in this difficult-to-treat population and support further testing in this Phase 3 study (Rao et al 2019). Further details are provided in the current INCMGA00012 IB.

Accumulating evidence indicates that the efficacy of conventional and targeted anticancer agents does not only involve direct cytostatic/cytotoxic effects, but also relies on the (re)activation of tumor-targeting immune responses. While chemotherapy has largely been thought to be immunosuppressive and exert its effect via direct cytotoxicity, there is an emerging body of evidence to suggest that some chemotherapies may influence an immune response to tumors via induction of ICD, elimination of immunosuppressive cells, or sensitization of tumor cells to immune effector cells (Apetoh et al 2015). Some standard chemotherapy agents can impact both the tumor and host immune system, which provides strong rationale for their combination with selective immunotherapeutic interventions (Bracci et al 2014, Hato et al 2014); especially in patients for whom these chemotherapies are the accepted standard of care. In particular, platinum agents have demonstrated immunogenic effects via ICD and enhancement of effector immune response through PD-L1 receptor expression (Hato et al 2014). Paclitaxel has also been shown to restore antitumor activity of CD8+ T cells (Sevko et al 2013).

Experience with combinations of platinum-based chemotherapy and PD-(L)1 inhibitors in other tumors has been good. Safety at full dosing has been manageable (Gamerith et al 2018, Zhou et al 2018). Major improvements in PFS and OS have been demonstrated over standard of care chemotherapy in NSCLC (Gandhi et al 2018, Gentzler et al 2018, Jotte et al 2018, Langer et al 2016, Socinski et al 2018), breast cancer (Schmid et al 2018), squamous cell carcinoma of the head and neck (Burtness et al 2018), urothelial carcinoma (Grande et al 2019), small cell lung cancer (Horn et al 2018), and gastric cancer (Tabernero et al 2019). Based on the above evidence, this study has been designed to demonstrate the benefit of adding a PD-1 inhibitor (INCMGA00012) to standard of care chemotherapy in the setting of advanced or metastatic SCAC.

2.1.1. Rationale for Fixed Doses of INCMGA00012

INCMGA00012 will be administered at [redacted] mg Q4W. The selection of this dose was based on modeling of clinical PK data from the first-in-human monotherapy study, INCMGA 0012-101 (NCT03059823), in which 37 participants were treated at doses of [redacted] mg/kg Q2W, [redacted] mg/kg Q2W, [redacted] mg/kg Q4W, [redacted] mg/kg Q2W, and [redacted] mg/kg Q4W.

A simulation was conducted to investigate the use of weight-based and fixed doses for INCMGA00012 with the aim of targeting a steady-state trough concentration of approximately [redacted] µg/mL, which is the median trough concentration for pembrolizumab [redacted] mg/kg Q3W (Freshwater et al 2017). The median INCMGA00012 exposure and distribution around the median at [redacted] mg Q4W were similar to [redacted] mg/kg Q4W in the simulated population, which justified clinical exploration in an expansion cohort of the INCMGA 0012-101 study.

Pharmacokinetic data were obtained from 15 participants who received INCMGA00012 [redacted] mg Q4W in Study INCMGA 0012-101. The observed $AUC_{0-\infty}$ for [redacted] mg Q4W is close to the steady-state AUC_{0-t} based on the population PK analysis of weight-based doses, as is the estimated clearance. The estimated apparent terminal-phase disposition half-life (333 hours) is slightly shorter than the previous estimate of [redacted] hours. The mean trough plasma concentration at Cycle 2 was [redacted] µg/mL, and the mean projected plasma $C_{min,ss}$ was [redacted] µg/mL with a mean accumulation index of [redacted] In addition, the [redacted] mg Q4W dose has approximately a 58% probability to obtain a steady-state trough plasma concentration ≥ [redacted] µg/mL, which is associated with maximum target engagement and greatest probability of efficacy, based on pembrolizumab

data (Chen et al 2019). Based on these observations, [redacted] mg Q4W was chosen as the dose regimen.

2.1.2. Justification for Study Drug Dose

The dosing regimen of paclitaxel and carboplatin will be identical to the regimen established as the new standard of care by the InterAACT study and participants will receive up to [redacted] cycles of chemotherapy, corresponding to the median exposure in that trial. Compared to the old standard of 5-FU with platinum, carboplatin with weekly paclitaxel demonstrated improved survival with less toxicity (Rao et al 2018). The Q4W recommended Phase 2 dose of INCMGA00012, or placebo, will be administered in combination with carboplatin and paclitaxel in order to align with the Q4W chemotherapy cycles. Based on extensive previous experience with other PD-(L)1 inhibitor chemotherapy combinations full dose combinations are feasible (Borghaei et al 2018, Borghaei et al 2019, Gandhi et al 2018, Jotte et al 2018, Paz-Ares et al 2018, Socinski et al 2018); however, an early DMC safety review is planned as a prudent precautionary measure (see Section 5.5).

2.2. Benefit/Risk Assessment

Treatment directed at the PD-1/PD-L1 axis is a promising approach to SCAC. Phase 2 results with both nivolumab and pembrolizumab in chemotherapy-refractory populations show promising efficacy in terms of durable tumor response (Marabelle et al 2020, Morris et al 2017, Ott et al 2017). Importantly, no unexpected safety findings have been reported in this population, despite the frequent association of SCAC with HIV infection.

No interactions are expected between INCMGA00012 or placebo and standard antiretroviral medications (ART/HAART) used in HIV treatment and suppression. In ongoing trials of INCMGA0012 that include participants known to be HIV-positive (POD1UM-202, POD1UM-201 NCT03599713), no drug interactions were observed, and no opportunistic infections or unexpected immune-related adverse events were reported (see INCMGA00012 IB). Despite the potential for DDIs and overlapping toxicities between HIV therapy and the chemotherapy regimen, select antiretrovirals can be safely coadministered with chemotherapy. HIV viral control has also been well-maintained in trials of INCMGA00012 (POD1UM-202) and in SCAC patients who received the carboplatin/paclitaxel regimen under study (Rao et al 2020). Participants should remain under the care of the specialist managing their HIV care, and the proposed therapy and ART/HAART for potential DDIs should be reviewed. Local product labeling should be consulted for additional information as well, and local guidance should be followed in management of these participants (NCCN 2019b).

Programmed cell death protein 1 inhibitors have proven efficacy against a wide variety of cancer types and the available preclinical and clinical data suggest that the pharmacologic activity of INCMGA00012 should be consistent with experience with other drugs in this class.

Combining potentially immunomodulatory agents (ie, cytotoxic chemotherapy) to overcome drug resistance is an established therapeutic strategy that has proven clinically meaningful efficacy with a well-characterized tolerability profile. The combination selected for this study represents an appropriate standard of care chemotherapy regimen and the dose of INCMGA00012 is supported by substantial preclinical and clinical experience. Combinations of chemotherapy with other PD-(L)1 inhibitors have been extensively studied and safety is both

acceptable and manageable. 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 with appropriate guidance provided to investigators for their assessment and management. In addition, a DMC will be formed to monitor safety and efficacy in this study, with an early safety look planned once the first 30 participants have completed a cycle of treatment.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of INCMGA00012 or each chemotherapy agent may be found in the INCMGA00012 IB and the local product labeling for each chemotherapy agent, respectively.

Overall, the sponsor considers that this study will be conducted in a population with a potential clinical benefit and with an acceptable risk profile.

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

In 2020, ESMO and others highlighted the importance of clinical cancer research with immunotherapy or treatment with immunotherapy for patients with advanced cancer even during the unexpected COVID-19 pandemic, including potential investigational therapies similar to immunotherapy with a known survival benefit (Curigliano et al 2020). Real-world data have indicated that the use of immunotherapy either alone or in combination with chemotherapy does not increase the risk of hospitalization upon SARS-CoV-2 infection (Horn et al 2020, Malek et al 2021, Ribas et al 2021) or cause an increased risk of mortality (Cohn et al 2021, Lee et al 2020, Ribas et al 2021, Sharafeldin et al 2021, Tenforde et al 2021). While many efforts continue to be made to avoid becoming infected with SARS-CoV-2 (eg, proper social distancing, avoid unnecessary traveling) it is not always completely possible to avoid the infection; however, immunotherapy does not more negatively affect patients with cancer who are SARS-CoV-2–positive than those who test negative for SARS-CoV-2.

In a recent observational prospective study, Mandala et al (2021) screened 293 patients with cancer for SARS-CoV-2 and further identified patients who were treated with immunotherapy and compared them with patients with the same cancer subtypes treated with targeted therapy or chemotherapy. Cancer subtypes included melanoma, NSCLC, renal cell carcinoma, and other. Mortality of SARS-CoV-2–positive patients was statistically significantly higher compared with SARS-CoV-2–negative patients (8/89 vs 3/204, respectively, $p = 0.004$). All deaths were due to COVID-19. The incidence of SAEs in SARS-CoV-2–positive compared with SARS-CoV-2–negative patients was similar in patients treated with immunotherapy and chemotherapy (17.3% and 3.7% respectively for positive and negative patients treated with immunotherapy and 15.4% and 2.7% respectively for those treated with chemotherapy; Breslow-Day test $p = 0.891$). Serious AEs were COVID-19–related rather than treatment–related, confirming previous studies that treatment with immune checkpoint inhibitors does not significantly increase the risk of SAEs compared with chemotherapy (Mandala et al 2021). Vaccinated patients with cancer living in areas of high SARS-CoV-2 infectivity may still contract COVID-19 but generally develop less severe disease and are less frequently hospitalized (Cohn et al 2021, Tenforde et al 2021). The prevention of severe COVID-19 is particularly important considering that patients with cancer are already immunocompromised, which puts them at risk for infections and opportunistic complications due to treatment. A diagnosis of SARS-CoV-2 infection may also delay critical cancer treatment or cause the patient not to receive the full course of therapy.

The availability of approved vaccines have provided an increased chance for patients with advanced cancer to be protected from or have less severe cases of COVID-19 (Cohn et al 2021, Malek et al 2021, Ribas et al 2021, Sharafeldin et al 2021, Tenforde et al 2021). Aligned with the published data and recommendations from many international oncology societies, such as ASCO, SITC, ESMO, NCCN, and AACR, the sponsor requires that potential participants are vaccinated before entering the study or become fully vaccinated during the trial. This protocol inclusion requirement, in parallel with globally and publicly known principles to increase vaccination rates, is to minimize deaths related to COVID-19 and prevent severe cases of COVID-19 (ASCO 2021, ESMO 2021, Malek et al 2021, NCCN 2021b, Ribas et al 2021, SITC 2021).

Further, the sponsor has implemented guidance for participation in the study in the context of the COVID-19 pandemic and study-treatment management in the event of SARS-CoV-2 infection (see Appendix D). During the COVID-19 pandemic, unknown additional risks to participants may exist either related to going to a health care facility or as a result of study-related activities. The investigators need to frequently assess the participant's available medical data (eg, performance status, past medical history, comorbidities) at screening coupled with the need to conduct the needed primary endpoint trial procedures, in order to determine whether it is in best interests of the potential participant to enroll and participate into the study during peaks and troughs of the COVID-19 pandemic. Consented participants who are suspected of being exposed to SARS-CoV-2 or have symptoms will undergo COVID-19 testing to demonstrate recovery prior to randomization.

Due to the dynamic changes of the COVID-19 pandemic, evolving country-specific requirements may be followed with regard to COVID-19 testing frequency. As per the investigator's clinical judgment and/or local practices to diagnose and treat potential SARS-CoV-2 infections, participants may have additional COVID-19 testing performed. Participants will be monitored with safety procedures as described in Section 8 and with additional safety assessments as per standard of care. Information regarding the flexibility of assessment/visit scheduling, where possible and warranted, and the strategy for participant management during the dynamic pandemic is described in Appendix D.

3. OBJECTIVES AND ENDPOINTS

Table 6 presents the objectives and endpoints.

Table 6: Objectives and Endpoints

Objectives	Endpoints
Primary	
To compare the efficacy of carboplatin-paclitaxel with INCMGA00012 versus carboplatin-paclitaxel with placebo in participants with inoperable locally advanced or metastatic SCAC not previously treated with systemic chemotherapy.	PFS, defined as the time from the date of randomization until disease progression according to RECIST v1.1 by BICR or death due to any cause.
Key Secondary	
To compare the efficacy of carboplatin-paclitaxel with INCMGA00012 versus carboplatin-paclitaxel with placebo in participants with inoperable locally advanced or metastatic SCAC not previously treated with systemic chemotherapy.	OS, defined as the time from the date of randomization until death due to any cause.
Secondary	
To determine additional measures of clinical benefit.	ORR, defined as the percentage of participants having a CR or PR, according to RECIST v1.1 as determined by BICR.
	DOR, defined as the time from the first documented response (CR or PR) according to RECIST v1.1 until disease progression as determined by BICR or death due to any cause.
	DCR, defined as the number of participants maintaining either an ORR or stable disease according to RECIST v1.1 as determined by BICR.
To evaluate the safety of carboplatin-paclitaxel with INCMGA00012 or placebo in participants with SCAC not previously treated with systemic chemotherapy.	Number of participants experiencing AEs and number of participants discontinuing study drug due to AEs.
To determine the PK of INCMGA00012 when administered with carboplatin-paclitaxel to participants with SCAC not previously treated with systemic chemotherapy.	Population PK, including C_{max}, t_{max}, C_{min}, and AUC_{0-t}, will be summarized.

Table 6: Objectives and Endpoints (Continued)

Objectives	Endpoints
Exploratory	
[redacted]	

4. STUDY DESIGN

4.1. Overall Design

This study is a Phase 3 global, multicenter, placebo-controlled double-blind randomized study that will enroll participants with inoperable locally recurrent or metastatic SCAC not previously treated with systemic chemotherapy. Participants with well-controlled HIV infection will be eligible. Participants will receive up to [redacted] induction cycles ([redacted] weeks) of carboplatin ([redacted] on Day 1) and paclitaxel ([redacted] mg/m^2 on Days [redacted] concurrently with INCMGA00012 or placebo. INCMGA00012 [redacted] mg Q4W or placebo will be administered for up to [redacted] cycles ([redacted]) in the absence of disease progression, intolerable toxicity, death, withdrawal of consent, lost to follow-up, or premature discontinuation of all assigned study drug administration or for any other reason. Randomization to INCMGA00012 or placebo will be 1:1 and blinded. Stratification factors are presented in Table 7. For the stratification category of PD-L1 status, participants with tumor results of PD-L1 negative and nonevaluable are grouped in the PD-L1 < 1% stratum. Participants with nonevaluable tumors for PD-L1 status will be capped at 10% of total population.

Table 7: Stratification Factors

Stratification Factory Category	Stratum
PD-L1 expression	< 1%, ≥ 1%
Extent of disease	Locally recurrent, metastatic
Region	AUS/EU/NA/UK, ROW

The study consists of 4 periods: Screening, Study Drug Administration, Crossover, and Follow-Up. The date of Cycle 1 Day 1 is the date of administration of the first dose of INCMGA00012 or placebo.

INCMGA00012 or placebo will be administered by IV infusion of [redacted] minutes (-5/+15 minutes) prior to the scheduled chemotherapy on Day 1 of each 28-day cycle (+/- 3 days).

In the event that chemotherapy must be discontinued for toxicity, INCMGA00012 or placebo should be continued if the participant is able to tolerate INCMGA00012 or placebo. Similarly, chemotherapy should be continued, if able, when INCMGA00012 or placebo is stopped for unacceptable toxicity (see Section 6.5).

Crossover will be allowed for participants who received placebo in combination with chemotherapy, following BICR verification of disease progression (see Section 8.7).

Once participants complete or discontinue administration of all assigned study drugs in the Study Drug Administration Period, they enter the Crossover or Follow-Up Period as applicable and continue disease assessments until the second disease progression. Upon second disease progression, participants will be followed for safety and/or survival as applicable until withdrawal of consent, lost to follow-up, the end of the study, or death.

Immune-related AEs will be collected for 90 days after the last dose of INCMGA00012 or placebo, regardless of continuation of chemotherapy during induction cycles or start of a new anticancer therapy.

4.2. Overall Study Duration

The study begins when the first participant signs the ICF. The end of the study is defined as the last visit of the last participant that is required for OS analyses. If at the time of the final OS analyses there are still participants being treated with INCMGA00012, the participants may continue treatment at the discretion of the investigator if they are deriving benefit, and the study will end after last participant treated completes safety follow-up.

Eligible participants who demonstrate clinical benefit with INCMGA00012 may be considered for poststudy drug provisions allowing them to continue receiving INCMGA00012 until a suitable alternative treatment option is identified. Poststudy drug provision at study closure will be in accordance with local laws and regulations.

