Official Title:	A Randomized, Double Blind, Phase 3 Study of Platinum-Based Chemotherapy With or Without INCMGA00012 in First-Line Metastatic Squamous and Nonsquamous Non–Small Cell Lung Cancer (POD1UM-304)
NCT Number:	NCT04205812
Document Date:	Protocol Amendment Version 3: 18 October 2022

Clinical Study Protocol

INCMGA 0012-304

A Randomized, Double Blind, Phase 3 Study of Platinum-Based Chemotherapy With or Without INCMGA00012 in First-Line Metastatic Squamous and Nonsquamous Non–Small Cell Lung Cancer (POD1UM-304)

Product:	**INCMGA00012**
IND Number:	**141,702**
EudraCT Number:	**2019-003372-39**
EU CT Number:	**2022-501987-16-00**
Phase of Study:	**3**
Global Sponsor:	**Incyte Corporation 1801 Augustine Cut-Off Wilmington, DE 19803**
Original Protocol:	**14 NOV 2019**
Amendment 1:	**16 DEC 2021**
Amendment 2:	**16 MAY 2022**
Amendment 3:	**18 OCT 2022**
Execution of the Study in China:	[redacted] [redacted] [redacted] [redacted] **China**

INVESTIGATOR'S AGREEMENT

I have read the INCMGA 0012-304 Protocol Amendment 3 dated 18 OCT 2022 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
AACR	American Association of Cancer Research
ABCP	atezolizumab plus bevacizumab plus carboplatin plus paclitaxel
[redacted]	[redacted]
AE	adverse event
AJCC	American Joint Committee on Cancer
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the plasma or serum concentration curve
$AUC_{0-\infty}$	area under the single-dose plasma or serum concentration-time curve extrapolated to time of infinity
BCG	Bacillus Calmette-Guérin
BCP	bevacizumab plus carboplatin plus paclitaxel
BICR	blinded independent central review
BID	twice daily
BRAF	B-Raf proto-oncogene, serine/threonine kinase
CI	confidence interval
CFR	Code of Federal Regulations
C_{max}	maximum observed plasma or serum concentration
C_{min}	minimum observed plasma or serum concentration over the dose interval
$C_{min,ss}$	minimum observed plasma or serum concentration at steady state
COVID-19	coronavirus disease 2019
CNS	central nervous system
CR	complete response
CrCl	creatinine clearance
CRF	case report form
CSR	Clinical Study Report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
D1	Day 1

Abbreviations and Special Terms	Definition
DILI	drug-induced liver injury
DL	dose level
DNA	deoxyribonucleic acid
DOR	duration of response
EC	ethics committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
eDMC	external Data Monitoring Committee
EEA	European Economic Area
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency
[redacted]	[redacted]
[redacted]	[redacted]
EOT	end of treatment
ESMO	European Society for Medical Oncology
EU	European Union
FAS	full analysis set
Fc	fragment crystallizable
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
FT3	Free triiodothyronine
FT4	Free thyroxine
g	grams
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GFR	glomerular filtration rate
Gy	gray
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act of 1996
HIV	human immunodeficiency virus

Abbreviations and Special Terms	Definition
HR	hazard ratio
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
iCPD	confirmed progressive disease per iRECIST
iCR	complete response per iRECIST
IEC	independent ethics committee
IgG4	immunoglobulin G4
ILD	interstitial lung disease
INR	international normalized ratio
iPD	progressive disease per iRECIST
irAE	immune-related adverse event
IRB	institutional review board
iRECIST	modified RECIST v1.1 for immune-based therapies
IRR	infusion-related reaction
IRT	interactive response technology
iSD	stable disease per iRECIST
ITT	intent-to-treat
iUPD	unconfirmed progressive disease per iRECIST
IV	intravenous(ly)
IVRS	interactive voice response system
MASCC	Multinational Association of Supportive Care in Cancer
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NE	not evaluable
NSAID	nonsteroidal anti-inflammatory drugs
NSCLC	non–small cell lung cancer
ORR	objective response rate
OS	overall survival
PCR	polymerase chain reaction
PD	progressive disease

Abbreviations and Special Terms	Definition
PD-1	programmed cell death protein 1
PD-L1	programmed cell death ligand 1
PET	positron emission tomography
PFS	progression-free survival
[redacted]	[redacted]
PK	pharmacokinetic
PPS	per Protocol set
PR	partial response
PRO	patient-reported outcome
PT	prothrombin time
PTT	partial thromboplastin time
QXW	every X weeks
RECIST v1.1	Response Evaluation Criteria in Solid Tumors version 1.1
RNA	ribonucleic acid
ROS1	receptor tyrosine kinase (encoded by the gene *ROS1*)
RT-PCR	reverse transcription-polymerase chain reaction
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SITC	Society for Immunotherapy of Cancer
SJS	Stevens-Johnson syndrome
SoA	schedule of activities
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic-pyruvic transaminase
SOC	standard of care
Study drug	INCMGA00012/placebo
Study treatment	INCMGA00012/placebo plus chemotherapy
$t_{½}$	apparent terminal-phase disposition half-life
T3	free or total triiodothyronine
TEAE	treatment-emergent adverse event
TEN	toxic epidermal necrolysis
TPS	tumor proportion score
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
WBC	white blood cell
WOCBP	women of childbearing potential

1. PROTOCOL SUMMARY

This is a randomized, double-blind, study of IV INCMGA00012 or placebo combined with platinum-based chemotherapy in participants with metastatic nonsquamous or squamous NSCLC who have not previously received systemic therapy for advanced disease and who do not have sensitizing driver mutations or gene rearrangements of EGFR, ALK, BRAF, or ROS1.

Protocol Title: A Randomized, Double Blind, Phase 3 Study of Platinum-Based Chemotherapy With or Without INCMGA00012 in First-Line Metastatic Squamous and Nonsquamous Non-Small Cell Lung Cancer (POD1UM-304)

Protocol Number: INCMGA 0012-304

Objectives and Endpoints:

Table 1 presents the primary and secondary objectives and endpoints.

Table 1: Primary and Secondary Objectives and Endpoints

Objectives	Endpoints
Primary	
To compare the OS of the combinations of INCMGA00012 and chemotherapy versus placebo and chemotherapy.	OS, defined as the time from randomization until death due to any cause.
Secondary	
To compare the PFS of the combinations of INCMGA00012 and chemotherapy versus placebo and chemotherapy.	PFS, defined as the time from randomization until disease progression by RECIST v1.1 as determined by BICR or death due to any cause.
To compare ORR of the combinations of INCMGA00012 and chemotherapy versus placebo and chemotherapy.	ORR, defined as the proportion of participants who have a confirmed CR or PR per RECIST v1.1 based on BICR.
To compare DOR of the combinations of INCMGA00012 and chemotherapy versus placebo and chemotherapy.	DOR defined as the time from the earliest date of documented response until earliest date of disease progression or death from any cause, whichever comes first, per RECIST v1.1 based on BICR.
To evaluate the safety and tolerability of the combination of INCMGA00012 and chemotherapy and the combination of placebo and chemotherapy.	Number of participants experiencing AEs and number of participants discontinuing study drug due to AEs.
To evaluate the PK of INCMGA00012 375 mg Q3W when administered with chemotherapy.	Population PK parameters (including C_{max}, AUC) will be summarized.