In the EU/EEA, the results of the study will be based on the date of the last visit of the last participant in the study globally to ensure the results are robust, meaningful, and representative of all multi-regions by having complete follow-up data determined by the statistical hypotheses for the objectives established. Not using the global date could potentially jeopardize the trial integrity and invalidate the trial conclusions due to potential bias, thus potentially violating the statistical analysis assumptions described in Section 10.

Participants will be followed until all participants have completed [redacted] of administration of INCMGA00012 or placebo, have discontinued all assigned study drugs, or have experienced second disease progression or conditions above are met. A participant is considered to have completed the study if he/she has completed all periods of the study including Survival Follow-Up.

4.3. Study Termination

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

The sponsor may terminate the study electively if, for example, required by regulatory decision or upon advice of the DMC. If the study is terminated prematurely, the sponsor will notify the investigators/head of the study site (Japan), the IRBs and IECs, and the regulatory bodies of the decision and reason for termination of the study. Reduced data collection activities and procedures as per standard of care for the remaining participants on study drug may be performed for participants who wish to remain on-study if they derive clinical benefit as per investigator. The DMC will recommend termination of the study if warranted, as described in Section 5.5. For Japan, the decision from the sponsor will be via the head of the study site(s) who will notify the investigators and the IRBs of the decision and the reason for termination of the study.

In addition, further recruitment in the study or at a particular study site may be stopped due to insufficient compliance with the Protocol, GCP and/or other applicable regulatory requirements, procedure-related problems, or the number of discontinuations for administrative reasons is too high.

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. Able to comprehend and willing to sign a written ICF for the study.
2. Are 18 years of age or older (or as applicable per local country requirements).
3. Histologically or cytologically verified, inoperable locally recurrent or metastatic SCAC.
4. No prior systemic therapy other than the following:
   a. Chemotherapy administered concomitantly with radiotherapy as a radiosensitizing agent is permitted.
   b. Prior neoadjuvant or adjuvant therapy if completed ≥ 6 months before study entry.
5. Has measurable disease per RECIST v1.1 as determined by local site investigator/radiology assessment, and after any tissue collected during biopsy. Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.
6. Able and willing to provide adequate tissue sample and whole blood sample with central testing result prior to randomization. Biopsy for archival samples should have occurred within 9 months prior to randomization.
7. ECOG performance status 0 to 1.
8. If HIV-positive, then must be stable as defined by:
   a. CD4+ count ≥ 200/μL,
   b. Undetectable viral load per standard of care assay,
   c. Receiving antiretroviral therapy (ART/HAART) for at least 4 weeks prior to study enrollment, and have not experienced any HIV-related opportunistic infection for at least 4 weeks prior to study enrollment.

9. 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 120 days after the last dose of INCMGA00012 or placebo or through 180 days after the last dose of chemotherapeutic agents, whichever occurs later (or longer as appropriate based on country-specific requirements) and must refrain from donating sperm during this period. Permitted methods that are at least 99% effective in preventing pregnancy (see Appendix A) should be communicated to the participants and their understanding confirmed.
    b. Women of childbearing potential must have a negative serum pregnancy test at screening, agree to take appropriate precautions to avoid pregnancy (with at least 99% certainty), and refrain from donating oocytes from screening through 120 days after the last dose of INCMGA00012 or placebo or through 180 days after the last dose of chemotherapeutic agents, whichever occurs later. Permitted methods that are at least 99% effective in preventing pregnancy (see Appendix A) should be communicated to the participants and their understanding confirmed. The definition of WOCBP is located in Appendix A.
    c. Women of nonchildbearing potential (ie, as per Appendix A) are eligible.
10. Removed during Protocol Amendment 2.

5.2. Exclusion Criteria

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

1. Has received prior PD-(L)1 directed therapy
2. Has received prior radiotherapy with or without radiosensitizing chemotherapy within 28 days of Cycle 1 Day 1; or 14 days for palliative radiotherapy (30 Gy or less) that is not directed to the pelvic region. (Note: all toxicities associated should have resolved to Grade ≤ 1).
3. Participants with laboratory values at screening defined in Table 8.

Table 8: 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	≥ 1.5 × ULN unless conjugated bilirubin ≤ ULN (conjugated bilirubin only needs to be tested if total bilirubin exceeds ULN). If there is no institutional ULN, then direct bilirubin must be < 40% of total bilirubin.
Renal		
g	CrCl	< 50 mL/min calculated by Cockcroft-Gault equation (glomerular filtration rate can also be used in place of CrCl)
Coagulation		
h	INR or PT	> 1.5 × ULN, for participants not receiving anticoagulant therapy
i	aPTT	> 1.5 × ULN for participants not receiving anticoagulant therapy

4. 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.
5. Active autoimmune disease requiring systemic immunosuppression in excess of physiologic maintenance doses of corticosteroids (> 10 mg of prednisone or equivalent).
6. Evidence of interstitial lung disease or active noninfectious pneumonitis.
7. History of organ transplant, including allogeneic stem cell transplantation.
8. Known active CNS metastases and/or carcinomatous meningitis, per Section 8.2.1.1.
9. Known active HAV, HBV, or HCV infection, as defined by elevated transaminases with the following serology: positivity for HAV IgM antibody, anti–HCV, anti–HBc IgG or IgM, or HBsAg (in the absence of prior immunization).
10. Active infections requiring systemic therapy, or IV antibiotic use up to 7 days before Cycle 1 Day 1.

    Note: If required by country or local regulations to be tested for COVID-19 during screening, a participant should be excluded if they have a positive test result for SARS-CoV-2 infection until both the retest result is negative and clinical recovery is obtained.

11. Known hypersensitivity to platinum, paclitaxel, another monoclonal antibody, or any of the excipients that cannot be controlled with standard measures (eg, antihistamines, corticosteroids).
12. Participants with impaired cardiac function or clinically significant cardiac disease:
    a. New York Heart Association Class III or IV cardiac disease, including preexisting clinically significant ventricular arrhythmia, congestive heart failure, or cardiomyopathy.
    b. Unstable angina pectoris.
    c. Acute myocardial infarction ≤ 6 months before study participation.
    d. Other clinically significant heart disease (ie, ≥ uncontrolled Grade 3 hypertension or high-grade conduction disturbance.)
13. Participant is pregnant or breastfeeding.
14. Has received a live vaccine within 28 days of Cycle 1 Day 1.

    Note: Examples of live vaccines include but are not limited to measles, mumps, rubella, chicken pox/zoster, yellow fever, rabies, BCG, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live-attenuated vaccines and are not allowed.
15. Current use of prohibited medication as specified in Section 6.6.2.
16. Has pre-existing peripheral neuropathy that is ≥ Grade 2 by CTCAE v5.
17. Any condition that would, in the investigator's judgment, interfere with full participation in the study, including administration of study drug and attending required study visits; pose a significant risk to the participant; or interfere with interpretation of study data.

5.3. Lifestyle Considerations

Not applicable.

5.4. Screen Failures

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

Tests with results that fail eligibility requirements may be repeated during screening. Additionally, a participant who fails screening may repeat the screening process once if the investigator believes that there has been a change in eligibility status. Rescreening more than once for administrative purposes (eg, scheduling logistics) may be allowed with sponsor approval. Participants who rescreen must reconsent and be assigned a new participant number.

5.5. Data Monitoring Committee

This study will use an external DMC to monitor safety and efficacy throughout the duration of the study as specified in the DMC charter. The voting members of the DMC will be external to the sponsor. The members of the DMC will not be involved with the trial in any other way and will have no competing interests that could affect their roles with respect to the trial.

Safety will be reviewed by the DMC after approximately 30 participants have been enrolled and have completed at least 1 cycle of study drug(s) administration and at regular intervals throughout the duration of the study until the study is unblinded. No interim analyses for efficacy are planned.

Specific details regarding composition, responsibilities, and governance of the DMC, including the roles and responsibilities of the various members and the sponsor and protocol team, and requirements for proper documentation of DMC activities will be described in the DMC charter.

5.6. Replacement of Participants

No participants will be replaced at any time during this study.

6. STUDY DRUGS

6.1. Study Drugs Administered

Table 9 presents the study drug information.

INCMGA00012 and placebo will be provided centrally by the sponsor, and commercial and local supplies of chemotherapy agents will be used where allowable.

Table 9: Study Drug Information

Study drug name:	INCMGA00012	Placebo	Carboplatin	Paclitaxel
Dosage formulation:	Liquid	Liquid	Liquid	Liquid
Unit dose strength(s)/ dosage level(s):	[redacted] mg	N/A	[redacted] (using Calvert formula; see Section 6.1.3) Carboplatin not to exceed [redacted] mg	[redacted] mg/m^2
Dose frequency/ reason for use:	Day 1 of each 28-day cycle Investigational	Day 1 of each 28-day cycle Placebo	Day 1 of each 28-day cycle Cancer treatment	Days [redacted] of each 28-day cycle Cancer treatment
Administration instructions:	IV infusion of [redacted] minutes (-5/+15)	IV infusion of [redacted] minutes (-5/+15)	IV infusion of [redacted] minutes	IV infusion of [redacted] minutes
Packaging and labeling:	INCMGA00012 25 mg/mL in a glass vial for single use. Each vial will be labeled as required per country requirement.	Placebo in a glass vial for single use. Each vial will be labeled as required per country requirement.	Marketed product	Marketed product
Storage:	Upright under refrigeration at 2°C-8°C (36°F-46°F) Protected from light	Upright under refrigeration at 2°C-8°C (36°F-46°F) Protected from light	Per product label	Per product label
Source:	Sponsor	Sponsor	Locally by the study site, or designee as permissible per regulatory requirements, or centrally by the sponsor.	
Study Drug Administration Period:	Up to [redacted] [redacted] cycles)	Up to [redacted] [redacted] cycles)	Up to [redacted] months/[redacted] weeks ([redacted] cycles)	Up to [redacted] months/[redacted] weeks ([redacted] cycles)
Premedication:	Antipyretics and/or antihistamine blockers should be considered for participants who have had previous systemic reactions to protein product infusions or when recommended by institutional policy.	Antipyretics and/or antihistamine blockers should be considered for participants who have had previous systemic reactions to protein product infusions or when recommended by institutional policy.	Prior to administration of carboplatin, participants should receive appropriate premedications based on institutional guidelines, investigator practice, local prescribing information, or standards of care.	All participants should be premedicated with oral or IV steroid and antihistamines according to the approved label and/or standard practice. Additional premedications should be administered as per standard practice.

6.1.1. Timing of Dose Administration

Study drugs should be administered as per Table 9 and Section 6.1.2 through Section 6.1.4. Once randomization has occurred, Cycle 1 Day 1 study drug administration should occur within 3 days after randomization. It is expected all study drugs will be administered on an outpatient basis.

In regions or countries where an inpatient stay is required for administration of chemotherapy on its own or in combination with INCMGA00012 is allowed. Hospitalizations due only to infusion of study treatment or study agents, regardless of the cycle number, are not SAEs. In those situations, investigators should follow standard of practice or institutional guidelines for discharging participants. For example, hospitalized Japanese participants may have investigators discharge them as per safety guidelines described in Appendix E.

6.1.2. Paclitaxel

Paclitaxel [redacted] mg/m^2 will be administered as an IV infusion on [redacted] of each 28-day cycle of [redacted] minutes. On Day 1 of each cycle, paclitaxel infusion will follow the INCMGA00012 or placebo infusion. On [redacted] of each cycle, paclitaxel infusion will occur after review of safety labs (see Table 4). All participants should be premedicated with oral or intravenous steroid and antihistamines according to the approved product label and/or standard practice. Additional premedications should be administered as per standard practice. Paclitaxel should be completely administered before initiating carboplatin dose.

For participants known to be HIV-positive, consultations should occur prior to dosing and throughout the study to determine any potential DDIs and modification to anti-HIV medications, in particular protease inhibitors.

6.1.3. Carboplatin

Carboplatin [redacted] mg/mL per minute (using Calvert Formula) will be administered as an IV infusion of [redacted] minutes Q4W immediately after paclitaxel as per local practice and the approved product label. Carboplatin dose is not to exceed [redacted] mg. Prior to administration of carboplatin, participants should receive appropriate premedications based on institutional guidelines, investigator practice, local prescribing information, or standards of care.

Calvert Formula:

Total dose (mg) = (target AUC) × (CrCl + 25)

The CrCl used in Calvert formula should not exceed 125 mL/min

Maximum carboplatin dose (mg) = target AUC5 (mg•min/mL) × ([redacted]) = [redacted] mL/min = [redacted] mg

For participants known to be HIV-positive, consultations should occur prior to dosing and throughout the study to determine any potential DDIs and modification to anti-HIV medications, in particular protease inhibitors.

6.1.4. INCMGA00012 or Placebo

INCMGA00012 or placebo will be administered in a blinded fashion by IV infusion of [redacted] minutes (-5/+15 minutes) on Day 1 of each 28-day cycle. INCMGA00012 or placebo infusion should precede that of chemotherapy.

Premedication with antipyretics and/or antihistamine blockers should be considered for participants who have had previous systemic reactions to protein product infusions or when recommended by institutional policy. Participants may receive INCMGA00012 or placebo for up to [redacted] (or up to [redacted] administrations of INCMGA00012/placebo) unless criteria for early discontinuation from INCMGA00012 or placebo are met as per Section 7.1.1.

Participants who received placebo in combination with chemotherapy who experience documented disease progression verified by BICR will have the opportunity to receive INCMGA00012 in the Crossover Period (see Section 8.7).

Details on the preparation, reconstitution, and administration of the INCMGA00012 infusion and placebo infusion are provided in the Pharmacy Manual.

6.2. Preparation, Handling, and Accountability

The investigator or designee, or investigational drug storage manager (for Japan), must confirm appropriate temperature conditions have been maintained during transit for all vials of INCMGA00012 and placebo received and any discrepancies are reported and resolved before use.

Only participants enrolled in the study may receive INCMGA00012 or placebo, and only authorized site staff may supply or administer these study drugs. INCMGA00012 and placebo vials 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, investigational drug storage manager (for Japan), and authorized site staff.

The investigator, investigational drug storage manager (for Japan), (or designee) is responsible for accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records) of vials of INCMGA00012 and placebo. 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, investigational drug storage manager (for Japan), or designee must maintain records that document:

- Delivery of INCMGA00012 and placebo vials to the study site.
- Inventory of INCMGA00012 and placebo vials at the site.
- Lot numbers and/or vial numbers (as applicable) of INCMGA00012 and placebo vials used to prepare the infusion solution.

INCMGA00012 and placebo must be used only in accordance with the Protocol. The investigator, investigational drug storage manager (for Japan), or designee 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 INCMGA00012 or placebo vials and study participants.

Completed accountability records will be archived by the site. The investigator, investigational drug storage manager (for Japan), or designee will be expected to collect and retain all used, unused, and partially used INCMGA00012 and placebo vials until verified by the study monitor (unless otherwise agreed to by the sponsor). At the conclusion of the study, the investigator, investigational drug storage manager (for Japan), or designee will oversee the destruction of any remaining study drug according to institutional SOPs. If, however, local procedures do not allow on-site destruction, shipment of the study drug back to the sponsor is allowed. In this case, 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 INCMGA00012 and placebo vials are destroyed before monitor inspection, the monitors rely on documentation of destruction per the site SOP.

Further guidance and information for the final disposition of unused INCMGA00012 or placebo vials are provided in the POD1UM-303 Pharmacy Manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

All participants will be centrally assigned to INCMGA00012 or placebo using an IRT/IVRS/IWRS. Before the study is initiated, the telephone number and call-in directions for the IVRS and/or the log in information and directions for the IWRS will be provided to each site. Full details will be provided in the IRT Manual.

Participants will be assigned to INCMGA00012 or placebo in accordance with the randomization schedule. Participants, investigators, and the sponsor will remain blinded to each participant's assignment to INCMGA00012 or placebo throughout the study, until the Crossover Period. Additionally, PK results will not be shared with the investigative sites or study team prior to unblinding of the study, as PK is planned to be analyzed after the study is unblinded. Emergency unblinding will occur if an AE requires the investigator to be made aware of the participant's assignment to INCMGA00012 or placebo (see emergency unblinding procedures in Section 9.5) and the POD1UM-303 Investigator Site File.

A sponsor statistician who is not part of the study team may be unblinded and may provide summary aggregated data by Group to the sponsor and/or the DMC, but individual participant data will remain blinded.

6.4. INCMGA00012 and Placebo Compliance

Compliance with all study-related activities should be emphasized to the participant by the site personnel, and appropriate steps should be taken to optimize compliance during the study.

Compliance with INCMGA00012 and placebo will be calculated by the sponsor based on the infusion records and monitored by the sponsor/designee.

6.5. Dose Modifications

6.5.1. General Dose Modifications

Management guidelines for toxicities related to chemotherapy, INCMGA00012, or placebo are provided in the following sections.