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	Treatment of metastatic NSCLC, first line
Population	Male and female participants at least 18 years of age (or as per adult age applicable per local country requirements) who have metastatic nonsquamous or squamous NSCLC. Male and female participants who have not previously received systemic therapy for advanced disease and do not have sensitizing driver mutations or gene rearrangements of EGFR, ALK, BRAF, or ROS1. Participants who received adjuvant/neoadjuvant therapy are permitted onto the study as long as therapy was completed at least 12 months before the diagnosis of metastatic disease.
Number of Participants	Approximately 600 participants will be enrolled.
Study Design	This is a global, randomized, double-blind, study of IV INCMGA00012 or placebo combined with platinum-based chemotherapy in participants with metastatic nonsquamous or squamous NSCLC who have not previously received systemic therapy for advanced disease and who do not have sensitizing driver mutations or gene rearrangements of EGFR, ALK, BRAF, or ROS1. The primary endpoint is OS. INCMGA00012 or placebo will be administered for approximately 2 years (35 cycles) along with a standard of care chemotherapy regimen. Participants assigned to placebo and chemotherapy will have the option of receiving open-label monotherapy INCMGA00012 in the crossover period following BICR documentation of PD. Randomization will be stratified by PD-L1 TPS score (ie, < 1%, ≥ 1% to 49%, ≥ 50%), site geographic region (ie, East Asia vs non–East Asia), and predominant tumor histology (ie, squamous vs nonsquamous).
Estimated Duration of Study Participation	Each participant will join in the study from the time of a signed ICF through the final contact. After a screening period of up to 28 days, eligible participants will receive assigned treatment on Day 1 of each 3-week dosing cycle. Treatment with INCMGA00012 or placebo will continue until 35 cycles of INCMGA00012 or placebo have been administered, documented disease progression, unacceptable adverse events(s), intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the participant, participant withdraws consent, pregnancy of the participant, noncompliance with the study treatment or procedure requirements, or administrative reasons. Participants will have post-treatment follow-up for disease status, including radiographic imaging every 12 weeks, until initiating a new nonstudy cancer treatment, experiencing disease progression, death, withdrawing consent, or becoming lost to follow-up. Once a participant has received the last dose of study drug/treatment, has disease progression, or starts a new anticancer therapy, the participant moves into the survival follow up period. The participant should be contacted by telephone, email, or visit at least every 12 weeks (± 14 days) to assess for survival status until death, withdrawal of consent, the end of the study, or the participant is lost to follow-up, whichever occurs first.

Table 2: Key Study Design Elements (Continued)

Randomization Ratio	2:1 to either INCMGA00012 combined with pemetrexed and platinum-based chemotherapy (investigator's choice of cisplatin or carboplatin) or placebo combined with pemetrexed and platinum-based chemotherapy (investigator's choice of cisplatin or carboplatin) for nonsquamous NSCLC. 2:1 to either INCMGA00012 combined with carboplatin plus paclitaxel OR nab-paclitaxel or placebo combined with carboplatin plus paclitaxel OR nab-paclitaxel for squamous NSCLC.
eDMC	Yes

Treatment Groups and Duration:

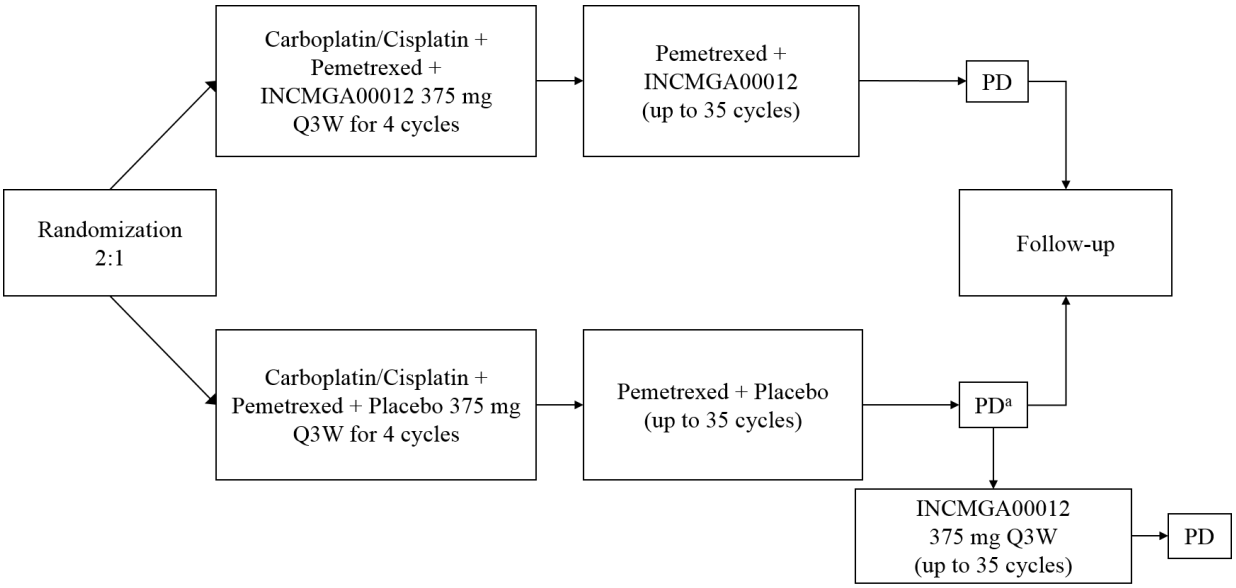
Approximately 600 participants with NSCLC will be randomized 2:1 to either receive INCMGA00012 375 mg IV Q3W or placebo along with the standard of care platinum-based chemotherapy regimens as per below.