If appropriate, the investigator may attribute each toxicity event to carboplatin, paclitaxel, or INCMGA00012 or placebo alone or to the combination. Dose modifications must be based on the maximum toxicity experienced during a cycle.

Dose interruption, delay, or discontinuation of 1 chemotherapy agent and not the other agent is appropriate if, in the opinion of the investigator, the toxicity is clearly related to 1 of the agents. If, in the opinion of the investigator, the toxicity is related to the combination of both chemotherapy agents, both chemotherapy drugs should be interrupted, delayed, or discontinued according to recommended dose modifications. If the toxicity is deemed related to the combination of chemotherapy and INCMGA00012 or placebo, all 3 agents should be delayed, interrupted, or discontinued according to the recommended dose modifications.

In the event that chemotherapy must be discontinued for toxicity, INCMGA00012 or placebo should be continued if the participant is able to tolerate INCMGA00012 or placebo. Similarly, chemotherapy should be continued, if able, when INCMGA00012 or placebo is stopped for immune-related unacceptable toxicity.

It is important to note that some chemotherapy-related AEs will overlap with potential irAEs (including but not limited to gastrointestinal toxicity, including diarrhea; renal insufficiency; high-grade laboratory abnormalities; rash/hypersensitivity). In these cases, both the chemotherapy-related AE and irAE management guidance should be reviewed to determine the most appropriate management of therapy.

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), refer to Appendix D.

6.5.2. Management of Suspected Infusion Reactions

6.5.2.1. Paclitaxel and Carboplatin

All participants should be premedicated with oral or intravenous steroid and antihistamines according to the approved product label and/or standard practice. Additional premedications should be administered as per standard practice.

Minor symptoms such as flushing, skin reactions, dyspnea, hypotension, or tachycardia do not require interruption of paclitaxel. However, severe reactions, such as hypotension requiring treatment, dyspnea requiring bronchodilators, angioedema, or generalized urticaria require immediate discontinuation of paclitaxel and aggressive symptomatic therapy.

6.5.2.2. INCMGA00012 or Placebo

Infusion or hypersensitivity reactions may be observed with administration of any foreign protein. Premedication with an antipyretic (eg, acetaminophen/paracetamol or equivalent) and a histamine blocker (eg, diphenhydramine or equivalent) 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 to INCMGA00012 or placebo are provided in Table 10.

Table 10: Guidelines for Management of Suspected Infusion Reactions for Study Drug

Grade	Description[a]	Treatment	Subsequent Infusions
1	Mild reaction; infusion interruption not indicated; intervention not indicated.	Monitor vital signs closely until medically stable.	Premedication with an antipyretic (eg, acetaminophen/paracetamol) and a histamine blocker (eg, diphenhydramine) should be considered for participants who have had previous systemic reactions to protein product infusions or when recommended by institutional policy.
2	Requires infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hours.	**First occurrence:** Stop infusion and initiate appropriate medical measures (eg, IV fluids, antihistamines NSAIDs, acetaminophen/paracetamol, narcotics, per institutional preferences). Monitor vital signs until medically stable. If symptoms resolve within 1 hour, infusion may be resumed at 50% of the original infusion rate. **Subsequent occurrences (after recommended prophylaxis):** Permanently discontinue INCMGA00012 or placebo.	Premedicate at least 30 minutes before infusion with antihistamines (eg, diphenhydramine 50 mg PO) and acetaminophen/paracetamol (500-1000 mg PO). Additional supportive measures may be acceptable (per institutional preference) but should be discussed with medical monitor. Next infusion should start at 50% of the original infusion rate. If no reaction, rate of infusion can be increase by 25% every 15 minutes until a rate of 100% has been reached. Subsequent infusions can begin at 100%.
3 or 4	**Grade 3:** Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates). **Grade 4:** Life-threatening; pressor or ventilatory support indicated.	Stop infusion and initiate appropriate medical therapy (eg, IV fluids, antihistamines NSAIDs, acetaminophen/paracetamol, narcotics, oxygen, pressors, epinephrine, corticosteroids, per institutional preferences). Monitor vital signs frequently until medically stable. Hospitalization may be indicated.	Permanently discontinue INCMGA00012 or placebo. Note for NCI CTCAE (v5.0) Grade 3 infusion related reactions: if rapidly responsive to symptomatic medication and/or to brief interruption of infusion, study drug 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.

6.5.3. Dose Modifications of Paclitaxel and Carboplatin

Refer to local approved product labels and Table 11 for dose modifications regarding the chemotherapy regimen. If a dose reduction for toxicity occurs with any chemotherapy agent, the dose may not be re-escalated. Participants can have a maximum of 2 dose modifications to each of the chemotherapy drugs throughout the course of the study for toxicities. If a participant experiences several toxicities and there are conflicting recommendations, the most conservative dose adjustment recommended should be followed (dose reduction appropriate to the most severe toxicity). Participants who require a third dose modification to a particular chemotherapy drug will have that agent discontinued. Participants who experience severe hypersensitivity reactions to paclitaxel should not be rechallenged with the drug.

Reduction of 1 chemotherapy agent and not the other agent is appropriate if, in the opinion of the investigator, the toxicity is clearly related to 1 of the agents. If, in the opinion of the investigator, the toxicity is related to the combination of both chemotherapy agents, both drugs should be reduced according to recommended dose modifications.

Chemotherapy may be interrupted for a maximum of 6 weeks (INCMGA00012/placebo may be interrupted for a maximum of 12 weeks).

CTCAE v5.0 must be used to grade the severity of AEs. All dose modifications should be based on the AE requiring the greatest dose modification.

Table 11: Suggested Dose Reduction for Paclitaxel and Carboplatin

Study Drug	Dose Level 0	Dose Reduction 1	Dose Reduction 2	Additional Dose Reductions
Paclitaxel[a]	[redacted] mg/m^2 Days [redacted]	[redacted] mg/m^2	[redacted] mg/m^2	Discontinue
Carboplatin[a]	[redacted] Maximum dose [redacted] mg	[redacted] Maximum dose [redacted] mg	[redacted] Maximum dose [redacted] mg	Discontinue

[a] For participants known to be HIV-positive, consultations should occur before dosing and throughout the study to determine any potential DDIs and modification to anti-HIV medications, in particular protease inhibitors.

6.5.4. Dose Modification of INCMGA00012 or Placebo

Dose reduction of INCMGA00012 or placebo is not allowed. If a dose hold or infusion interruption is necessary for the management of treatment-related TEAEs, INCMGA00012 or placebo may be held for a maximum of 12 weeks. INCMGA00012 or placebo will be discontinued for participants requiring more than 12 weeks of interruption of INCMGA00012 or placebo. Instructions for management in the event of irAEs are outlined in Section 6.5.4.1.

6.5.4.1. Procedures for Participants Exhibiting Immune-Related Adverse Events

Adverse events of a potential immunologic etiology, or irAEs, may be defined as AEs 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 INCMGA00012 or placebo.

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

Recommendations for management of specific immune-mediated AEs known to be associated with other PD-1 inhibitors (eg, pembrolizumab, nivolumab) are detailed in Table 12. Algorithms for the evaluation of selected immune toxicities that have previously been attributed to PD-1 inhibitors and management guidelines for irAEs not detailed elsewhere in the Protocol should follow the ASCO or ESMO Clinical Practice Guidelines (Haanen et al 2017, NCCN 2021a, Schneider et al 2021).

Table 12: Dose Modifications of INCMGA00012 or Placebo and Toxicity Management Guidelines for Immune-Related Adverse Events

Immune-Related Adverse Event	Toxicity Grade or Conditions (CTCAE v5.0)	Action Taken With INCMGA00012or Placebo	AE Management With Corticosteroid and/or Other Supportive Care Therapies[a]
Pneumonitis	Grade 1	No action.	None.
	Grade 2	Withhold until ≤ Grade 1.	• Administer systemic corticosteroids per local practice followed by taper. • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment. • Add prophylactic antibiotics for opportunistic infections.
	Grades 3 or 4, or recurrent Grade 2	Permanently discontinue.	
Diarrhea/colitis	Grade 1	No action.	• None.
	Grades 2 or 3	Withhold until ≤ Grade 1.	• Consider prompt initiation of standard anti-diarrheal agents. • 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 Clostridioides difficile and infectious etiologies.
	Grade 4 or recurrent Grade 3	Permanently discontinue.	
AST/ALT elevation and/or increased total bilirubin/hepatitis	Grade 1	No action.	None
	Grade 2 ALT or AST increase OR Total bilirubin increases to more than 1.5 and up to 3 times ULN	Withhold until ≤ Grade 1.	• Administer systemic corticosteroids per local practice followed by taper. • Consider monitoring liver enzymes weekly (or more frequently) until liver enzyme value returns to baseline or is stable. • Consider monitoring total bilirubin, direct bilirubin, and alkaline phosphatase weekly (or more frequently)
	Grade 3 or 4 ALT or AST increase OR In participants with liver metastases with baseline Grade 2 elevation of AST or ALT, hepatitis with AST or ALT increases ≥ 50% and lasts ≥ 1 week OR Total bilirubin increases to more than 3 times ULN.	Permanently discontinue.	
Endocrinopathies Hyperglycemia Hyperthyroidism Hypothyroidism Type 1 diabetes mellitus	Grades 1 and 2	No action.	• None.
	Grades 3 or 4 hypothyroidism	Withhold until ≤ Grade 1 or is otherwise clinically stable.	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine per standard of care).
	Grades 3 or 4 hyperthyroidism	Withhold until ≤ Grade 1 or is otherwise clinically stable.	• Initiate symptomatic management
	Grades 3 and 4 Type 1 diabetes mellitus (or hyperglycemia)	Withhold until ≤ Grade 1 or is otherwise clinically stable.	• Initiate treatment with antihyperglycemics as clinically indicated.

Table 12: Dose Modifications of INCMGA00012 or Placebo and Toxicity Management Guidelines for Immune-Related Adverse Events (Continued)

Immune-Related Adverse Event	Toxicity Grade or Conditions (CTCAE v5.0)	Action Taken With INCMGA00012or Placebo	AE Management With Corticosteroid and/or Other Supportive Care Therapies[a]
Adrenal insufficiency	Grade 1	No action.	• None
	Grade 2	Withhold until ≤ Grade 1 or is otherwise clinically stable.	• Initiate treatment with hormonal 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.
Hypophysitis	Grade 1	No action.	• None.
	Grade 2 (asymptomatic)	Withhold until ≤ Grade 1. May restart INCMGA00012 treatment after controlled by hormone replacement therapy.	• Administer hormonal replacement.
	Grade 2 (symptomatic, eg headaches, visual disturbances)	Withhold until ≤ Grade 1. May restart INCMGA00012 after controlled with hormone replacement, if indicated, and steroid taper is complete.	• Administer corticosteroids at initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper and initiate other hormonal replacements as clinically indicated. • Consult with endocrinologist as needed.
	Grade 3 or 4 (symptomatic)	Permanent discontinuation should occur if after withholding INCMGA00012 the toxicity does not resolve to ≤ Grade 1 within 12 weeks after last dose of INCMGA00012 treatment, or if corticosteroid dosing cannot be reduced to ≤ 10 mg prednisone or equivalent per day within 12 weeks. Permanent discontinuation of INCMGA00012 should take place earlier at the investigator's discretion, if corticosteroids and/or hormone replacement therapy cannot balance the participant's pituitary function.	• Administer corticosteroids at initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper and initiate other hormonal replacements as clinically indicated. • Consult with endocrinologist as needed.
Nephritis with renal dysfunction	Grade 1	No action.	• None.
	Grade 2 increased blood creatinine	Withhold until ≤ Grade 1.	• Administer corticosteroids per local practice followed by taper.
	Grades 3 or 4 increased blood creatinine	Permanently discontinue.[b]	

Table 12: Dose Modifications of INCMGA00012 or Placebo and Toxicity Management Guidelines for Immune-Related Adverse Events (Continued)

Immune-Related Adverse Event	Toxicity Grade or Conditions (CTCAE v5.0)	Action Taken With INCMGA00012or Placebo	AE Management With Corticosteroid and/or Other Supportive Care Therapies[a]
Skin Reactions	Grade 1	No action.	• None.
	Grade 2	No action.	• Manage with topical steroids with or without drug interruption.
	Grade 3[c] or persistent Grade 2 (≥ 2 weeks) or Grade 3 SJS or suspected SJS or suspected TEN	Withhold until ≤ Grade 1 after corticosteroid taper to ≤ 10 mg/day prednisone or equivalent.	• Administer corticosteroids per local practice followed by taper. Additionally, oral antihistamines such as diphenhydramine or famotidine (per institutional preference) may be utilized as needed. • Should refer to dermatology if no resolution with these measures or if SJS or TEN is suspected.
	Grade 4 or Grade 4 SJS or TEN	Permanently discontinue.	• Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper. • Refer to dermatology consult.
Myocarditis	Grade 2	Depending on severity of symptoms, withhold until symptoms fully resolve and management with corticosteroids is complete. Permanent discontinuation of INCMGA00012 may take place earlier at the investigator's discretion.	• Treatment with systemic corticosteroids should be initiated (initial dose of 1-2 mg/kg per day of prednisone or equivalent). Taper as appropriate. • Manage cardiac symptoms according to standard of care and with guidance from cardiology. Consider cardiac MRI and myocardial biopsy for diagnosis.
	Grades 3 or 4	Permanently discontinue.	
Important nervous system events (eg, Guillain-Barre syndrome, autoimmune encephalitis, myasthenia gravis, autonomic neuropathy, or transverse myelitis)	Grade 2	Withhold until ≤ Grade 1.	• Neurology consultation is recommended for all neurologic irAEs ≥ Grade 2. • Treatment with systemic corticosteroids should be initiated (initial dose of 1-2 mg/kg per day of prednisone or equivalent). Taper as appropriate. • For Grade 2 transverse myelitis, consider permanent discontinuation. • Manage symptoms according to standard of care and with guidance from neurology.
	Grade 3 or 4	Permanently discontinue.	

Table 12: Dose Modifications of INCMGA00012 or Placebo and Toxicity Management Guidelines for Immune-Related Adverse Events (Continued)

Immune-Related Adverse Event	Toxicity Grade or Conditions (CTCAE v5.0)	Action Taken With INCMGA00012or Placebo	AE Management With Corticosteroid and/or Other Supportive Care Therapies[a]
All other irAEs	Grade 2 or Grade 3 based on severity and type of reaction	Withhold until ≤ Grade 1.	• Based on severity of AE, administer corticosteroids. • Ensure adequate evaluation to confirm etiology or exclude other causes.
	Recurrent Grade 3 or Persistent Grade 2 and Grade 3	Permanently discontinue.	
	Grade 4[d] (excluding endocrinopathies)	Permanently discontinue.	

[a] As general instructions, the following should be followed: if treatment-related toxicity does not resolve to Grade 0-1 within 12 weeks after the last dose of study drug, or if the corticosteroid dose cannot be reduced to ≤ 10 mg prednisone or equivalent per day within 12 weeks, study drug should be permanently discontinued. Severe and life-threatening irAEs should be treated with IV corticosteroids followed by oral corticosteroids. Other immunosuppressive treatment should begin if irAEs are not controlled by corticosteroids.

[b] If INCMGA00012 and/or placebo is directly implicated in the renal toxicity.

[c] Participants with Grade 3 rash in the absence of desquamation, with no mucosal involvement, not requiring systemic corticosteroids, and resolving or improving to ≤ Grade 1 within 14 days do not have to interrupt study drug/treatment. Permanent discontinuation of study drug/treatment may be necessary if there is recurrence of Grade 3 or higher rash after resuming study drug/treatment.

[d] If Grade 4 lipase/amylase elevation is asymptomatic and abdominal imaging suggests no pathology, then study drug administration may continue with medical monitor approval.

6.6. Concomitant Medications and Procedures

All concomitant medications and treatments (including over-the-counter or prescription medicines, vitamins, vaccines, and/or herbal supplements) must be recorded in the eCRF. Any medication received up to 30 days before the first dose of study drug and 28 days after the last dose of study drug(s) (unless associated with the treatment of an AE), will be recorded in the eCRF. Antibiotics received up to 90 days before the first study drug administration must be reported. Any addition, deletion, or change in the dose of these medications will also be recorded.