- Participants with **nonsquamous** NSCLC will be randomized to receive 1 of the following:
  - INCMGA00012 375 mg IV (D1) Q3W with pemetrexed 500 mg/m^2 + cisplatin 75 mg/m^2 (D1) Q3W OR carboplatin AUC 5 (D1) Q3W for 4 cycles followed by INCMGA00012 375 mg IV plus pemetrexed 500 mg/m^2 Q3W until progression
  - Placebo IV (D1) Q3W with pemetrexed 500 mg/m^2 + cisplatin 75 mg/m^2 (D1) Q3W OR carboplatin AUC 5 (D1) Q3W for 4 cycles followed by placebo IV plus pemetrexed 500 mg/m^2 Q3W until progression
- Participants with **squamous** NSCLC will be randomized to receive 1 of the following:
  - INCMGA00012 375 mg IV (D1) Q3W with carboplatin AUC 6 (D1) plus paclitaxel 200 mg/m^2 (D1) OR nab-paclitaxel 100 mg/m^2 (D1, D8, D15) Q3W for 4 cycles followed by INCMGA00012 375 mg IV Q3W until progression
  - Placebo IV (D1) Q3W with carboplatin AUC 6 (D1) plus paclitaxel 200 mg/m^2 (D1) OR nab-paclitaxel 100 mg/m^2 (D1, D8, D15) Q3W for 4 cycles followed by placebo IV Q3W until progression
- Participants randomized to placebo and chemotherapy who have verification of PD by BICR and qualify for the crossover period will have the option to receive the following:
  - INCMGA00012 monotherapy 375 mg IV Q3W for approximately 2 years (35 cycles)

The study design schema for nonsquamous and squamous NSCLC participants is shown in Figure 1.

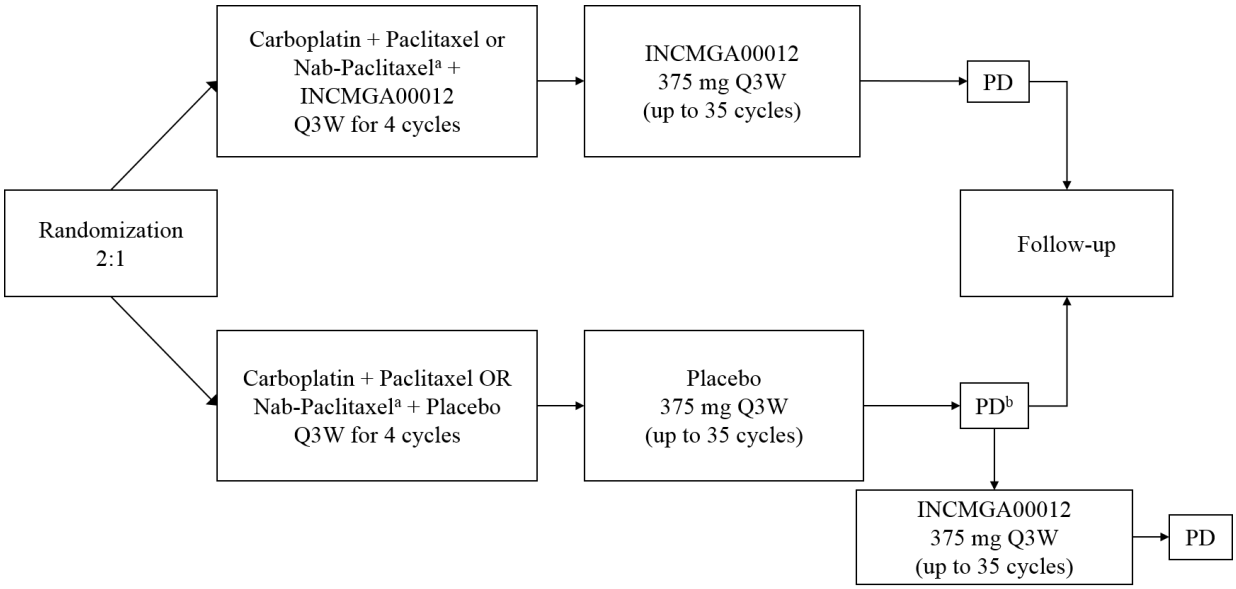
Figure 1: Study Design Schemas

For nonsquamous NSCLC participants



[a] Optional crossover for qualified participants.

For squamous NSCLC participants



[a] Nab-paclitaxel is administered on Days 1, 8, and 15 of each Q3W cycle.
[b] Optional crossover for qualified participants.

Adherence to the study design requirements, including those specified in the SoA (see Table 3 and Table 4) is essential and required for study conduct.

The SoA in Table 5 is only applicable for participants randomized to placebo who have verification of PD by blinded central imaging review and qualify for crossover period (see Section 6.7).

Table 3: Schedule of Activities for Participants With Nonsquamous Non–Small Cell Lung Cancer

Visit	Screening	Treatment Cycles (3-Week Cycles)							EOT/ at Time of Discontinuation	Post-Treatment		Notes
		C1	C2	C3	C4	C5	C6 to C17	C18 to C35		Safety Follow-Up	Survival Follow-Up	
			D1	D1	D1	D1	D1	D1				
Evaluation Window	Days -28 to -1	D1	± 3 d	± 3 d	± 3 d	± 3 d	± 3 d	± 3 d	+ 3 d of discon[a]	EOT + 30 d (± 7 d)	Q12W (± 14 d)	
Administrative procedures												
Informed consent	X											
Contact IRT	X	X	X	X	X	X	X	X	X			
Inclusion/exclusion criteria	X											
General and NSCLC-specific medical history	X											
Prior/concomitant medications	X	X	X	X	X	X	X	X	X	X	X*	*After the safety follow-up visit, record all medication taken for SAEs as defined in Section 9.4.
Participant Identification Card	X											After the participant is found eligible.
Clinical procedures/assessments												
AE assessment (CTCAE v5)	X	X	X	X	X	X	X	X	X	X*		*Participants will be evaluated for AEs/SAEs from the consent through 90 days after the last dose of study drug or until 30 days if a new anticancer therapy was initiated. See Section 8.7.1 and Section 9.
Physical examination/body weight, height*	X	X	X	X	X	X	X	X	X	X		Comprehensive examination at screening and safety follow-up; targeted examination for all other assessments. *Height at screening or before dosing on Cycle 1, only.
Vital signs	X	X	X	X	X	X	X	X	X	X		
12-lead ECG	X									X		
ECOG performance status	X*	X**	X	X	X	X	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 if screening ECOG was performed within 3 days before Cycle 1.
Discuss if SARS-CoV-2 vaccination/booster is applicable	X											Vaccination is recommended but not required. See Section 5.1 and Appendix G.