Concomitant medications administered for the management of SAEs or irAEs should be recorded regardless of when they are provided. Concomitant treatments/procedures that are required to manage a participant's medical condition during the study will also be recorded in the eCRF. The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.6.1. Permitted Medications and Procedures

The following medications and procedures are permitted:

- Antiretroviral therapy should be continued for participants who are known to be HIV-positive. Participants should remain under the care of their specialist managing their HIV care, and the proposed therapy and ART/HAART for potential DDIs should be reviewed (NCCN 2019b).
  - Use of growth factors on a nonroutine basis (and following ASCO guidelines for CSF use), anticoagulants, and transfusional support will be permitted.
  - Bisphosphonates will also be permitted. Of note: Regular concomitant use of bisphosphonates and RANK-L inhibitors for the prevention or reduction of skeletal-related events in participants with bone metastases is allowed and should preferably be initiated prior to the first dose of study drug.
- Prior to administration of INCMGA00012 or placebo, premedication with an antipyretic (eg, acetaminophen/paracetamol or equivalent) and a histamine blocker (eg, diphenhydramine or equivalent) should be considered for participants who have had previous systemic reactions to protein product infusions or when recommended by institutional policy.
- Premedications prior to administration of chemotherapy agents should be given in accordance with prescribing information and standard practice.
- SARS-CoV-2 vaccines.
- Applicable ancillary procedures and tests (eg, SARS-CoV-2 RT-PCR test, chest x-ray, or chest CT scan) to fully diagnose, monitor, and treat COVID-19.

6.6.2. Prohibited Medications and Procedures

The following medications and procedures are prohibited:

- Other anticancer therapies, including investigational treatments within 21 days before the first administration of any study drug (6 weeks for mitomycin C), and throughout the Study Drug Administration Period of the study.
- Immunosuppression in excess of physiologic maintenance corticosteroid doses (> 10 mg of prednisone or equivalent) within 14 days of the first dose of INCMGA00012 or placebo and throughout the Study Drug Administration Period of the study (with the exception of premedication for chemotherapy per SOC, and with the exception of acute treatment for an AE, see Section 6.5).
- Probiotic dietary supplements.

- Live vaccines within 28 days before the first administration of INCMGA00012 or placebo, throughout the Study Drug Administration Period of the study, and for a duration of 90 days after the last dose of INCMGA00012 or placebo.

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

- Investigators should refer to the local product labelling for the chemotherapy drugs selected for use in this study.

6.7. Treatment After the End of the Study

Once a participant has discontinued all assigned study drug administration, including INCMGA00012 to qualified participants in the Crossover Period, no further study drug will be provided in this study.

Upon second disease progression, participants will be followed for safety and/or survival as applicable per Table 4 or Table 5 until withdrawal of consent, lost to follow-up, the end of the study, or death.

Eligible participants who are deriving clinical benefit with INCMAG00012 may be considered for poststudy drug provisions allowing them to continue receiving INCMGA00012 until a suitable alternative treatment option is identified.

7. DISCONTINUATION OF STUDY DRUG ADMINISTRATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Drug Administration

7.1.1. Reasons for Discontinuation of Study Drug Administration

Participants **must** discontinue from assigned study drug(s) for the following reasons:

- Completion of the assigned study drug(s) regimen.
- Confirmed radiologic disease progression verified by BICR (see Section 8.2.1).

  Note: If radiographic progression of disease is verified by BICR using RECIST v1.1, the site may request unblinding of the Group in order to assess eligibility for the Crossover Period of the study (see Section 8.7).
- Unacceptable toxicity as noted in Section 6.5.
- Consent is withdrawn.
  Note: Consent withdrawn means that the participant has explicitly indicated that they do not want to participate in the study or be followed any longer; in this case no further data, except data in public domain, may be solicited from or collected on the participant. Participants who discontinue all study drug(s), including INCMGA00012 received by eligible participants in the Crossover Period will remain in the study to be followed for progression and survival.
- Further study drug administration would be injurious to the participant's health or well-being, in the investigator's medical judgment.
- The study is terminated by the sponsor.
- The study is terminated by the local health authority, IRB, or IEC.

A participant **may** be discontinued from assigned study drug(s) as follows:

- The participant becomes pregnant. If the female participant is no longer pregnant and meets the treatment continuation criteria within 12 weeks of the scheduled start of a cycle, study drug administration may be resumed after approval has been received from the medical monitor (see Section 9.6).
- If, during the course of the study, a participant is found not to have met eligibility criteria, the medical monitor, in collaboration with the investigator, will determine whether the participant should be withdrawn from study drug administration.
- If a participant is noncompliant with study procedures or study drug administration in the investigator's opinion, the sponsor should be consulted for instruction on handling the participant.

7.1.2. Discontinuation Procedures

In the event that the decision is made to permanently discontinue all assigned study drugs including administration of INCMGA00012 during the Crossover Period for eligible participants, the EOT visit should be conducted. Following the EOT visit, the Follow-Up Period (28-day Safety Follow-Up, Disease Follow-Up, and Survival Follow-Up) visits will be performed as applicable. These visits are described in Table 4 and Table 5. The EOT and

28-day Safety Follow-Up visit may be combined if necessary provided all assessments for both visits are completed. The last date of the last dose of all assigned study drug(s) and the reason for discontinuation will be recorded in the eCRF.

If a participant is discontinued from all assigned study drug(s):

- Adverse events including SAEs and irAEs must be collected as per Section 8.3.1.
- The study monitor or sponsor must be notified.
- The reason(s) for discontinuation from study drug must be documented in the participant's medical record, and the primary reason must be included in the eCRF.
- The EOT visit should be performed. The EOT and 28-day Safety Follow-Up visit may be combined if necessary provided all assessments for both visits are completed.
- The date of the EOT visit should be recorded in the IRT.

Completion of or early discontinuation of all study drugs, including INCMGA00012 received in by eligible participants during the Crossover period does not mean withdrawal from the study, and remaining study procedures should be completed as indicated by the Protocol.

If a participant actively withdraws consent for collection of follow-up data (safety follow-up or disease assessment), then no additional data collection should occur (with the exception of data in the public domain).

7.2. Participant Withdrawal From the Study

A participant may withdraw from the study at any time at the participant's 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.

7.3. Lost to Follow-Up

A participant will be considered lost to follow-up if the participant 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, the participant 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 investigator's representative will explain the nature of the study to the participant or the participant's 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 the participant's 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 the participant's medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must provide consent to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

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

8.1.2. Screening Procedures

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

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

Results from the screening visit evaluations will be reviewed to confirm eligibility as applicable before randomization or the administration of study treatment. Tests with results that fail eligibility requirements may be repeated. For screening assessments that are repeated, the most recent available result before randomization will be used to determine eligibility. Administration of study drug(s) should start as soon as possible after randomization, but within 3 days after the date of randomization.

See Section 5.4 and Section 5.6 for information regarding screen failures and replacement of participants, respectively.

For tumor tissue requirements collected during screening to conduct central assessments (eg, PD-L1) see Section 8.5.1.

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 determining that the participant is eligible for randomization, the IRT will be contacted to obtain the study drug(s) assignment. Additionally, the IRT will be contacted at each regular study visit to update the study drug(s) supply. Additional details are provided in the IRT Manual.

Once a randomization number is assigned to a participant, it cannot be reassigned to another participant.

A single participant cannot be assigned more than 1 randomization number.

8.1.4. Distribution of Reminder Cards

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

8.1.5. Distribution of Participant Identification Cards

All participants will be given a participant identification card identifying them as participants in a research study. The card will contain trial site contact information (including direct telephone numbers) to be utilized in the event of an emergency. The investigator or qualified designee will

provide the participant with a participant identification card upon written informed consent. At the time of randomization, site personnel will add the randomization number to the participant identification card.

8.1.6. COVID-19 Vaccination

Although highly recommended, prior vaccination against SARS-CoV-2 is not required to participate in the study. Investigators should strongly encourage vaccination in potential participants for whom no contraindication for vaccination exists. For participants who are vaccinated while on study, refer to Appendix D for guidance on timing of vaccine with respect to study treatment administration.

Applicable ancillary procedures and/or tests to supplement diagnosis (eg, SARS-CoV-2 RT-PCR test, chest x-ray, or chest CT scan), monitoring, and treatment of COVID-19 are allowed. These procedures and/or tests will be documented in eCRFs as due to COVID-19 (see Section 6.6.1).

Potential participants may need to be tested for COVID-19 during the study screening period and/or during the study as per local requirements or health authority requirements. Participants with a positive SARS-CoV-2 test during screening are ineligible to be randomized until normalization of a test is obtained and clinical recovery from the infection is observed as per investigator's evaluation (see Section 5.2). During the study, if participants are suspected of COVID-19 and test positive, they should recover first and be retested before continuing with study treatment. If the SARS-CoV-2 test is negative, those participants can continue to be administered study treatment. In addition, investigators in some countries may be obliged to report SARS-CoV-2–positive test results directly to the responsible health authority according to the local regulations at any time during the study. Investigators are required to check health authority and/or local requirements for any possible specific obligations.

8.1.7. Demography and Medical History

8.1.7.1. Demographics and General Medical History

Demographic data and general medical history will be collected at screening by the investigator or qualified designee and will include age, medical and surgical history, and current illnesses. Medical history will include relevant medical or surgical treatment within the last 10 years that are considered to be clinically significant by the investigator.

Data on ethnic group (eg, ancestry, ethnic origin) and gender will also be collected to evaluate differences in participants' efficacy outcomes. Anal cancer is slightly more common in women than men (2.3 vs 1.6 cases per 100,000, respectively), black men than white men (2.2 vs 1.6 cases per 100,000, respectively), and white women than black women (2.5 vs 1.8 cases per 100,000, respectively) (NCI 2021). It has been reported that black, gay and bisexual men with HIV had a significantly higher risk for anal cancer than nonblack men with the same characteristics (McNeil et al 2022). In general, patients with HIV and HPV are noted to have higher incidence of anal cancer; therefore, studying these populations is warranted, as well as participants from varying demographic backgrounds such as ancestry, geographic location, and prior history of known risk factors. Additionally, subgroup analysis of outcomes may be performed based on gender.

8.1.7.2. 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.

8.1.8. ECOG Performance Status

ECOG performance status will be assessed according to the criteria in Table 13.

Table 13: ECOG Performance Status

Grade	Performance Status
0	Fully active, able to carry on all predisease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (eg, light house work, 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.

8.2. Efficacy Assessments

Objective assessment of disease status will be evaluated according to RECIST v1.1 (Eisenhauer et al 2009) as described in Appendix B, by the investigator and BICR. The investigator's assessments will be recorded in the appropriate eCRF.

8.2.1. Tumor Imaging and Assessment of Disease

The process for image collection and transmission to the central imaging vendor can be found in the Imaging Manual. All imaging supporting disease assessment must be submitted to the central imaging vendor. For example, images (including via other modalities) that are obtained at an unscheduled timepoint to determine disease progression, as well as imaging obtained for other reasons that demonstrate radiologic progression, should also be submitted to the central imaging vendor as well as imaging performed at the scheduled timepoints.

The recommended method for measuring and following tumor burden will be CT, which should be performed using consistent techniques and facilities. The CT portion of PET-CT may be acceptable if it is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast).

Alternative modalities may be necessary, but must be consistent with RECIST v1.1. The same imaging techniques regarding modality, ideally the same scanner, and the use of contrast should be used in a participant throughout the study to optimize the reproducibility of the assessment of existing and new tumor burden and improve the accuracy of the assessment of response or progression based on imaging.

Imaging of the chest, abdomen, and pelvis are required for all participants at all scheduled imaging timepoints. Imaging of other anatomical sites (ie, head, neck, and extremities) should

be performed as applicable if participant has disease involvement or suspected disease involvement in those areas. Computed tomography or MRI scan of the brain will be performed if there are signs or symptoms suggesting that the participant has disease involvement in the CNS.

Confirmation of CR or PR should be confirmed by imaging at least 4 weeks after initial documentation.

Per iRECIST, participants with initial evidence of disease progression may continue to receive study drug pending confirmation of PD if they are clinically stable and per the investigator's discretion.

In the Crossover Period, participants who have unconfirmed second disease progression may continue receiving INCMGA00012 at the discretion of the site investigator until second disease progression is confirmed by the site provided they have met the conditions detailed by iRECIST (see Section 8.2.2). Participants who have confirmed second disease progression by iRECIST in the Crossover Period will discontinue administration of INCMGA00012 and continue to the next segment of the study (End of Treatment/Follow-Up).

Imaging timepoints are provided in Table 4 and Table 5. Imaging must follow calendar days based upon the date of Cycle 1 Day 1 and is not to be delayed for treatment holds or interruptions. If a study participant is hospitalized due to a medical emergency during the study that causes a delay in imaging, the participant must undergo the imaging procedures as soon as the participant is recovered or stable.

8.2.1.1. Initial Tumor Imaging and Eligibility Assessment During the Screening Period

Initial tumor imaging must be performed within 28 days prior to the date of randomization, per Table 4. Images performed as part of routine clinical management are acceptable for use as the screening images if they are of diagnostic quality and performed within 28 days prior to the date of randomization and can be provided to the central imaging vendor and assessed by BICR.

The site study team must review screening images prior to randomization to confirm the participant has measurable disease per RECIST v1.1. The screening images must be submitted to the central imaging vendor for retrospective confirmation of eligibility.

Tumor lesions that are located in a previously irradiated area or in an area subjected to other loco regional therapy should not be selected as target lesions unless there has been demonstrated progression in the lesion. Additionally, it is recommended that tumor lesions selected for excisional biopsy not be selected as target lesions.

Participants with previously treated brain metastases may participate provided they have radiographically stable brain metastases, that is, without evidence of progression by imaging during screening, and confirmed by MRI if MRI was used at prior imaging, or confirmed by CT imaging if CT used at prior imaging obtained at least 4 weeks apart and show no evidence of intracranial progression. Any neurologic symptoms must have returned to baseline and participants must have no clinical evidence of new or enlarging brain metastases, and have not used steroids for brain metastases for at least 14 days before the start of study drug administration. This exception does not include carcinomatous meningitis, as participants with carcinomatous meningitis are excluded regardless of clinical stability.

8.2.1.2. Tumor Imaging During Study Drug Administration Period

Imaging and response assessment should be performed every 8 weeks (56 days ± 7 days) until the Week 56 assessment and during the Crossover Period or Disease Follow-Up Period as appropriate until second disease progression, withdrawal of consent, death, or notification to site by the sponsor, whichever occurs first.

Verification of disease progression by BICR: The central imaging vendor will expedite the verification of PD upon request following local site investigator-assessed radiologic evidence of PD. Expedited verification of radiologic PD by the central imaging vendor will be communicated to the study site and sponsor in order to determine eligibility for Crossover Period. Investigator radiology assessments may be used to determine participant management; however, radiologic assessment for the primary study endpoint is according to BICR.

8.2.1.3. Tumor Imaging During the Crossover Period

For participants eligible to enter the Crossover Period (see Section 8.7), documented disease progression must be verified by BICR prior to starting the first cycle of INCMGA00012 monotherapy in the Crossover Period. Imaging must be performed within 28 days before starting treatment with the first cycle of INCMGA00012 monotherapy in the Crossover Period. There must not be more than 12 weeks (+ 7 days) between the last imaging assessment during the main study that confirmed PD as verified by central imaging vendor and the first scan in the Crossover Period.

In the Crossover Period, the imaging schedule is every 8 weeks (56 days ± 7 days), until the participant experiences second disease progression, withdrawal of consent, death, or end of the study, whichever occurs first.

8.2.1.4. Tumor Imaging During Disease Follow-up

For participants who discontinue or complete all assigned study drug(s) but have not experienced second disease progression, continued monitoring of disease status by radiographic imaging will be performed every 8 weeks (56 days ± 7 days), until the participant experiences second disease progression, withdrawal of consent, death, or notification to site by the sponsor, whichever occurs first.

Upon implementation of Amendment 3, imaging may be performed at intervals according to local institution standard practice (eg, every 3-4 months) but at least every 6 months.

8.2.2. iRECIST Assessment of Disease

Modified RECIST v1.1 for immune-based therapeutics may be used to assess tumor response to guide treatment decisions for discontinuation of INCMGA00012 due to disease progression (Seymour et al 2017).

These disease assessments for clinically stable participants will be performed by the study site, and participants will need to have the opportunity to be reconsented in the case of administration of study treatment pending confirmation of PD.

Participants may receive study drug administration pending confirmation of disease progression if they are clinically stable as defined by the following criteria:

- Absence of clinically significant signs and symptoms (including worsening of laboratory values) indicating disease progression.
- No decline in ECOG performance status.
- No requirement for intensified management of disease-related symptoms.
- Absence of rapid progression of disease.
- Absence of progressive tumor at critical anatomical sites (eg, spinal cord compression) requiring urgent alternative medical intervention.

If radiologic imaging shows iUPD, tumor assessment should be repeated ≥ 4 weeks later (but no later than 8 weeks) to confirm iCPD with the option of continuing treatment while awaiting radiologic confirmation of progression. Details of iRECIST categories and implementation are in Appendix C.

8.2.3. Health Economics

Not applicable.

8.2.4. Health-Related Patient-Reported Outcomes

Health-related patient-reported outcome assessments will be performed at Cycle 1 and Cycle 2, then in alignment with imaging assessments, and at EOT or at safety follow-up if EOT and safety follow-up visits are combined. Examples of HR-PRO assessments may include EQ-5D, EORTC-QLQ-C30, and QLQ-ANL27.