Table 3: Schedule of Activities for Participants With Nonsquamous Non–Small Cell Lung Cancer (Continued)

Visit	Screening	Treatment Cycles (3-Week Cycles)							EOT/ at Time of Discontinuation	Post-Treatment		Notes
		C1	C2	C3	C4	C5	C6 to C17	C18 to C35		Safety Follow-Up	Survival Follow-Up	
			D1	D1	D1	D1	D1	D1				
Evaluation Window	Days -28 to -1	D1	± 3 d	± 3 d	± 3 d	± 3 d	± 3 d	± 3 d	+ 3 d of discon[a]	EOT + 30 d (± 7 d)	Q12W (± 14 d)	
Efficacy assessments												
Tumor imaging	X			X*		X*	X*	X**	X***			*First on-study image will be performed at 6 weeks (± 7 days) from date of randomization. Imaging performed to assess response every 6 weeks (42 ± 7 days) for 24 weeks, then every 9 weeks (63 ± 7 days) for the next 27 weeks, and subsequently every 12 weeks (84 ± 14 days) until PD is verified by BICR. Imaging assessments are to be performed using the same imaging schedule regardless of dose delays. **Imaging performed every 12 weeks (84 days ± 14 days) subsequently until PD. ***If a previous scan was obtained within 4 weeks before the date of discontinuation, then a scan at EOT is not mandatory.
[redacted]												
Brain MRI	X											Perform only if signs or symptoms suggestive of brain metastases at/during screening, or required by local SOC. See Section 8.3.2.
Survival status		X	X	X	X	X	X	X	X	X	X*	*After documented disease progression, the start of new anticancer therapy, or discontinuation of study treatment/drug; contacts are approximately every 12 weeks. Updated survival status may be requested by the sponsor at any time during the course of the study.
[redacted]												
Poststudy anticancer therapy									X	X	X	Subsequent anticancer therapy types, duration dates, response, disease progression assessed by investigator will be collected in the eCRF.

Table 3: Schedule of Activities for Participants With Nonsquamous Non–Small Cell Lung Cancer (Continued)

Visit	Screening	Treatment Cycles (3-Week Cycles)							EOT/ at Time of Discontinuation	Post-Treatment		Notes
		C1	C2	C3	C4	C5	C6 to C17	C18 to C35		Safety Follow-Up	Survival Follow-Up	
			D1	D1	D1	D1	D1	D1				
Evaluation Window	Days -28 to -1	D1	± 3 d	± 3 d	± 3 d	± 3 d	± 3 d	± 3 d	+ 3 d of discon[a]	EOT + 30 d (± 7 d)	Q12W (± 14 d)	
Local laboratory assessments												
Blood chemistries	X*		X	X	X	X	X	X	X	X		Laboratory results must be known before dosing. *Laboratory tests for screening are to be performed within 10 days before the first dose of study treatment.
Hematology	X*		X	X	X	X	X	X	X	X		Laboratory results must be known before dosing. *Laboratory tests for screening are to be performed within 10 days before the first dose of study treatment.
Endocrine function (T3 or FT3, FT4, and TSH)	X		X		X		X*	X*	X	X		Participants may be dosed in subsequent cycles after Cycle 1 Day 1 while thyroid function tests are pending. Tests will be performed by a central laboratory only if the local laboratory is unable to perform this service. *To be repeated every other cycle beginning with Cycle 6.
Coagulation parameters	X											To be repeated as clinically indicated.
Urinalysis	X						X*	X*	X	X		*To be repeated every 6 cycles beginning with Cycle 6.
Pregnancy testing	X*		X**	X**	X**	X**	X**	X**	X**	X*		Results must be known before dosing. *Serum pregnancy test is performed at screening (within 72 hours of C1D1) and safety follow-up. **During treatment for every cycle and at EOT, urine pregnancy testing is acceptable.
Serology (Hepatitis B & C)	X											May use central lab only if local lab is not capable. If serology is conducted within 60 days before randomization, testing does not need to be repeated. See Section 8.1.2 and Appendix D.
HIV testing	X											Not required unless mandated by local health authority.

Table 3: Schedule of Activities for Participants With Nonsquamous Non–Small Cell Lung Cancer (Continued)

Visit	Screening	Treatment Cycles (3-Week Cycles)							EOT/ at Time of Discontinuation	Post-Treatment		Notes
		C1	C2	C3	C4	C5	C6 to C17	C18 to C35		Safety Follow-Up	Survival Follow-Up	
			D1	D1	D1	D1	D1	D1				
Evaluation Window	Days -28 to -1	D1	± 3 d	± 3 d	± 3 d	± 3 d	± 3 d	± 3 d	+ 3 d of discon[a]	EOT + 30 d (± 7 d)	Q12W (± 14 d)	
EGFR, ALK, BRAF, ROS1 testing documentation	X											Needs to be previously documented only; if it is not previously documented, testing will need to be performed locally by the site or it can be sent for testing to the sponsor's central laboratory upon request.
Pharmacokinetic/[redacted] assessments (central/sponsor)												
INCMGA00012		X	X		X		X	X	X	X		See Table 16
[redacted]												
Tumor tissue collection (central)												
Archival or newly obtained tissue collection for PD-L1 analysis	X											
Study treatment administration (no more than 3 days after randomized assignment)												
Cisplatin or carboplatin		X	X	X	X							
Pemetrexed		X	X	X	X	X	X	X				Participants on pemetrexed who complete 35 cycles of INCMGA00012 or placebo may continue pemetrexed until reaching any other stopping criteria as per approved labeling. Laboratory test of hematology and blood chemistry are minimally required at each cycle beyond 35 cycles.
INCMGA00012 or placebo		X	X	X	X	X	X	X				Participants assigned to the placebo arm may have the option of receiving INCMGA00012 open-label monotherapy in the crossover period if there is documented PD by central radiological review and study entry criteria are met (see Table 5).

[a] If the EOT visit occurs > 21 days after the last study treatment, only a single EOT/30-day follow-up visit is required, and all unique assessments for the EOT and 30-day follow-up visit will be performed once.

Table 4: Schedule of Activities for Participants With Squamous Non–Small Cell Lung Cancer

Note: Squamous NSCLC histology enrollment cap was met prior to Protocol Amendment 1; therefore, only applicable updates for ongoing participants will be made.

Visit	Screening	Treatment Cycles (3-Week Cycles)						EOT/ at Time of Discontinuation	Post-Treatment		Notes
		Cycles 1-4			C5	C6 to C17	C18 to C35		Safety Follow-Up	Survival Follow-Up	
			D8[a]	D15[a]	D1	D1	D1				
Evaluation Window	**Days -28 to -1**	**D1**	**± 1 d**	**± 1 d**	**± 3 d**	**± 3 d**	**± 3 d**	**+ 3 d of discon[b]**	**EOT + 30 d (± 7 d)**	**Q12W (± 14 d)**	
Administrative procedures											
Informed consent	X										
Contact IRT	X	X	X	X	X	X	X	X			
Inclusion/exclusion criteria	X										
General and NSCLC-specific medical history	X										
Prior/concomitant medications	X	X	X	X	X	X	X	X	X	X*	*After the safety follow-up visit, record all medication taken for SAEs as defined in Section 9.4.
Participant Identification Card	X										After the participant is found eligible.
Clinical procedures/assessments											
AE assessment (CTCAE v5)	X	X	X	X	X	X	X	X	X*		*Participants will be evaluated for AEs/SAEs from the consent through 90 days after the last dose of study drug or until 30 days if new anticancer therapy was initiated. See Section 8.7.1 and Section 9.
Physical examination/body weight, height*	X	X			X	X	X	X	X		Comprehensive examination at screening and safety follow-up; targeted examination for all other assessments. *Height at screening or before dosing on Cycle 1, only.
Vital signs	X	X	X	X	X	X	X	X	X		
12-lead ECG	X								X		
ECOG performance status	X*	X**			X	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 if screening ECOG was performed within 3 days before Cycle 1.

Table 4: Schedule of Activities for Participants With Squamous Non–Small Cell Lung Cancer (Continued)

Visit	Screening	Treatment Cycles (3-Week Cycles)						EOT/ at Time of Discontinuation	Post-Treatment		Notes
		Cycles 1-4			C5	C6 to C17	C18 to C35		Safety Follow-Up	Survival Follow-Up	
Evaluation Window	Days -28 to -1	D1	D8[a] ± 1 d	D15[a] ± 1 d	D1 ± 3 d	D1 ± 3 d	D1 ± 3 d	+ 3 d of discon[b]	EOT + 30 d (± 7 d)	Q12W (± 14 d)	
Efficacy assessments											
Tumor imaging	X	X*			X*	X*	X**	X***			*First on-study image will be performed at 6 weeks (± 7 days) from the randomization date. Imaging performed to assess response every 6 weeks (42 ± 7 days) for 24 weeks, then every 9 weeks (63 ± 7 days) for the next 27 weeks, and subsequently every 12 weeks (84 ± 14 days) until PD is verified by BICR. Imaging assessments are to be performed using the same imaging schedule regardless of dose delays. **Imaging performed every 12 weeks (84 days ± 14 days) subsequently until PD. ***If a previous scan was obtained within 4 weeks before the date of discontinuation, then a scan at EOT is not mandatory.
[redacted]											
Brain MRI	X										Perform only if signs or symptoms suggestive of brain metastases at screening, or required by local SOC. See Section 8.3.2.
Survival status		X	X	X	X	X	X	X	X	X*	*After documented disease progression, the start of new anticancer therapy, or discontinuation of study treatment/drug; contacts are approximately every 12 weeks. Updated survival status may be requested by the sponsor at any time during the course of the study.
[redacted]											

Table 4: Schedule of Activities for Participants With Squamous Non–Small Cell Lung Cancer (Continued)

Visit	Screening	Treatment Cycles (3-Week Cycles)						EOT/ at Time of Discontinuation	Post-Treatment		Notes
		Cycles 1-4			C5	C6 to C17	C18 to C35		Safety Follow-Up	Survival Follow-Up	
			D8[a]	D15[a]	D1	D1	D1				
Evaluation Window	**Days -28 to -1**	**D1**	**± 1 d**	**± 1 d**	**± 3 d**	**± 3 d**	**± 3 d**	**+ 3 d of discon[b]**	**EOT + 30 d (± 7 d)**	**Q12W (± 14 d)**	
Poststudy anticancer therapy								X	X	X	Subsequent anticancer therapy types, duration dates, response, disease progression assessed by investigator will be collected in the eCRF.
Local laboratory assessments											
Blood chemistries	X*	X**	X***	X***	X	X	X	X	X		Laboratory results must be known before dosing. *Laboratory tests for screening are to be performed within 10 days before the first dose of study drug. **To be performed at Cycles 2, 3, and 4. ***Applicable only to participants receiving nab-paclitaxel.
Hematology	X*	X**	X***	X***	X	X	X	X	X		Laboratory results must be known before dosing. *Laboratory tests for screening are to be performed within 10 days before the first dose of study drug. **To be performed at Cycles 2, 3, and 4. ***Applicable only to participants receiving nab-paclitaxel.
Endocrine function (T3 or FT3, FT4, and TSH)	X	X*				X**	X**	X	X		Participants may be dosed in subsequent cycles after Cycle 1 Day 1 while thyroid function tests are pending. Tests will be performed by a central laboratory only if the local laboratory is unable to perform this service. *To be performed at Cycle 2 and Cycle 4 **To be repeated every other cycle beginning with Cycle 6.
Coagulation parameters	X										To be repeated as clinically indicated.
Urinalysis	X					X*	X*	X	X		*To be repeated every 6 cycles beginning with Cycle 6.

Table 4: Schedule of Activities for Participants With Squamous Non–Small Cell Lung Cancer (Continued)

Visit	Screening	Treatment Cycles (3-Week Cycles)						EOT/ at Time of Discontinuation	Post-Treatment		Notes
		Cycles 1-4			C5	C6 to C17	C18 to C35		Safety Follow-Up	Survival Follow-Up	
			D8[a]	D15[a]	D1	D1	D1				
Evaluation Window	Days -28 to -1	D1	± 1 d	± 1 d	± 3 d	± 3 d	± 3 d	+ 3 d of discon[b]	EOT + 30 d (± 7 d)	Q12W (± 14 d)	
Pregnancy testing	X*	X**			X**	X**	X**	X**	X*		Results must be known before dosing. *Serum pregnancy test is performed at screening (within 72 hours of C1D1) and safety follow-up. **During treatment, starting with C2D1, at every cycle and at EOT, urine pregnancy testing is acceptable.
Serology (Hepatitis B & C)	X										May use central lab only if local lab is not capable. If serology is conducted within 60 days before randomization, testing does not need to be repeated. See Section 8.1.2 and Appendix D.
HIV testing	X										Not required unless mandated by local health authority.
EGFR, ALK, ROS1, BRAF testing documentation	X										Not required for pure squamous histology. In cases where the tumor is mixed or not completely known, testing must be performed locally (or it can be sent for testing to the sponsor's central laboratory upon request), or previous documentation showing the absence of these mutations must be available.
Pharmacokinetic [redacted] assessments (central/sponsor)											
INCMGA00012		X*				X	X	X	X		See Table 16. *Not at Cycle 3.
[redacted]											

Table 4: Schedule of Activities for Participants With Squamous Non–Small Cell Lung Cancer (Continued)

Visit	Screening	Treatment Cycles (3-Week Cycles)						EOT/ at Time of Discontinuation	Post-Treatment		Notes
		Cycles 1-4			C5	C6 to C17	C18 to C35		Safety Follow-Up	Survival Follow-Up	
Evaluation Window	Days -28 to -1	D1	D8[a] ± 1 d	D15[a] ± 1 d	D1 ± 3 d	D1 ± 3 d	D1 ± 3 d	+ 3 d of discon[b]	EOT + 30 d (± 7 d)	Q12W (± 14 d)	
Tumor tissue collection (central)											
Archival or newly obtained tissue collection for PD-L1 analysis	X										
Study treatment administration (no more than 3 days after randomized assignment)											
Carboplatin		X									Carboplatin is administered on Day 1 for Cycles 1, 2, 3, and 4. See Section 6.1.3.
Paclitaxel		X									Paclitaxel is administered on Day 1 for Cycles 1, 2, 3, and 4. Paclitaxel should be completely administered before initiating carboplatin dose. See Section 6.1.3.
Nab-paclitaxel		X	X	X							Nab-paclitaxel is administered on Days 1, 8, and 15 for Cycles 1, 2, 3, and 4. Nab-paclitaxel should be completely administered before initiating carboplatin dose. See Section 6.1.3.
INCMGA00012 or placebo		X			X	X	X				Participants assigned to the placebo arm may have the option of receiving INCMGA00012 open-label monotherapy in the crossover period if there is documented PD by central radiological review and study entry criteria are met (see Table 5).