8.2.4.1. EuroQol-5D

EuroQol-5D is a standardized instrument developed by the EuroQol Group as a measure of health-related QoL that can be used in a wide range of health conditions and treatments. The EQ-5D consists of a descriptive system and the EQ VAS.

The descriptive system comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The EQ VAS records the participant's self-rated health on a vertical visual analogue scale. This can be used as a quantitative measure of health outcome that reflects the participant's own judgement. The scores on these 5 dimensions can be presented as a health profile or can be converted to a single summary index number (utility) reflecting preferability compared with other health profiles.

The 5L version of the EQ-5D will be utilized in this study.

8.2.4.2. European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire

The QLQ-C30 is a validated, self-administered questionnaire. It incorporates 9 multi-item scales: 5 functional scales (physical, role, cognitive, emotional, and social); 3 symptom scales (fatigue, pain, and nausea and vomiting); and a global health and QoL scale. Several single-item symptom measures are also included.

8.2.4.3. Quality of Life Questionnaire for Anal Cancer

The QLQ-ANL27 is a self-administered anal cancer–specific supplemental questionnaire, developed using EORTC QLG guidelines, and is available for use in clinical studies (Sodergren et al 2018). This module is expected to be validated by the EORTC QLG before the end of this study.

8.3. Safety Assessments

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

8.3.1. Adverse Events

Adverse events will be monitored from the time the participant signs the ICF until at least 28 days after the last dose of study drug, regardless of whether a new anticancer therapy is started. Immune-related AEs will be collected until 90 days after the last dose of INCMGA00012 or placebo, regardless of continuation of chemotherapy during induction cycles or start of a new anticancer therapy. Adverse events that begin or worsen after informed consent should be recorded on the Adverse Events Form in the eCRF regardless of the assumption of a causal relationship with the study drug. Conditions that were already present at the time of informed consent should be recorded on the Medical History Form in the eCRF. Adverse events (including laboratory abnormalities that constitute AEs) should be described using a diagnosis whenever possible rather than by individual underlying signs and symptoms.

Adverse events 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 chemotherapy and/or INCMGA00012 or placebo, including INCMGA0012 received by eligible participants during Crossover study procedures, or that caused the participant to discontinue chemotherapy and/or INCMGA00012 or placebo, including INCMGA00012 received by eligible participants during Crossover. 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 irAEs regardless of severity will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

The severity of AEs will be determined per CTCAE v5.0.

8.3.2. Physical Examinations

Physical examinations must be performed by a medically qualified individual, such as a licensed physician, physician's assistant, or an advanced registered nurse practitioner, as local law permits. Comprehensive and targeted examinations are to be conducted as scheduled in Table 4 and Table 5.

The comprehensive physical examination will include 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. For chemotherapy agents, additional testing may be necessary. Refer to approved product label information for each chemotherapy agent used as study treatment, and perform additional tests as clinically indicated and as recommended in the approved labels.

During the study, targeted examinations will be conducted unless otherwise clinically indicated. Participants will be assessed by the investigator or medically qualified designee per institutional standard of care. These assessments should be an evaluation as indicated by participant symptoms, AEs, or other findings and documented on the AE eCRF.

Abnormalities identified after the first dose of chemotherapy and/or INCMGA00012 or placebo, including INCMGA00012 received by eligible participants during Crossover constitute an AE if they are considered clinically meaningful, induce clinical signs or symptoms, require concomitant therapy, or require changes in chemotherapy and/or INCMGA00012 or placebo, including INCMGA00012 receive by eligible participants during Crossover.

8.3.3. Vital Signs

Vital sign measurements (to be taken before blood collection for laboratory tests) include blood pressure, pulse, respiratory rate, body temperature, height (at screening or before any study drug administration on Cycle 1 Day 1 only) and body weight. Blood pressure and pulse will be taken with the participant in the recumbent, semirecumbent, or sitting position after 5 minutes of rest. Abnormal vital sign results identified after the first dose of study treatment constitute an AE if they are considered clinically meaningful, induce clinical signs or symptoms, require concomitant therapy, or require changes in chemotherapy and/or INCMGA00012 or placebo, including INCMGA00012 received by eligible participants during Crossover.

8.3.4. Electrocardiograms

Electrocardiograms will be obtained as outlined in Table 4 and Table 5 according to the institutional standard of care. A 12-lead machine that automatically calculates heart rate and measures PR, QRS, QT, and QTc intervals is recommended. All ECGs should be performed with the participant in a recumbent or semirecumbent position after 5 minutes of rest.

The 12-lead ECGs will be interpreted by the investigator at the site to be used for immediate participant management. Additional 12-lead ECGs may be performed as clinically indicated to manage participant safety. The decision to include or exclude a participant or discontinue study drug(s) 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.

The Fridericia (preferred) or Bazett correction method for calculating QTc will be used for reporting in the eCRF.

8.3.5. Laboratory Assessments

Clinical safety laboratory analyses (ie, blood chemistries, hematology assessments, coagulation tests, endocrine function, 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 drug administration, according to the schedules in Table 4 and Table 5. The laboratory analytes to be evaluated are presented in Table 14. Additional testing may be required by the sponsor based on emerging safety data. Additional tests may also be performed if clinically indicated or due to COVID-19.

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

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

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

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

If screening laboratory assessments are performed more than 7 days before Cycle 1 Day 1, then the tests must be repeated and eligibility confirmed as applicable before the start of initial study drug administration on Cycle 1 Day 1. After Cycle 1, predose laboratory procedures can be conducted up to 72 hours before study drug 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 safety follow-up visit. These laboratory assessments should only be performed at the EOT visit if the EOT visit is also serving as the 28-day safety visit.

For participants who are known to be HIV-positive, laboratory checks of HIV viral load and CD4+ cell count will be performed per the frequency in Table 4 and Table 5.

Table 14: Required Laboratory Analytes

<table>
<tr><th>Blood Chemistries</th><th>Hematology</th><th>Urinalysis With Microscopic Examination (only if blood or protein is abnormal)</th><th>Coagulation</th><th>Pregnancy Testing</th></tr>
<tr><td rowspan="16">Albumin
Alkaline phosphatase
ALT
AST
Amylase
Bicarbonate or carbon dioxide[a]
Blood urea nitrogen or urea[a]
Calcium
Chloride
Creatinine
Glucose
Lactate dehydrogenase
Lipase
Phosphate
Potassium
Sodium
Total bilirubin
Direct bilirubin (if total bilirubin is elevated above ULN)
Total protein</td><td rowspan="16">Complete blood count, including:
• Hemoglobin
• Hematocrit
• Platelet count
• Red blood cell count
• WBC count

Differential count, including:
• Basophils
• Eosinophils
• Lymphocytes
• Monocytes
• Neutrophils

Absolute values must be provided for:
WBC differential laboratory results</td><td rowspan="16">Color and appearance
pH and specific gravity
Bilirubin
Glucose
Ketones
Leukocytes
Nitrite
Occult blood
Protein</td><td>PT
PTT or aPTT
INR</td><td rowspan="2">Human chorionic gonadotropin</td></tr>
<tr><td>Endocrine Function</td><td>HIV Management Testing[b]</td></tr>
<tr><td>TSH
T4 or FT4[a]
T3 or FT3[a]
FSH (as needed)</td><td rowspan="3">HIV viral load
CD4+ cell count</td></tr>
<tr><td>SARS-CoV-2 Tests</td></tr>
<tr><td>SARS-CoV-2 tests (including types of approved tests) as per local clinical practice standards and evolving needs of the COVID-19 pandemic.</td></tr>
</table>

Note: Additional tests may be required, as agreed by investigator and sponsor, based on emerging safety data, or based on regional geographical differences, or depending on the extent of COVID-19 pandemic. Relevant test results will be documented in eCRFs. Tests are performed locally; if particular analytes may not feasible locally, the sponsor will arrange for those tests to be performed centrally. Additional tests (eg, ILD) may be performed at any time during the study as determined necessary by the investigator or required by local regulations, or necessary to resolve and diagnose irAEs, or required by regions. Specialized tests (eg, endocrine function tests) can be sent for testing to the sponsor's central laboratory upon request if local site testing is not available.

[a] If considered standard by the region.

[b] Only participants who are known to be HIV-positive.

8.3.6. Pregnancy Testing

Serum pregnancy tests are required for all women of childbearing potential during screening, at either the EOT or safety follow-up visit, and through 120 days after the last dose of INCMGA00012 or placebo or through 180 days after the last dose of chemotherapeutic agents, whichever occurs later (additional testing may be performed during the post-treatment follow-up period if recommended by the investigator, or required by local regulation, or local practice). Telephone visits or telehealth/video visits can be utilized to check pregnancy status (via testing, including home pregnancy tests) during the same period when contraception is mandatory. Pregnancy testing is required on Day 1 of all cycles and can be either serum- or urine-based as applicable per country-specific requirements as per Table 4 and Table 5, and will be performed before administration of study drug(s). If a pregnancy test is performed during screening within 7 days of Cycle 1 Day 1, it is not necessary to repeat on Cycle 1 Day 1 (unless necessary based on country-specific requirements).

A positive urine pregnancy should be confirmed with a serum pregnancy test. If a pregnancy is confirmed by a serum pregnancy test, see Section 9.6.

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

8.4. Pharmacokinetic and Antidrug Antibody Assessments

Blood samples for PK and ADA analysis will be obtained at the visits and timepoints indicated in Table 4 and Table 15. Pharmacokinetic sample sets are planned to be collected for approximately 20% of participants receiving INCMGA00012 (approximately 120 participants, as the study is blinded and randomized 1:1). After the INCMGA00012 or placebo preinfusion PK sample is drawn, participants will receive premedication as applicable and begin infusion of INCMGA00012 or placebo. Adjustments to the collection of and timing of 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.

Drug concentration information that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded, as PK is planned to be analyzed after the study is unblinded.

Table 15: Pharmacokinetic and Antidrug Antibody Blood Sample Timing

Study Visit	Assessments	Timing of Sample for PK[a]	Timing of Sample for ADA[a]
Cycle 1 Day 1	PK, ADA	Preinfusion Postinfusion	Preinfusion
Cycle [redacted] Day 1	PK, ADA	Preinfusion	Preinfusion
Cycle [redacted] Day 1	PK, ADA	Preinfusion Postinfusion	Preinfusion
Cycle [redacted] Day 1	PK, ADA	Preinfusion	Preinfusion
Cycle [redacted] Day 1	PK, ADA	Preinfusion	Preinfusion
Cycle [redacted] Day 1	PK, ADA	Preinfusion	Preinfusion

[a] Preinfusion: within 24 hours before the start of infusion (within 2 hours before the start of infusion at Cycle 1 Day 1). Postinfusion: immediately after INCMGA00012/placebo infusion (+ 10 minutes). Sample must be collected before dose/infusion of other agents.

8.5. Pharmacodynamic, Biomarker, and Translational Assessments

Translational assessments have been included in the Protocol to identify tumor characteristics and explore the relationships between tumor and host factors and clinical outcomes. These studies will also help to further an understanding of the mechanism of action of INCMGA00012 as well as potential avenues for addressing resistance. The proposed analyses will provide important hypotheses for further testing that may extend beyond the disease under study.

Translational assessments may include but are not limited to the following:

- [redacted]
- [redacted]
- [redacted]
- [redacted]

Biological samples will be stored for up to 10 years from the date of the last participant's last visit. The research performed on those samples will be study-related. Additional research outside of study-related research will not be performed.

8.5.1. Tumor Tissue Biopsies

A formalin-fixed tumor tissue sample or a fresh tumor biopsy at screening will be used for central laboratory confirmation of PD-L1 status and stratification using the SP263 PD-L1 (Ventana) assay.

Testing will also include HPV and DNA-repair abnormalities such as MSI. The PD-L1 results from a central laboratory are required before randomization and stratification.

If sufficient tumor tissue is available, additional biomarker work such as expression analysis and mutation status will be performed.

Fine-needle aspirates are not acceptable for use in this assay. An adequate tumor sample must be available at the time of screening for PD-L1 assessment; results from a central laboratory are required in order to perform randomization.

Fresh tumor biopsies should be taken from nontarget lesions when possible. Participation in this study requires tumor tissue from locations not radiated before biopsy; formalin-fixed fresh biopsy samples are preferred for determination of PD-L1 status. Detailed information regarding procedures on tumor tissue sampling and time window, and information of handling and shipping of tissue samples will be provided in the Laboratory Manual.

8.5.2. Blood Sample Collection

Additional blood samples will be collected from participants the according to the schedule outlined in Table 4. Detailed information regarding procedures for handling and shipping of specimens will be provided in a separate laboratory manual.

8.5.3. Stool Sampling

Stool samples will be analyzed for the [redacted]

A stool sample will be collected from participants according to the schedule outlined in Table 4. Participants will be provided a collection kit to obtain the sample. Further details will be provided in the Laboratory Manual.

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. Crossover Period

Participants who received placebo in combination with chemotherapy who experience documented disease progression verified by BICR will have the opportunity to receive INCMGA00012 in the Crossover Period. While pending verification, these participants may continue study drug administration at the discretion of the investigator. The participants with verified disease progression by BICR will have treatment assignment unblinded and be able to receive INCMGA00012 monotherapy. Table 5 shows the activities to be performed in the Crossover Period. Criteria for crossover are provided in Section 8.7.1. Participants who received active treatment in the blinded phase of the study will be ineligible for treatment in Crossover Period and should have the EOT visit performed and enter follow-up phases of the study.

Crossover Period participants must not initiate administration of INCMGA00012 any earlier than 3 weeks (21 days ± 3 days) after their last dose of chemotherapy regardless of the time of progression.

8.7.1. Crossover Criteria

Eligible participants may be considered for crossover to INCMGA00012. Crossover is optional and is at the discretion of the investigator (with the sponsor's agreement).

Participants who meet the following criteria are eligible for crossover:

- Must have documentation of verified radiographic progression of disease by BICR assessment.
- Must have confirmation of receipt of placebo in the main study.
- Adverse events (except alopecia and peripheral neuropathy) due to therapy must have improved to CTCAE v5.0 ≤ Grade 1 prior to the first dose of INCMGA00012 during the Crossover Period.
- Must not be unstable as a result of a new or progressing brain metastasis(es).
- Must have an ECOG performance status of 0 to 2.

- Participant must have not received any other systemic anticancer therapies since study start other than the chemotherapy administered during the Study Drug Administration Period.
- If required, the participant must have completed palliative radiotherapy (30 Gy or less) ≥ 7 days before the first dose of INCMGA00012 during the Crossover Period.
- Must have adequate organ function as indicated by the laboratory values in Table 8.

8.8. End of Treatment and/or Early Termination

Once a participant permanently discontinues or completes all assigned study drug administration, 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 all assigned study drug discontinuation occur < 21 days after the final dose of study drug(s) administration, a 28-day safety follow-up visit is required and should be conducted according to Table 4 and Table 5.

If the EOT visit occurs ≥ 21 days after the last study drug administration, only a single EOT/28-day safety follow-up is required, and all unique assessments for the EOT and 28-day follow-up visit will be performed once.

8.9. Follow-Up

The study design includes a Follow-Up Period for participants subsequent to the end of the Study Drug Administration Period or Crossover Period, as appropriate. After discontinuation of all assigned study drugs, including administration of INCMGA00012 to qualified participants in the Crossover Period, all study participants continue in the Follow-Up Period of the study as described in Table 4 and Table 5.

8.9.1. Safety (28-Day) Follow-Up

The Safety (28-day) Follow-Up starts once the participant discontinues all assigned study drug(s). Approximately 28 days after the final dose of study drug(s) (± 7 days), participants are to attend a clinical visit for a safety evaluation. During this visit, blood will be collected for safety laboratory analysis, a physical exam will be performed, and AEs and concomitant medications will be assessed according to the scheduled assessments found in Table 4 and Table 5.

Immune-related AEs will be collected for 90 days after the last dose of INCMGA00012 or placebo, regardless of continuation of chemotherapy during induction cycles or start of a new anticancer therapy. Reasonable efforts should be made to align the first 12-week follow-up visit with the end of the 90-day irAE reporting period when applicable. 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 Safety Follow-Up, the Safety Follow-Up visit should be performed before a new anticancer therapy is started.

8.9.2. Post-Treatment Disease Follow-Up

Participants who complete or early discontinue all assigned study drug(s) and have not experienced second disease progression, will move into Disease Follow-Up and should be assessed every 8 weeks (56 days ± 7 days) by radiologic imaging to monitor disease status.

Upon implementation of Amendment 3, imaging may be performed at intervals according to local institution standard practice, but at least every 6 months.