[a] Cycle 1-4 Days 8 and 15 procedures apply only to participants receiving nab-paclitaxel.

[b] If the EOT visit occurs > 21 days after the last study treatment, only a single EOT/30-day follow-up visit is required, and all unique assessments for the EOT and 30-day follow up visit will be performed once.

Table 5: Crossover Period Schedule of Activities

Visit	Entry Study Criteria/ Screening	Treatment Cycles (3-Week Cycles)							EOT/ at Time of Discontinuation[a]	Post-Treatment		Notes
		C1	C2	C3	C4	C5	C6 to C13	C14 to C35		Safety Follow-Up[b]	Survival Follow-Up	
			D1	D1	D1	D1	D1	D1				
Evaluation Window	**Days -28 to -1**	**D1**	**± 3 d**	**± 3 d**	**± 3 d**	**± 3 d**	**± 3 d**	**± 3 d**	**+ 3 d of discon**	**EOT + 30 d (± 7 d)**	**Q12W (± 14 d)**	
Administrative procedures												
Contact IRT	X	X	X	X	X	X	X	X	X			
Prior/concomitant medications	X	X	X	X	X	X	X	X	X	X	X*	*After the safety follow-up visit record all medication taken for SAEs as defined in Section 9.2.
Poststudy anticancer therapy									X	X	X	
Survival status	X	X	X	X	X	X	X	X	X	X	X	After documented disease progression, the start of new anticancer treatment, or discontinuation of study drug; contacts are approximately every 12 weeks.
Clinical procedures/assessments												
AE assessment (CTCAE v5)	X	X	X	X	X	X	X	X	X	X*		*Once a participant discontinues study drug (INCMGA00012), report all AEs/SAEs, occurring within 90 days following cessation of study drug, or 30 days following cessation of treatment if new anticancer therapy is initiated. See Section 8.7.1 and Section 9.
Physical examination/body weight	X	X	X	X	X	X	X	X	X	X		Comprehensive examination at safety follow-up; targeted examination for all other assessments.
Vital signs	X	X	X	X	X	X	X	X	X	X		
ECOG performance status	X*	X**	X	X	X	X	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 if screening ECOG was performed within 3 days before Cycle 1.

Table 5: Crossover Period Schedule of Activities (Continued)

Visit	Entry Study Criteria/ Screening	Treatment Cycles (3-Week Cycles)							EOT/ at Time of Discontinuation[a]	Post-Treatment		Notes
		C1	C2	C3	C4	C5	C6 to C13	C14 to C35		Safety Follow-Up[b]	Survival Follow-Up	
			D1	D1	D1	D1	D1	D1				
Evaluation Window	Days -28 to -1	D1	± 3 d	± 3 d	± 3 d	± 3 d	± 3 d	± 3 d	+ 3 d of discon	EOT + 30 d (± 7 d)	Q12W (± 14 d)	
Efficacy assessments												
Tumor imaging	X*					X**	X**	X**	X		X***	BICR verifying progressive disease is 1) required for crossover (no exceptions), and 2) based on RECIST v1.1. *There must not be more than 12 weeks (84 days + 14 days) between last scan on study treatment that confirmed PD by central imaging vendor and first scan in crossover period. **Once in crossover period, tumor response by the investigator's assessment is required every 12 weeks (84 days ± 14 days) regardless of any treatment delays, until the participant starts another subsequent anticancer treatment. Once participant stops imaging assessments (eg, PD or starting a new anticancer therapy) the participant moves into the survival follow-up period. [redacted]

Table 5: Crossover Period Schedule of Activities (Continued)

Visit	Entry Study Criteria/ Screening	Treatment Cycles (3-Week Cycles)							EOT/ at Time of Discontinuation[a]	Post-Treatment		Notes
		C1	C2	C3	C4	C5	C6 to C13	C14 to C35		Safety Follow-Up[b]	Survival Follow-Up	
			D1	D1	D1	D1	D1	D1				
Evaluation Window	Days -28 to -1	D1	± 3 d	± 3 d	± 3 d	± 3 d	± 3 d	± 3 d	+ 3 d of discon	EOT + 30 d (± 7 d)	Q12W (± 14 d)	
Local laboratory assessments												
Blood chemistries	X*		X	X	X	X	X	X	X	X		Laboratory results must be known before dosing. *Laboratory tests for screening are to be performed within 10 days before the first dose of study drug.
Hematology	X*		X	X	X	X	X	X	X	X		Laboratory results must be known before dosing. *Laboratory tests for screening are to be performed within 10 days before the first dose of study drug.
Endocrine function (T3 or FT3, FT4, and TSH)	X	X	X		X		X*	X*	X	X		Participants may be dosed at subsequent cycles after Cycle 1, Day 1 while thyroid function tests are pending. Tests will be performed by a central laboratory only if the local laboratory is unable to perform this service. *To be repeated every other cycle beginning with Cycle 6.
Coagulation parameters	X											To be repeated as clinically indicated.
Urinalysis	X					X	X*	X*	X	X		*To be performed at Cycles 9 and 13 and to be repeated every 6 cycles beginning with Cycle 13.
Pregnancy testing	X		X	X	X	X	X	X	X	X*		Results must be known before dosing. Urine or serum test. *Serum pregnancy test is performed at safety follow-up.

Table 5: Crossover Period Schedule of Activities (Continued)

Visit	Entry Study Criteria/ Screening	Treatment Cycles (3-Week Cycles)							EOT/ at Time of Discontinuation[a]	Post-Treatment		Notes
		C1	C2	C3	C4	C5	C6 to C13	C14 to C35		Safety Follow-Up[b]	Survival Follow-Up	
			D1	D1	D1	D1	D1	D1				
Evaluation Window	**Days -28 to -1**	**D1**	**± 3 d**	**± 3 d**	**± 3 d**	**± 3 d**	**± 3 d**	**± 3 d**	**+ 3 d of discon**	**EOT + 30 d (± 7 d)**	**Q12W (± 14 d)**	
Study drug administration												
Administer INCMGA00012 monotherapy		X*	X	X	X	X	X	X				Up to 35 cycles (~2 years) If treatment is adjusted, all procedures except imaging will be completed according to the cycle number and not weeks on treatment. *Treatment should not initiate until at least 21 days after last dose of chemotherapy regardless of the time of progression.