Immune-related AEs will be collected for 90 days after the last dose of INCMGA00012 or placebo, regardless of continuation of chemotherapy during induction cycles or start of a new anticancer therapy. Reasonable efforts should be made to align the first 12-week Follow-Up Period visit with the end of the 90-day irAE reporting period when applicable. 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.

Information regarding disease status will be collected until:

- Second disease progression.
- Death.
- The end of the study.
- Participant is lost to follow-up.

8.9.3. Survival Follow-Up

Once a participant has experienced second disease progression, the participant moves into Survival Follow-Up and should be contacted by telephone, email, or visit at least every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

Immune-related AEs will be collected for 90 days after the last dose of INCMGA00012 or placebo, regardless of continuation of chemotherapy during induction cycles or start of a new anticancer therapy. Reasonable efforts should be made to align the first 12-week follow-up visit with the end of the 90-day irAE reporting period when applicable. 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.

For participants having entered the Survival Follow-Up, the site will use continuing participant records to supply data on subsequent treatment regimens, tumor assessments, and OS in the eCRF. For participants who do not intend to return to the study investigator for their ongoing care, follow-up should be maintained by phone contact, patient records, and public records/databases at intervals of no longer than every 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.
Additional Guidance for Events Meeting the Adverse Event Definition
• Any safety assessments (eg, ECG, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease), should be reported as an AE. • 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 laboratory test 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 constitute an AE. • New conditions detected or diagnosed after study treatment administration even though they may have been present before the start of the study, should be reported as an AE. • Signs, symptoms, or the clinical sequelae of a suspected DDI constitute an AE. • 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 (including disease progression). Such instances will be captured in the efficacy assessments. • A condition that leads to a medical or surgical procedure (eg endoscopy, appendectomy) is an 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) need not be considered adverse events. • Anticipated day-to-day fluctuations of pre-existing disease(s), or condition(s) present, or detected at the start of the study judged by the investigator to have worsened more than expected for the participant's condition since study participation, should be reported as an AE.

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 or planned surgery (eg, stent replacement, hip surgery) is not considered an SAE.

Hospitalization for medical interventions in which no unfavorable medical occurrence occurred (ie, elective procedures or routine medical visits) are not considered SAEs.

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 1 of the outcomes listed in the above definition. Examples of such events include invasive or malignant cancers (excluding the disease[s] under study), 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. Secondary malignancies should always be considered SAEs.

For Japan, an event that may lead to disability is also considered an important medical event. It includes a case that is exposed to a risk of dysfunction to an extent that interferes with daily life when the adverse drug reaction occurs. It does not include an adverse drug reaction that, had the reaction been more severe, may have caused disability.

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. AEs/SAEs should be reported for enrolled participants, but only SAEs need to be reported for screen failure participants. 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. These records can be submitted to Incyte Pharmacovigilance by email/fax per the contact information listed in the Investigator Site File or as per SAE completing guidelines.
- 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 drug(s): 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 chemotherapy and/or INCMGA00012 or placebo, including INCMGA00012 received by eligible participants during Crossover as a result of the AE/SAE(s).
- The event outcome (eg, not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown).
- The seriousness, as per the SAE definition provided in Section 9.2.
- The action taken with regard to the event. Note: If an AE is treated with a concomitant medication or nondrug therapy, this action should be recorded on Adverse Event Form and the treatment should be specified on the appropriate eCRF (eg, Prior/Concomitant Medications, Procedures and Non-Drug Therapy).

Assessment of Intensity

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

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

- **Grade 1:** Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; treatment not indicated.
- **Grade 2:** Moderate; minimal, local, or noninvasive treatment indicated; limiting age appropriate activities of daily living.
- **Grade 3:** Severe or medically 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 drug and each occurrence of each AE/SAE. If reference therapy is used in combination with an Incyte study drug or multiple Incyte study drugs are used, the relationship to each study drug must be assessed (ie, for the Incyte product(s) and for the other product(s) that is used in combination with the Incyte product). If appropriate, the relationship to the combination may be assessed as well.
- 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 RSI in the IB and/or Product Information, for marketed products, in his/her assessment.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study drug administration, will be considered and investigated.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- With regard to assessing causality of SAEs:
  - There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report. However, the causality assessment is one of the criteria used when determining regulatory reporting requirements. **Therefore, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE.**
  - The investigator may change his/her opinion of causality in light of follow-up information and send a follow-up SAE report with the updated causality assessment.

Follow-Up of Adverse Events and Serious Adverse Events

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the originally completed eCRF and reported to Incyte Pharmacovigilance (in the SAE EDC CRF) until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up.
- Any updated SAE data (including SAEs being downgraded to nonserious) will be submitted to the sponsor (or designee) within 24 hours of receipt of the information.

- Once an AE is detected, it should be followed until it has resolved or until it is judged to be permanent; assessment should be made at each visit (or more frequently if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat the event, and the outcome.
- When the severity of an AE changes over time for a reporting period (eg, between visits), each change in severity will be reported as a separate AE until the event resolves.

9.4. Reporting of Serious Adverse Events

Regardless of suspected causality (eg, relationship to study drug or study procedures), all SAEs occurring after the participant has signed the ICF through 28 days after the last dose of study drug, regardless of whether a new anticancer therapy is started, must be reported to the sponsor (or designee) within **24 hours** of learning of its occurrence, unless otherwise specified by the Protocol. Serious AEs that are irAEs must be reported until 90 days after the last dose of INCMGA00012 or placebo, regardless of continuation of chemotherapy during induction cycles or start of a new anticancer therapy. The investigator will submit any updated SAE data to the sponsor (or designee) within 24 hours of it being available.

For Japan, this information must also be reported immediately to the head of the study site.

Investigators are not obligated to actively seek AE or SAE information after conclusion of the above-defined timeframes. 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 chemotherapy and/or INCMGA00012 or placebo, including INCMGA00012 received by eligible participants during Crossover 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 irAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

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

If the SAE is not documented in the RSI of 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. All SUSARs will be collected and reported to the competent authorities via the EudraVigilance database and to relevant ethics committees in accordance with the Clinical Trials Regulation (EU) No. 536/2014, Clinical Trials Information System guidelines, or as per current national regulatory requirements in participating countries.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study drug under clinical investigation. The sponsor

will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.

For Japan, the sponsor will report suspected expected deaths and life-threatening events to the PMDA as per local regulatory requirements.

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 may also need to complete the Incyte Serious Adverse Event Report Form, in English. Refer to the Incyte Reference Guide for Completing the Serious Adverse Event Report Form.
- The investigator must report within 24 hours of learning of its occurrence any SAE via the EDC system (primary method) or by completing the Serious Adverse Event Report Form in English (only if the EDC system is not available). The contact information for Incyte Pharmacovigilance by email/fax is listed in the Investigator Site File.
- In circumstances where the EDC system is not accessible for reporting SAE information (initial and/or follow-up SAE information) to the sponsor within 24 hours, refer to the Incyte Reference Guide for Completing the Serious Adverse Report Form. Once the EDC system is functional, the SAE report should be retrospectively added to the EDC system and follow-up should be completed through the EDC. The original copy of the Serious Adverse Event Report Form and the email or facsimile confirmation sheet must be kept at the study site (refer to the Incyte Reference Guide for Completing the Serious Adverse Report Form or Investigator Site File).
- Follow-up information is also recorded in the eCRF and transmitted to Incyte Pharmacovigilance via the EDC system. The follow-up report should include information that was not provided previously, such as the outcome of the event, treatment provided, action taken with study drug(s) 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.

9.5. Emergency Unblinding of Study Drug Assignment

In case of a medical emergency, for a participant's safety management, the procedure for emergency unblinding is provided to the investigator in the IRT Manual. If a participant's drug assignment undergoes emergency unblinding, the sponsor or its designee should be notified immediately for awareness.

If an investigator, site personnel performing assessments, or participant is unblinded during emergency unblinding, the participant must be withdrawn from the study drug, unless there are ethical reasons to have the participant remain on the study drug. In these cases, the investigator must obtain specific approval from the sponsor's (or its designees) medical monitor for the participant to continue to receive the unblinded study drug.

9.6. 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:

- Chemotherapy and INCMGA00012 or placebo, including INCMGA00012 received during Crossover, must be interrupted immediately (female participants only).
- If the female participant is no longer pregnant and meets the treatment continuation criteria within 12 weeks of the scheduled start of a cycle, study drug may be resumed after approval has been received from the sponsor medical monitor.
- The investigator must complete and submit the Incyte Clinical Trial Pregnancy Form to the sponsor or its designee within **24 hours** of learning of the pregnancy.

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

Any SAE occurring during pregnancy of a study participant must be recorded and reported as described in Section 9.4.

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.

9.7. Warnings and Precautions

Special warnings or precautions for INCMGA00012, derived from safety information collected by the sponsor or its designee, are presented in the IB. Additional safety information collected between IB updates will be communicated in the form of Investigator Notifications. Special warnings or precautions to the chemotherapy agents used are further detailed in the approved labels.

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.

9.8. 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.

For Japan, complaints associated with unapproved medical devices will be reported to the sponsor with a Medical Device Report Form, and the sponsor will report medical device defects to the PMDA as per local regulatory requirements.

9.9. Treatment of Overdose of INCMGA00012

Overdose (accidental or intentional) is to be reported as an AE (see Section 9.1). If the overdose meets serious criteria, the overdose term should be reported as an SAE (see Section 9.2). Additionally, signs and/or symptoms resulting from overdose are to be reported as an AE/SAE.

For this study, any dose of INCMGA00012 ≥ [redacted] mg within a 24-hour time period (± 1 hour) will be considered an overdose.

The sponsor does not recommend specific treatment for an overdose. In the event of an overdose of INCMGA00012, the investigator should:

- Contact the medical monitor and sponsor immediately.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities as per Section 9.2.
- 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.

There has been no clinical experience with overdose of INCMGA00012. Treatment of overdose should consist of general supportive measures.

10. STATISTICS

10.1. Sample Size Determination

It is assumed that the median PFS will be 8 months with the carboplatin-paclitaxel arm (Rao et al 2018). It is expected that treatment with INCMGA00012 will result in a [redacted]% [redacted] in hazard rate (corresponding to an increase in median PFS from 8 months to 12 months under exponential model assumption).

If the true hazard ratio is [redacted] (under alternative hypothesis), a total of [redacted] PFS events are required to have 83% power at a 1-sided overall 2.5% level of significance to reject the null hypothesis (HR = 1) using a log-rank test. Considering a recruitment period of 32 months (2 years) at a uniform rate of [redacted] participants/month with a 6-month ramp up period, approximately [redacted] participants will be randomized to the 2 treatment arms in 1:1 ratio, assuming monthly drop out rate of 2% from exponential distribution for PFS.

It is assumed that the median OS will be 20 months with the chemotherapy arm (Rao et al 2018). It is expected that treatment with INCMGA00012 will result in a [redacted]% reduction in hazard rate (corresponding to an increase in median OS from 20 months to [redacted] months under exponential model assumption).

If the true hazard ratio is [redacted] (under alternative hypothesis), a total of approximately [redacted] participants (around [redacted] OS events) will provide around 73% power at a 1-sided overall 2.5% level of significance to reject the null hypothesis (HR = 1) using a log-rank test. The power estimation assumes 1% drop out from exponential distribution.

10.2. Populations for Analysis

Populations for analysis are listed in Table 16.

Table 16: Populations for Analysis

Population	Description
FAS	The FAS includes all randomized participants. According to the ITT principle, participants will be analyzed according to the treatment and strata they have been assigned during randomization. The FAS will be the primary population for all efficacy analysis.
Safety evaluable	The safety population includes all randomized participants who received at least 1 dose of study drug. Treatment groups for this population will be determined according to the actual treatment the participant received regardless of assigned study drug. All safety analyses will be conducted using the safety population.
PK evaluable	The PK evaluable population will include all participants who received at least 1 dose of study drug and provided at least 1 postdose sample (1 PK measurement).
Translational evaluable	The translational evaluable population will include all participants who received at least 1 dose of study drug and provided at least 1 postdose plasma sample.

10.3. Level of Significance

The level of significance for the primary and key secondary endpoints of PFS and OS, respectively, is strongly controlled at 1-sided 2.5%. A 1-sided 2.5% will be initially assigned to the PFS endpoint. If the hypothesis testing of the PFS endpoint is rejected, the alpha will be allocated to test the OS endpoint. Within the OS endpoint, the Type I error will be controlled by a group sequential design with Lan-DeMets (O'Brien and Fleming 1979) alpha spending function. If both the PFS and OS tests indicate statistical significance, ORR by RECIST v1.1 will be tested in an alpha-controlled manner.

10.4. Statistical Analyses

10.4.1. Efficacy Analyses

10.4.1.1. Primary Efficacy Analyses

Progression-free survival (PFS) is defined as the time from the date of randomization to the date of the first documented progression or death due to any cause. The PFS will be assessed via BICR according to RECIST v1.1. Survival data will be analyzed by the Kaplan-Meier method, treating participants with no observed death or disease progression as censored at the date of the last adequate tumor assessment before data cut off or new anticancer therapy. The PFS as assessed via investigator may be provided as supportive analysis of the primary endpoint.

The primary efficacy endpoint of PFS will be analyzed using a stratified log-rank test at an overall 1-sided 2.5% level of significance based on the data observed in the FAS population, according to the treatment group participants were randomized and the strata they were assigned at randomization. The distribution of PFS will be estimated using the Kaplan-Meier method. The median PFS along with 95% confidence intervals will be presented by treatment group. A stratified Cox regression with Efron's method for tie handling will be used to estimate the hazard ratio of PFS, along with 95% confidence intervals using the same strata information assigned at randomization.

10.4.1.2. Key Secondary Efficacy Analyses

Overall survival is defined as the time from the date of randomization to the date of death due to any cause. The efficacy analysis of OS comparing the 2 treatment groups will be a stratified log-rank test at an overall 1-sided 2.5% level of significance in the FAS population, according to the treatment group participants were randomized and the strata they were assigned at randomization. Kaplan-Meier curves, medians, and 95% confidence intervals of the median OS will be presented for each treatment group. The hazard ratio for OS will be calculated, along with its 95% confidence interval, from a stratified Cox model using the same stratification factors as for the log-rank test with Efron's likelihood approximation to account for ties in event times. The analysis of OS will follow gatekeeping procedure (ie, hypothesis testing on OS will only occur if hypothesis on PFS is rejected). An interim OS analysis will be performed at the time of the PFS analysis, and final OS analysis will be performed when there are at least [redacted] death events observed or later. Summary statistics of OS endpoint will still be provided if PFS does not cross boundary.

10.4.1.3. Secondary Efficacy Analyses

- Overall response rate is defined as the percentage of participants with CR or PR, according to RECIST v1.1 (Eisenhauer et al 2009) as determined by BICR. The analysis of ORR will be based on the FAS. Objective response rate and its exact 95% CI will be presented. Odds ratio from CMH test will also be provided.
- Duration of response is defined as the time from first documented response (CR or PR) to the time of first documented disease progression per RECIST v1.1 as determined by BICR or death due to any cause. If a participant does not have an event, DOR is censored at the date of the last adequate tumor assessment before data cut off or new anticancer therapy. The Kaplan-Meier estimate of the distribution function will be constructed for DOR. The estimated median along with 95% CIs will be reported.
- Disease control rate is defined as the proportion of participants with an overall response (CR and PR), or stable disease per RECIST v1.1, according to the BICR. The DCR will be estimated, and the exact 95% CI will be reported.

10.4.2. Safety Analyses

10.4.2.1. Adverse Events

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

10.4.2.2. Clinical Laboratory Tests

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

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

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

10.4.2.3. Vital Signs

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

10.4.2.4. 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.

10.4.2.5. Pharmacokinetics

If there is a sufficient amount of 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.

10.4.3. Exploratory Analyses

[redacted]

10.4.3.1. [redacted]

[redacted]

10.4.3.2. [redacted]

[redacted]

10.4.3.3. [redacted]

11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

11.1. Investigator Responsibilities

- The Protocol, Protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC and health authorities before the study is initiated. In accordance with EU CTR No. 536/2014, the sponsor will be responsible for submitting all documents in participating countries.
- 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 Authority 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:
  - Recording and documenting AEs or laboratory abnormalities identified in the Protocol as critical to the safety evaluation and reporting them to the sponsor according to the reporting requirements specified in the Protocol.
  - Recording and documenting all AEs, unless the Protocol provides different guidance in Section 9.
  - Reporting to the sponsor all SAEs occurring to participants treated by them in the clinical study unless the Protocol provides different guidance in Section 9.
  - Reporting an SAE to the sponsor per Section 9 procedures and timelines if they become aware of an SAE with a suspected causal relationship to the study treatment that occurs after the end of the study.
  - 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.
  - Ensuring (along with the sponsor) that the clinical study is conducted in accordance with the Protocol and with the principles of GCP.

  - 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.
  - Ensuring study-site compliance with the requirements of EU CTR No. 536/2014.
  - Assigning tasks among the members of the team of investigators in a way that does not compromise the safety of participants or the reliability and robustness of the data generated at the clinical study site.

- The investigator will adhere 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.
  - The investigator will retain the content of the clinical trial master file, essential documents, AE documentation, and medical and other study records in accordance with all local, national, and regulatory laws but for a minimum period of at least 30 years for the US, 25 years for EEA countries, and a flexible approach of up to 30 years for regions outside the US and EEA, unless specific country regulations dictate otherwise after completion or discontinuation of the study or as described in the final executed copy of the individual site agreement, or for 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 formal discontinuation of clinical development of the test article and the regulatory authority is notified, whichever is longer, 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 during the retention period 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.

- For Japan, the record retainer (delegated by head of study site) will retain the J-GCP–defined essential documentation at this site until the regulatory approval of study drug(s)/treatment, or at least 3 years after the discontinuation or completion of the study conduct, whichever is longer. If the sponsor requires retention of these documents for a longer period of time, the duration and method of retention will be decided upon through discussion between the sponsor and the study site. It is the responsibility of the sponsor to inform the head of the study site as to when the documents no longer need to be retained.

11.1.1. Identification of the Coordinating Principal Investigator

A coordinating principal investigator will be appointed by the sponsor medical monitor before the end of the study. As part of his or her responsibilities, the coordinating principal investigator will review the final CSR. Agreement with the final CSR will be documented by the dated signature of the coordinating principal investigator.

11.2. Data Management

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

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

The sponsor (or designee) will be responsible for the following:

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

The investigator will be responsible for the following:

- Recording, or ensuring the recording of, all relevant data relating to the study in the eCRF.
- Delivering, or ensuring the delivery of, all other results, documents, data, know-how, or formulas relating to the study to the sponsor or designee electronically and/or centrally (eg, laboratory data, imaging data, biomarker data, photographs, diary data), or as otherwise specified in the Protocol.
- Maintaining adequate and accurate source documents and study records that include all pertinent observations on each of the site's study participants. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail). Source data are, in general, all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the

reconstruction and evaluation of the study. Source data are contained in source documents (original records or certified copies).

- Verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- Maintaining accurate documentation (source data) that supports the information entered in the eCRF, or sent to a central vendor designated by the sponsor, or as described in other study and data flow manuals.
  - Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed and available at the investigator's site. Examples of source documents are original documents, data, and records (eg, hospital records; electronic hospital records; clinical and office charts; laboratory notes; memoranda; participants' diaries or evaluation checklists; pharmacy dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiches; photographic negatives; microfilm or magnetic media; x-rays; participants' files; and e-records/records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical study).
  - Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Current applicable medical records must be available.
- Sending participants' data, either as unique samples, copies, or photographs, to be evaluated centrally or analyzed centrally, or both, by a qualified vendor designated by the sponsor.
- Permitting study-related monitoring, sponsor audits, IRB/IEC review, and regulatory inspections by providing direct access to source data and other relevant clinical study documents.
  - Monitoring: Qualified representatives of the sponsor or its designee, study monitors, will monitor the study according to a predetermined plan. The investigator must allow the study monitors to review any study materials and participant records at each monitoring visit.
  - Auditing: Qualified representatives of the sponsor or its designee may audit the clinical study site and study data to evaluate compliance with the Protocol, applicable local clinical study regulations, and overall study conduct. The investigator must allow the auditors to review original source records and study documentation for all participants.

- Regulatory inspection: Regulatory authorities may conduct an inspection of the study and the site at any time during the development of an investigational product. The investigator and staff are expected to cooperate with the inspectors and allow access to all source documents supporting the eCRFs and other study-related documents. The investigator must immediately notify the sponsor when contacted by any regulatory authority for the purposes of conducting an inspection.

11.3. Data Privacy and Confidentiality of Study Records

The investigator and the sponsor or its designee must adhere to applicable data protection laws and regulations. The investigator and the sponsor or its designee are responsible for ensuring that personal information is handled in accordance with local data protection laws (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.

To ensure confidentiality of records and protect personal data, participant names will not be supplied to the sponsor or its designee. There may be certain duly authorized and contracted vendors managing participants' services such as for travel and meal reimbursement, home delivery services, and/or parking, in which case those vendors will have the participant's directly identifiable personal information but in no circumstances will that directly identifiable information be transferred or sent to the sponsor. 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.

In the event of a data breach involving participant data, the sponsor or its designee will follow the sponsor's incident response procedures. The precise definition of a data breach varies in accordance with applicable law but may generally be understood as a breach of security leading to the accidental or unlawful destruction, loss, alteration, unauthorized disclosure of, or access to, personal data. In accordance with its incident response procedures, the sponsor will assess the breach to consider its notification and remediation obligations under applicable law.

11.4. Financial Disclosure

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

Any new clinical investigators added to the covered clinical study during its conduct must also submit a completed Clinical Investigator Financial Disclosure Form. During a covered clinical study, any changes to the financial information previously reported by a clinical investigator

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

11.5. Publication Policy

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

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

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

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

11.6. Study and Site Closure

The sponsor designee reserves the right to close the study site or terminate the study at any time at the sole discretion of the sponsor or the IRB/IEC. 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.

For Japan, when the study is completed, the investigator should inform the head of the study site of the completion in writing and submit a written summary of the study's outcome, and then the head of the study site should promptly inform the IRB and sponsor or designee of the completion in writing.

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.

Further reasons for the early closure of a study site (eg, premature termination) by the sponsor, investigator, or the IRB/IEC may include but are not limited to the following:

- Failure of the investigator to comply with the Protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures or site agreement, or GCP guidelines.
- Inadequate recruitment of participants by the investigator.
- Discontinuation of further study drug development.
- Circumstances beyond the control of the sponsor or investigator that make it unreasonable to require the continuation of the study or site.
- Failure to carry out the study in the interest of the health of the participants.
- Failure to demonstrate that the continuation of an IRB-/IEC-approved study (ie, the IRB/IEC had previously issued a positive decision on the study) has scientific merit.
- Financial reasons (eg, the sponsor is declared insolvent or a bankruptcy petition has been filed).

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APPENDIX A. INFORMATION REGARDING EFFECTIVENESS OF CONTRACEPTIVE METHODS AND RELEVANT DEFINITIONS

Definitions:

WOCBP: A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

    Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
  - A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with 2 FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use 1 of the nonhormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

For male participants of reproductive potential in the study:

Male participants with female partners of childbearing potential are eligible to participate if they agree to 1 of the following during the protocol-defined timeframe in Section 5.1:

- Be abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and to the timeframe defined in Section 5.1 and the preferred and usual lifestyle of the participant. Sexual abstinence is not an approved method of contraception in Japan.
- Use a male condom plus partner use of an additional contraceptive method when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant.
- Male participants who have had a successful vasectomy (medically assessed) qualify as having met the requirement for a highly effective birth control method.

For female participants in the study who are WOCBP:

The following methods during the protocol-defined timeframe in Section 5.1 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 (administration route not approved in Japan)
  - transdermal (administration route not approved in Japan)
- Progestogen-only hormonal contraception associated with inhibition of ovulation[a] (progesterone-only hormonal contraception is not approved in Japan, so this bullet and its sub-bullets will not apply for Japan)
  - oral
  - injectable
  - implantable[b]
- Intrauterine device[b]
- Intrauterine hormone-releasing system[b]
- Bilateral tubal occlusion[b]
- Vasectomized partner[bc]
- Sexual abstinence[d] (sexual abstinence is not approved in Japan)

For female participants in the study who are WOCBP and male participants of reproductive potential in the study:

Please refer to local labeling for paclitaxel and carboplatin for additional information regarding contraception and fertility issues, including oocyte and sperm preservation advice, with the use of these chemotherapeutic agents.

[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 drugs. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study, the time duration mentioned in Section 5.1, and the preferred and usual lifestyle of the participant.

Source: Clinical Trials Facilitation and Coordination Group 2014.

APPENDIX B. RESPONSE CRITERIA FOR SOLID TUMORS VERSION 1.1

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

Evaluation of Target Lesions

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

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

Evaluation of Nontarget Lesions

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

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

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

Evaluation of Best Overall Response

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

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

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

Participants with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment.

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of CR depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the CR status.

Source: Eisenhauer et al 2009.

APPENDIX C. ASSESSMENT OF TUMOR RESPONSE FOR IMMUNE-BASED THERAPEUTICS (iRECIST)

A modified version of RECIST v1.1 for immune-based therapeutics will be used to assess tumor response to guide treatment decisions for discontinuation of therapy due to disease progression (Seymour et al 2017). These disease assessments for clinically stable participants will be performed by the study site and will be collected in the clinical database.

Participants may receive study drug pending confirmation of PD if they are clinically stable as defined by the following criteria:

- Absence of clinically significant signs and symptoms (including worsening of laboratory values) indicating disease progression.
- No decline in ECOG performance status.
- No requirement for intensified management of disease-related symptoms (requiring urgent medical intervention such as symptomatic pleural effusion, spinal cord compression).

If radiologic imaging shows iUPD, tumor assessment should be repeated ≥ 4 weeks later (but no later than 8 weeks) to confirm PD by iRECIST with the option of continuing treatment while awaiting radiologic confirmation of progression. Image measurements will be collected in the clinical database.

When clinically stable, participants should not be discontinued from treatment until progression is confirmed per iRECIST. The decision to continue treatment after iUPD is observed is at the investigator's discretion and should be based on the clinical status of the participant as described above.

Participants who are clinically unstable are not required to continue to receive study drug once the investigator has determined PD by RECIST v1.1, and they are not required to have repeat imaging for the iCPD.

If the participant continues to be clinically stable, and if the repeat imaging does not confirm PD by iRECIST as assessed by the investigator, study drug may continue and follow the imaging schedule.

If PD is confirmed by iRECIST, participants will be discontinued from study drug.

Every effort should be made to continue monitoring their disease status by radiologic imaging until the participant has iCPD, starts a new anticancer therapy, withdraws consent, or dies. If a follow-up scan was not performed after unconfirmed PD (eg, due to patient refusal or patient death), the initial date of unconfirmed progression will be considered the date of PD.

APPENDIX D. COVID-19 PANDEMIC GUIDANCE

Introduction

The COVID-19 global pandemic, including peaks and troughs, presents challenges to the ongoing conduct of clinical trials. In line with regulatory guidance regarding clinical study execution during the pandemic, the sponsor has standardized protocol considerations to ensure participant safety is maintained and adequate benefit/risk analyses are applied relative to participation in the study, completion of study procedures, and objectives (EMA 2021).

Recognizing the dynamic nature of the COVID-19 pandemic and the flexibility required to manage the impact of the pandemic on ongoing clinical studies, details and additions may need to be added to respective study manuals and site-specific monitoring plans as applicable, with institutional and health authority requirements and approvals 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-CoV-2 Infection and Participation in the Study

Benefit/risk assessment in the context of the COVID-19 pandemic is provided in Section 2.2.1.

COVID-19 Vaccination During Participation in the Study

The following are guidelines for SARS-CoV-2 vaccination, timing, and precautions:

- If participants are vaccinated during the study, it is recommended that a vaccine is not administered on the day of study treatment or study drug infusion. Administration of study treatment or study drug is recommended to be given at least 3 days later to ensure possible acute AEs due to the vaccine are managed and resolved or stable.
- The vaccination dose or doses and manufacturer, if known, must be entered in the EDC system as a concomitant medication.
- Since corticosteroids may be given for defined, relatively brief periods such as in the management of irAE toxicity investigators may consider delaying second dose of a vaccine against SARS-CoV-2 (if needed to be given during the study for example) until a corticosteroid regimen has been completed or the dose has been reduced to ≤ 10 mg of prednisone or equivalent.
- Any AEs resulting from the vaccination and medications for treating the AEs must be entered in the eCRFs.
- While based on approved vaccines available worldwide, many vaccines are not live (mRNA and adenovirus vaccines do not contain live virus), if a live vaccine against SARS-CoV-2 is the only available option, prior consultation with the medical monitor should be obtained.

- If a potential participant recovered from COVID-19 within approximately 6 months before signing the ICF, a negative test (PCR or antigen) and consultation with the sponsor's medical monitor are required for eligibility. This approach is necessary due to the dynamic changing nature of the COVID-19 pandemic, including but not limited to understanding of the available and approved (types) of tests, interpretation of SARS-CoV-2 antibody test results, prior possible relevant vaccination received, and safety of a potential participant.

Study Site Visits and Study Procedures

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:

- Predose laboratory procedures may be conducted ± 5 days before dosing (versus the ± 3-day time window described in Section 8.3.5) and must be reviewed before dosing. During COVID-19 pandemic restrictions, safety labs may be conducted at hospitals near the participant's home, provided the data can be transferred to the study site and entered in the eCRFs, or at a relevant clinical facility authorized/certified (as legally required nationally) to perform such tests routinely, if this can be done within local restrictions on social distancing.
  - The sites should inform the sponsor about such arrangements.
- In order to minimize participant risk, some study procedures such as a review of AEs and concomitant medications may be conducted via telemedicine modalities (phone or video) where appropriate or as per site institutional guidelines during the COVID-19 pandemic. Information reviewed must be available in the investigator's site binder and entered in the eCRFs. 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.
- If study procedures are anticipated to be missed, then a potential participant should not be consented, as it is important to assess the safety and efficacy of the investigational study treatment.
  - In general, compliance with the Protocol should be ensured to such an extent that an ongoing benefit-risk assessment for the clinical trial and potential participants is still possible.
- During COVID-19 pandemic restrictions only, scans for disease assessments may be delayed by an additional 7 days from the time allowed in the Protocol (see Table 4 and Table 5 for details).
- 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 properly 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.

Note: The sponsor has reviewed relevant guidance on the implications of COVID-19 on methodological aspects of ongoing clinical trials by the CHMP Biostatistics Working Party published on 25 MAR 2020 (EMA 2020).

Study Drug and Study Treatment Administration

If necessary, study treatment administration may be delayed up to 3 weeks due to COVID-19 pandemic restrictions unless otherwise discussed with the sponsor. The reason for interruption should be documented in the participant's medical records and eCRFs (eg, "due to COVID-19").

Chemotherapy and INCMGA00012/placebo cannot be administered at home.

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

The following recommendations are necessary in the event of SARS-CoV-2 infection during the trial:

- If a participant develops a SARS-CoV-2 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 should be provided.
- Postbaseline SARS-CoV-2 testing should follow country-specific requirements depending on the extent of the COVID-19 pandemic, local institutional guidance, or investigator's clinical judgment.
- For participants who are diagnosed with COVID-19 during the study (positive SARS-CoV-2 test) or presumed affected by SARS-CoV-2 infection (test pending), study treatment should be delayed until the SARS-CoV-2 test is negative and the participant has clinically recovered from symptoms.
  - In addition, prior to restarting treatment, the participant should be afebrile for 72 hours and SARS-CoV-2–related symptoms (if any) should have resolved for a minimum of 72 hours.
- Safety monitoring following COVID-19 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.

Clinical Study Monitoring

Site monitoring guidelines and principles are listed below:

- Study monitoring visits may be postponed; however, the site monitor and sponsor should continue to employ off-site monitoring practices such as routine communication methods (eg, phone calls, emails, video visits) with the sites to get information on study progress, participant status, and issue resolution.

- The study monitor may remotely review data entered into the eCRFs for accuracy and completeness if allowed and first approved by the national regulatory body or investigational site and/or in compliance with local authorities (EMA 2021).
  - If remote source data verification focusing on quality control of critical data as per the monitoring plan or equivalent is not permitted, an investigational site will not be able to enroll new participants.

Reimbursement of Additional Expenses

If permitted by local or legal requirements, the sponsor may reimburse participants for any extraordinary expenses, keeping appropriate documentation as evidence (eg, travel expenses for the local laboratory visit[s], private transportation, the costs of local [proximate] laboratory tests).

APPENDIX E. ADDITIONAL INFORMATION FOR HOSPITAL DISCHARGE FOR SITES IN JAPAN

Japanese participants are required to be hospitalized until the investigator assesses their ability to safely tolerate the study treatment after the first administration. The participant cannot be discharged if any of the following criteria are met on Cycle 1 Day 8:

- Grade 4 thrombocytopenia or ≥ Grade 3 thrombocytopenia with clinically significant bleeding (requires hospitalization, transfusion of blood products, or other urgent medical intervention).
- ≥ Grade 4 neutropenia.
- ≥ Grade 3 febrile neutropenia.
- Grade 4 anemia not explained by underlying disease or unrelated illnesses (eg, hemolysis).
- Thrombocytopenia requiring platelet transfusion or anemia requiring red blood cell transfusion.
- Grade 3 nausea/vomiting or diarrhea, which cannot be managed with adequate antiemetic and other supportive care.
- Grade 3 fatigue.