Note: Only for eligible participants as described in the Crossover Period Study Drug Treatment and Criteria (see Section 6.7). Eligible participants who had verified PD (RECIST v1.1) by blinded independent central radiologic review first and who after unblinding were on placebo plus chemotherapy arm after randomization. Eligible crossover participants may receive open-label monotherapy INCMGA00012 of up to 35 cycles, or up to 2 years.

[a] All procedures and assessments completed at the time of withdrawal from the main study (blinded) may be used as appropriate for the start of the crossover period of the study. If participants continue into the crossover period, the safety follow-up visit is not required from the main study.

[b] If the EOT visit occurs within 30 days from last dose of INCMGA00012, at the time of the required safety follow-up visit, procedures do not need to be repeated.

2. INTRODUCTION

2.1. Background

2.1.1. Metastatic Non–Small Cell Lung Cancer

The World Health Organization estimates that lung cancer is the cause of 1.59 million deaths globally per year (Planchard et al 2019). The worldwide numbers are still rising despite an ongoing small decline in the Western world (Postmus et al 2017). Non–small cell lung cancer accounts for 80% to 90% of lung cancers, while SCLC has been decreasing in frequency in many countries over the past 2 decades (Jemal et al 2011).

Approximately 70% of patients with NSCLC have advanced disease not amenable to surgical resection at the time of diagnosis. The 5-year relative survival for patients with any lung cancer overall and metastatic lung cancer specifically has been reported to be 17.7% and 4.3%, respectively (NCI 2019).

Immunotherapy has had a major impact on outcomes for patients with metastatic NSCLC with multiple PD-1 and PD-L1 inhibitors now approved in several countries for the treatment of locally advanced or metastatic disease. For chemotherapy-naive patients, pembrolizumab (Keytruda®) for example was originally approved as monotherapy in the setting of high PD-L1 expressing tumors (tumor proportion score of ≥ 50%) based on favorable survival outcome compared with platinum-based chemotherapy (Reck et al 2016). In this study, which compared pembrolizumab monotherapy with the investigator's choice of platinum-based chemotherapy, PFS, OS at 6 months, ORR, and incidence of treatment-related AEs of any grade favored the pembrolizumab treatment group.

The benefits of the combination of immunotherapy and conventional chemotherapy have been demonstrated extensively in some but not all randomized and controlled clinical studies. In the setting of chemotherapy-naive NSCLC regardless of PD-L1 expression, 6 randomized, controlled clinical studies showed significant prolongation of PFS and increased tumor response when adding a PD-(L)1 inhibitor to a platinum-based chemotherapy doublet (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). Pembrolizumab and atezolizumab are both approved in the first-line NSCLC population in combination with platinum-based chemotherapy based on Phase 3 data described below.

In Study KEYNOTE-189 (NCT02578680) in patients with previously untreated metastatic nonsquamous NSCLC without EGFR or ALK mutations, the addition of pembrolizumab to standard chemotherapy of pemetrexed and a platinum-based drug resulted in significantly longer OS and PFS than chemotherapy alone, regardless of PD-L1 expression level (Gandhi et al 2018). In this study, the estimated rate of OS at 12 months was 69.2% (95% CI: 64.1, 73.8) in the pembrolizumab-combination group versus 49.4% (95% CI: 42.1, 56.2) in the placebo-combination group (hazard ratio for death, 0.49; 95% CI: 0.38, 0.64; $p < 0.001$) after a median follow-up of 10.5 months. Median PFS was 8.8 months (95% CI: 7.6, 9.2) in the pembrolizumab combination group and 4.9 months (95% CI: 4.7, 5.5) in the placebo combination group (hazard ratio for disease progression or death, 0.52; 95% CI: 0.43, 0.64; $p < 0.001$). Likewise, in Study KEYNOTE-407 (NCT02775435) in patients with previously

untreated metastatic squamous NSCLC, the addition of pembrolizumab to chemotherapy (carboplatin and paclitaxel or nab-paclitaxel) with carboplatin plus paclitaxel or nab-paclitaxel resulted in significantly longer OS and PFS than chemotherapy alone (Paz-Ares et al 2018). The median OS was 15.9 months (95% CI: 13.2, not reached) in the pembrolizumab-combination group and 11.3 months (95% CI: 9.5, 14.8) in the placebo-combination group (hazard ratio for death, 0.64; 95% CI: 0.49, 0.85; $p < 0.001$) after a median follow-up of 7.8 months. The OS benefit was consistent regardless of the level of PD-L1 expression. The median PFS was 6.4 months (95% CI: 6.2, 8.3) in the pembrolizumab combination group and 4.8 months (95% CI: 4.3, 5.7) in the placebo combination group (hazard ratio for disease progression or death, 0.56; 95% CI: 0.45, 0.70; $p < 0.001$).

In IMpower150 (NCT02366143), metastatic nonsquamous NSCLC patients were randomly assigned to receive atezolizumab plus carboplatin plus paclitaxel, BCP, or ABCP every 3 weeks for 4 or 6 cycles, followed by maintenance therapy with atezolizumab, bevacizumab, or both. The addition of atezolizumab to bevacizumab plus chemotherapy significantly improved PFS and OS among patients with metastatic nonsquamous NSCLC, regardless of PD-L1 expression and EGFR or ALK genetic alteration status. The median PFS was longer in the ABCP group than in the BCP group (8.3 months vs 6.8 months; hazard ratio for disease progression or death, 0.62; 95% CI: 0.52, 0.74; $p < 0.001$). Progression-free survival was also longer in the ABCP group than in the BCP group in the entire intent-to-treat population and among patients with low or negative PD-L1 expression. Median OS among the patients in the wild-type genotype population was longer in the ABCP group than in the BCP group (19.2 months vs 14.7 months; hazard ratio for death, 0.78; 95% CI: 0.64, 0.96; $p = 0.02$; Socinski et al 2018).

Access to these important therapies is not universal, and clinical trials are an important mechanism for providing access to promising therapies where it may otherwise be limited (eg, due to labeling restrictions or insufficient reimbursement). In addition, questions still remain regarding optimization of therapy for patients with lower levels of PD-L1 expression and in those whose tumors exhibit targetable driver mutations such as EGFR, ALK, ROS1, or BRAF (ASCO 2017, da Veiga et al 2018, NCCN 2019). Based on the experience with pembrolizumab and atezolizumab, it is reasonable to anticipate that other PD-(L)1 inhibitors may provide clinical benefit in similar populations. In this study, we plan to determine whether the addition of the PD-1 inhibitor, INCMGA00012, to platinum-based chemotherapy will improve survival in the initial treatment of nonsquamous and squamous metastatic NSCLC.

2.1.2. INCMGA00012

INCMGA00012 is a humanized, hinge-stabilized, IgG4-κ 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 sustain/restore their effector function by blocking checkpoint inhibitory interactions between PD-1 and its 2 ligands, PD-L1 and PD-L2.