  Note: Updates may be included in an operational manual until a future amendment is planned.

APPENDIX F. PROTOCOL AMENDMENT SUMMARY OF CHANGES

Document	Date
Original Protocol (Version 1-UK)	01 SEP 2020
Amendment 1	21 DEC 2021
Amendment 2	25 MAY 2022
Amendment 3	04 FEB 2025

Amendment 3 (04 FEB 2025)

The primary purpose of the amendment is to update the frequency of imaging during the disease follow-up phase of the study and to incorporate administrative updates required by EU CTR. Additional changes are summarized below.

1. **Section 1, Protocol Summary (Table 2: Key Study Design Elements); (Table 4: Schedule of Activities; Table 5: Crossover Period Schedule of Activities); Section 8.2.1.4, Tumor Imaging During Disease Follow-up; Section 8.9.2, Post-Treatment Disease Follow-up**

   Description of change: Frequency of imaging during the disease follow-up period was updated to match local institution standard interval.

   Rationale for change: To add flexibility for participants now that the primary endpoint has been met.

2. **Title Page; Section 9.4, Reporting of Serious Adverse Events; Section 11.1, Investigator Responsibilities; Section 11.3, Data Privacy and Confidentiality of Study Records**

   Description of change: Added text as required by new EU CTR directives.

   Rationale for change: Health authority requirement.

3. **Section 3, Objectives and Endpoints (Table 6: Objectives and Endpoints); Section 10.4.3, Exploratory Analyses**

   Description of change: Removed the exploratory endpoint of [redacted]

   Rationale for change: This analysis will not be performed.

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

   Description of change: Updated definition of end of study.

   Rationale for change: To allow for timely study closure.

5. **Section 4.2, Overall Study Duration; Section 6.7, Treatment After the End of Study**

   Description of change: Added text regarding possible access to INCMGA00012 after the study is closed.

   Rationale for change: Declaration of Helsinki updates.

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

Amendment 2 (25 MAY 2022)

Overall Rationale for the Amendment: To update dose modification table, eligibility criteria for Japanese participants, SARS-CoV-2 vaccine requirement, and add justification for collection of participants' ethnic origin data. Additional changes are summarized below.

1. **Section 1, Protocol Summary (Table 4: Schedule of Activities); Section 5.1, Inclusion Criteria (Criterion 10); Section 8.1.6, COVID Vaccination; Appendix D, COVID-19 Pandemic Mitigation Strategies and Instructions**

   Description of change: Participant vaccination against SARS-CoV-2 changed from mandatory to highly recommended.

   Rationale for change: In view of waning incidence and severity of new COVID-19 cases in many geographic regions; and in order to be sensitive to potential participants who wish not to be vaccinated or have a contraindication to vaccination.

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

   Description of change: Added that in the EU/EEA, the results of the study will be based on the date of the last visit of the last participant in the study globally.

   Rationale for change: As per recent EU Clinical Trial Regulation, it is required in the EU to post results within 1 year of study completion. In this study, for analysis purposes, results will be posted after the last participant's last visit date has been reached globally (not just in the EU). This will ensure the results are robust, meaningful, and representative of all multi-regions by having complete follow-up data determined by the statistical hypotheses for the objectives established.

3. **Section 5.1, Inclusion Criterion 2**

   Description of change: The age requirement for the study population enrolled in Japan will be updated to indicate that participants enrolled in this study on or prior to 31 MAR 2022 must be aged ≥ 20 years; beginning 01 APR 2022, participants may be aged ≥ 18 years.

   Rationale for change: Effective 01 APR 2022, the age of adulthood in Japan changes from ≥ 20 years to ≥ 18 years.

4. **Section 6.1.3, Carboplatin**

   Description of change: Correction of typographical error for CrCl.

   Rationale for change: Editorial change.

5. **Section 6.5.2.2. INCMGA00012 or Placebo (Table 10: Guidelines for Management of Suspected Infusion Reactions for Study Drug)**

   Description of change: Added a note to clarify management of Grade 3 infusion reactions.

   Rationale for change: To allow for continued dosing for participants who are responsive to treatment.

6. **Section 6.5.4.1, Procedures for Participants Exhibiting Immune-Related Adverse Events (Table 12: Dose Modifications of INCMGA00012 or Placebo and Toxicity Management Guidelines for Immune-Related Adverse Events)**

   Description of change: Updated toxicity management for diarrhea/colitis, AST/ALT elevations, adrenal insufficiency, hypophysitis, nephritis, skin reactions, and all other irAEs.

   Rationale for change: To align with current toxicity management used for INCMGA00012 program-wide.

7. **Section 8.1.7.1, Demography and Medical History**

   Description of change: Added scientific rationale for the collection of participants' ethnic origin and gender. The term "race" was removed from the text.

   Rationale for change: To provide justification for collection of sensitive data needed for analyses.

8. **Section 8.2.1, Tumor Imaging and Assessment of Disease; Section 8.2.2, iRECIST Assessment of Disease**

   Description of change: Updated use of iRECIST for participant management to be applied during both blinded and crossover phases of the study.

   Rationale for change: To clarify intent of the protocol.

9. **Section 8.2.1.2, Tumor Imaging During Study Drug Administration Period; Section 8.7, Crossover Period**

   Description of change: Updated text to clarify eligibility for Crossover Period.

   Rationale for change: To clarify intent and align with the other sections of the protocol.

10. **Section 8.5.1, Tumor Tissue Biopsies**

    Description of change: Removed reference to China.

    Rationale for change: China will not be participating in the study.

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

Amendment 1 (21 DEC 2021)

Overall Rationale for the Amendment: To remove interim analyses, clarify eligibility criteria and contraceptive methods, and update dose modification table and other changes as requested by Health Authorities. Additional changes are summarized below.

1. **Section 1, Protocol Summary (Table 2: Key Study Design Elements); Section 5.5, Data Monitoring Committee; Section 10.1, Sample Size Determination; Section 10.4.1.1, Primary Efficacy Analyses; Section 10.5, Interim Analyses**

   Description of change: Removed planned interim analyses for efficacy.

   Rationale for change: To address regulatory concerns that an interim analysis may not provide an accurate or reproducible estimate of treatment effect.

2. **Section 1, Protocol Summary (Table 2: Key Study Design Elements); Section 4.1, Overall Design**

   Description of change: Added text to clarify that nonevaluable tumors refers to tumor tissue that cannot be analyzed for PD-L1 status.

   Rationale for change: To clarify that nonevaluable tumor tissue is for determination of PD-L1 status for the purposes of stratification is capped at 10%.

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

   Description of change: Added 3-day window to dosing visits for INCMGA00012 or placebo.

   Rationale for change: To allow for participant flexibility.

4. **Section 1, Protocol Summary (Table 4: Schedule of Activities); Section 5.1, Inclusion Criteria (Criterion 6)**

   Description of change: Updated timeframe for archive biopsy sampling from within 6 months to within 9 months.

   Rationale for change: To improve feasibility of obtaining this information which is required for stratification.

5. **Section 1, Protocol Summary (Figure 1: Study Design Schema); Section 5.1, Inclusion Criteria (Criterion 8a)**

   Description of change: Adjusted the CD4+ count criteria for HIV-positive participants from ≥ 300 to ≥ 200.

   Rationale for change: Change made in line with evolving recommendations for inclusion of HIV-positive participants in clinical trials (NCCN 2019).

6. **Section 1, Protocol Summary (Table 4: Schedule of Activities; Table 5: Crossover Period Schedule of Activities); Section 8.2.1.2, Tumor Imaging During Study Drug Administration Period; Section 8.2.1.3, Tumor Imaging During the Crossover Period; Section 8.2.1.4, Tumor Imaging During Disease Follow-up; Section 8.9.2, Post-Treatment Disease Follow-Up**

   Description of change: Updated the frequency of tumor imaging from Q12W to Q8W.

   Rationale for change: To support exploratory endpoint of [redacted] and new exploratory endpoint of [redacted] during Crossover Period.

7. **Section 1, Protocol Summary (Table 4: Schedule of Activities; Table 5: Crossover Period Schedule of Activities), Section 8.3.6, Pregnancy Testing**

   Description of change: Updated timing and methods for pregnancy testing.

   Rationale for change: To address comments from health authorities.

8. **Section 2.2.1, Benefit/Risk Assessment During the COVID-19 Pandemic; Section 6.5.1, General Dose Modifications; APPENDIX D: COVID-19 Pandemic Mitigation Strategies and Instructions**

   Description of change: Section and appendix were added to update the protocol with potential risks associated with the current COVID-19 outbreak along with risk mitigation measures.

   Rationale for change: To address comments from health authorities.

9. **Section 2.2 Benefit/Risk Assessment**

   Description of change: Added information from completed and ongoing trials with participants known to be HIV-positive.

   Rationale for change: To support risk:benefit assessment in HIV-positive participants.

10. **Section 3, Objectives and Endpoints (Table 6: Objectives and Endpoints); Section 10.4.3.1, Progression-Free Survival After Next Line of Treatment (Progression Free Survival 2); Section 10.1, Sample Size Determination; Section 10.3, Level of Significance; Section 10.4.1.3, Secondary Efficacy Analyses**

    Description of change: Added new exploratory endpoint and updated associated statistical methods.

    Rationale for change: To provide additional estimation of the treatment effect based on recommendations from health authorities.

11. **Section 4.3, Study Termination; Section 5.1, Inclusion Criteria (Criterion 2a); Section 6.1.1, Timing of Dose Administration; Section 6.2, Preparation, Handling, and Accountability; Section 9.2, Definition of Serious Adverse Event; Section 9.4, Reporting of Serious Adverse Events; Section 9.10, Product Complaints; Section 11.1, Investigator Responsibilities; Section 11.6, Study and Site Closure; APPENDIX A: Information Regarding Effectiveness of Contraceptive Methods and Relevant Definitions; APPENDIX E: Additional Information for Hospital Discharge for Sites in Japan**

    Description of change: Added clarifications and administrative procedures specific to sites participating in Japan.

    Rationale for change: To comply with Japanese GCP requirements.

12. **Section 5.1, Inclusion Criteria**

    Description of change: Updated inclusion criterion 5 to include any tissue collected during biopsy as a requirement for measurable disease.

    Rationale for change: For clarification.

13. **Section 5.1 Inclusion Criteria; Section 6.6.1, Permitted Medications and Procedures; Section 8.1.6, COVID-19 Vaccination**

    Description for Change: New inclusion criterion 10 was added. Potential participants are to be fully vaccinated against SARS-CoV-2 before randomization or complete vaccination during the trial. SARS-CoV-2 vaccines and applicable ancillary procedures and tests were added to the list of permitted medications and procedures.

    Rationale for Change: Participants with advanced cancer are at increased risk of developing severe COVID-19 and therefore will likely derive substantial benefit from vaccination against SARS-CoV-2. Due to expanding protection for potential participants participating in a research study and as per recommendations by the main international worldwide oncology societies (eg, ASCO, ESMO), participants with cancer, including those undergoing treatments (eg, chemotherapy, immunotherapy, and targeted treatment), should receive an approved COVID-19 vaccination. Thus, the sponsor is adding this new requirement as safety precaution.

14. **Section 5.2, Exclusion Criteria**

    Description of change: Added eligibility criteria to exclusion criterion 2 in regards to palliative radiotherapy.

    Rationale for change: For clarification.

15. **Section 5.2, Exclusion Criteria**

    Description of change: Updated eligibility criteria for exclusion criterion 10 in regards to prior antibiotic use.

    Rationale for change: To align with newer INCMGA00012 guidance regarding antibiotic use.

16. **Section 5.2, Exclusion Criteria**

    Description for Change: Under exclusion criterion 10, a note was added to indicate that participants may be tested for COVID-19 during screening if required by country or local regulations. A participant will be excluded if they have a positive screening test result for SARS-CoV-2 infection. Participants should be included only after they have a negative screening retest result for SARS-CoV-2 infection and no clinical symptoms.

    Rationale for Change: Part of dynamic COVID-19 safety, social, and community precautions. It is understood that this requirement may evolve depending on the COVID-19 prevalence rate or surges, and vaccination rates in a region; thus, this requirement may change and is dependent on local COVID-19 country and/or local and/or legal requirements. Documentation will be available in the investigator's site binder.

17. **Section 6.1, Study Drugs Administered (Table 9: Study Drug Information)**

    Description of change: Updated carboplatin infusion period from [redacted] minutes to [redacted] minutes.

    Rationale for change: To correct an existing discrepancy in the protocol for carboplatin infusion timeframe.

18. **Section 6.1, Study Drugs Administered (Table 9: Study Drug Information); Section 6.1.2, Paclitaxel**

    Description of change: Updated paclitaxel infusion period from [redacted] minutes to [redacted] minutes.

    Rationale for change: To add a window for paclitaxel infusion timeframe.

19. **Section 6.5.4.1, Procedures for Participants Exhibiting Immune-Related Adverse Events (Table 12: Dose Modifications of INCMGA00012 or Placebo and Toxicity Management Guidelines for Immune-Related Adverse Events)**

    Description of change: Updated toxicity management for hepatitis, endocrinopathies, hypophysitis, nephritis, skin reactions, myocarditis, and all other irAEs.

    Rationale for change: To align with current toxicity management used INCMGA00012 program-wide.

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

    Description of change: Updated exceptions for use of corticosteroids during study.

    Rationale for change: To align with standard of care premedication prior to administration of chemotherapy agents.

21. **Section 8.2.4 Health-Related Patient-Reported Outcomes**

    Description of change: Updated timing of health-related patient-reported outcome assessments.

    Rationale for change: For clarification.

22. **Section 8.3, Safety Assessments (Table 14: Required Laboratory Analytes)**

    Description of change: Added FT4 to the required laboratory analytes.

    Rationale for change: In consideration of local regions where this is standard testing, FT4, where appropriate, is allowed in place of T4.

23. **Section 9.2, Definition of Serious Adverse Event; Section 9.3, Recording and Follow-Up of Adverse Events and/or Serious Adverse Events**

    Description of change: Modified language to align with the most updated protocol template.

    Rationale for change: Updated based on current protocol template.

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

Original Protocol (Version 1-UK; 01 SEP 2020)

Overall Rationale for the Revised Version: To clarify the emergency unblinding process and clarify reproductive, fertility, and contraceptive protocol guidance. Additional changes are summarized below.

1. **Section 5.1, Inclusion Criteria**

   Description of change: Updated inclusion criterion 9 to include language for refraining from donating oocytes and to incorporate all language regarding WOCBP in Appendix A.

   Rationale for change: To include a definition of WOCBP in the study protocol and to clarify that the timing for refraining from donating oocytes is the same as that for appropriate precautions to avoid pregnancy.

2. **Section 8.3.5, Laboratory Assessments (Table 14: Required Laboratory Analytes)**

   Description of change: Added follicle-stimulating hormone to the required laboratory analytes.

   Rationale for change: To confirm a postmenopausal state in women as described in Appendix A.

3. **Section 9.5, Emergency Unblinding of Study Drug Assignment**

   Description of change: Removed the phrase "if knowledge of the study drug assignment is necessary to determine optimal medical management."

   Rationale for change: To clarify that the investigator cannot be required to discuss unblinding if he or she feels that emergent unblinding is necessary.

4. **Appendix A, Information Regarding Effectiveness of Contraceptive Methods and Relevant Definitions**

   Description of change: Added the definition of WOCBP.

   Rationale for change: To clarify that for female participants in the study for which this appendix applies, these are WOCBP, and to provide the definition of WOCBP.

   Description of change: Inserted the phrase "of reproductive potential" in the section regarding male participants in the study. Deleted language regarding the timing of use of contraception and donation of sperm to avoid duplication, and added text regarding eligibility to participate.

   Rationale for change: To clarify that for male participants in the study for which this appendix applies, these are men of reproductive potential, and the timing of use of contraception and donation of sperm already appears in inclusion criterion 10.

   Description of change: Inserted the phrase "who are WOCBP" in the section regarding female participants in the study.

   Rationale for change: To clarify that for female participants in the study for which this Appendix applies, these are WOCBP.

Description of change: Deleted birth control methods with a failure rate of more than 1% from the table and footnotes.

Rationale for change: To avoid confusion between highly effective contraceptive method (< 1% failure rate per year) and birth control methods with a failure rate of more than 1%.

Description of change: Inserted reference to local labeling for paclitaxel and carboplatin.

Rationale for change: To clarify the location of further information regarding contraception and fertility issues with the use of these chemotherapeutic agents, such as sperm preservation advice.

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.

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Approval Task	[redacted] Approver [redacted] Clinical Operations [redacted]
Approval Task	[redacted] Approver [redacted] Hematology Oncology Drug [redacted]
Approval Task	[redacted] Approver [redacted] Hematology Oncology Clinical [redacted]
Approval Task	[redacted] Approver [redacted] t
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