In vitro studies with INCMGA00012 have demonstrated high affinity binding to both recombinant human and cynomolgus monkey PD-1 as well as to PD-1 that is naturally expressed on the cell surface, including on T cells. Consistent with its intended mechanism of action and

functional properties, INCMGA00012 has been shown to inhibit the binding of PD-L1 and PD-L2 to PD-1, to disrupt the PD-1/PD-L1 inhibitory axis, and to enhance interferon-γ secretion in staphylococcus enterotoxin B–stimulated human peripheral blood mononuclear cells with activity comparable to pembrolizumab and nivolumab replicas (generated by MacroGenics, Inc. based on the published sequences of these antibodies). INCMGA00012 does not induce antibody-dependent cellular cytotoxicity or complement-dependent cytotoxicity, mitogenic activity, hemolysis, or cytokine release.

As of 23 SEP 2019, 230 participants have been enrolled in the first-in-human monotherapy study (INCMGA 0012-101, NCT03059823). Interim results of both the dose-escalation and the expansion portion of Study INCMGA 0012-101 have been reported along with updated clinical and translational pharmacology (Chen et al 2019, Condamine et al 2019, Lakhani et al 2017, Mehnert et al 2018, Mehnert et al 2019). Four expansion cohorts (ie, endometrial cancer, cervical cancer, soft tissue sarcoma, and NSCLC) treated with 3 mg/kg Q2W and 3 fixed dose cohorts (ie, 500 mg Q4W, 750 mg Q4W, and 375 mg Q3W; Mehnert et al 2018) were enrolled. Results of the dose-escalation portion of Study INCMGA 0012-101 demonstrated acceptable tolerability with no DLTs observed at any dose level up to 10 mg/kg Q2W. An MTD was not reached. For both the 3 and 10 mg/kg dose levels, C_{max} and $AUC_{0-\infty}$ were dose-proportional. The $t_{½}$ (β) was approximately 17 days, and steady state was achieved in approximately 85 days. Full and sustained receptor occupancy of INCMGA00012 on both CD4+ and CD8+ T cells along with complete loss of competing fluorescently labeled anti–PD-1 staining were seen at all dose levels (Condamine et al 2019, Lakhani et al 2017).

Among the 230 participants receiving INCMGA00012 in Study INCMGA 0012-101, 171 participants received weight-based doses of 1 mg/kg, Q2W, 3 mg/kg Q2W or Q4W, or 10 mg/kg Q2W or Q4W, and 59 participants received flat dosing at 375 mg Q3W, 500 mg Q4W, or 750 mg Q4W with acceptable tolerability. Overall, 92% of participants had at least 1 TEAE, including 57% of participants with treatment-related TEAEs, and 46.1% of participants with ≥ Grade 3 TEAEs. Serious TEAEs, most of which were not considered related to study treatment, were reported for 27% of participants. Twenty-nine participants had irAEs, most of which were not serious. Most irAEs were transient, with the exception of endocrine-related irAEs. Nonendocrine irAEs that had not resolved as of the data cutoff date of 23 SEP 2019 were lipase increased, diarrhea, ALT increased, blood bilirubin increased, fatigue, colitis, and hyperglycemia (all 1 participant each).

Confirmed RECIST v1.1 responses were observed in all the expansion cohorts, none of which had been enriched by a predictive biomarker (eg, microsatellite instability [MSI] or PD-L1 status). Specifically, 5/35 (14.3%) of the evaluable NSCLC participants 4/29 (13.8%) endometrial cancer participants, 1/35 sarcoma participant, and 6/35 (17.1%) cervical cancer participants had confirmed RECIST responses (data on file; Mehnert et al 2019). Participants in the NSCLC cohort (3 mg/kg Q2W) were required to have previously received platinum-based chemotherapy. Of the 5 evaluable NSCLC participants who had confirmed RECIST v1.1 responses, 1 had PD-L1 TPS < 1%, 3 had PD-L1 TPS ≥ 50%, and 1 was unknown. In the cohort of NSCLC participants, the clinical activity of INCMGA00012 is similar to published experience for pembrolizumab and atezolizumab in platinum-refractory NSCLC (Herbst et al 2016, Peters et al 2017).

Based on clinical experience, the safety profile of INCMGA00012 appears to be representative of the PD-(L)1 inhibitor class.

2.2. Study Rationale

2.2.1. Rationale for Study Design

Non–small cell lung cancer remains the most common non–skin cancer worldwide and, despite recent advances in treatment for advanced disease, the survival outcomes are measured only in months. Incremental progress has been made with platinum-based chemotherapy, and more recently with the addition of the PD-(L)1 inhibitors pembrolizumab or atezolizumab to standard of care chemotherapy (Gandhi et al 2018, Paz-Arez et al 2018, Socinski et al 2018). Despite these notable advances, access to life-saving therapies is frequently limited by regulatory approval or reimbursement considerations (ASCO 2017, da Veiga et al 2018). This study incorporates a crossover design so that all participants who meet study criteria will have the opportunity to receive INCMGA00012.

2.2.2. Scientific Rationale for Study Design

Similar inclusion and exclusion criteria that were used in the pivotal Phase 3 studies of KEYNOTE-189 and KENOTE-407 as first-line therapy for participants with metastatic NSCLC (Gandhi et al 2018, Paz-Arez et al 2018) will be used to determine eligibility in this study in order to define a population with high likelihood of benefit to anti–PD(L)-1 monoclonal antibodies.

Participants who are eligible for effective targeted therapy against a known driver mutation such as EGFR, ALK, ROS1, or BRAF will not be included in the study population since the effectiveness of PD-(L)1 chemotherapy combinations has not been definitively established in these tumor types (Lisberg et al 2018, NCCN 2019). As the current research study will enroll both nonsquamous and squamous NSCLC histologies (versus a single study for each histologic subtype of NSCLC), enrollment of participants will approximate the expected frequency of these histologies in the general population. This expected frequency is in order to account for any potential differences in prognosis and/or the effect of INCMGA00012 treatment. For OS analysis, the target of OS events will provide 87% power for detection of the planned HR. Refer to Section 10 for details.

2.2.3. Justification for INCMGA00012 Dose

INCMGA00012 has been administered in the clinic as both a weight-based dose (ranging from 1 to 10 mg/kg Q2W) and at fixed doses of 375 mg Q3W, 500 mg Q4W, and 750 mg Q4W. Treatment has been well tolerated over the entire dosing range, and an MTD has not been reached (Lakhani et al 2017, Mehnert et al 2018).

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

A flat dose of 500 mg was explored in an expansion cohort of Study INCMGA 0012-101. Based on this experience, the 500 mg Q4W dose had very similar PK properties to 3 mg/kg Q2W dosing and had approximately a 58% probability for steady-state trough serum concentration ≥ 21 µg/mL (Chen et al 2019), which is associated with maximum target engagement and greatest probability of efficacy, based on pembrolizumab data (Freshwater et al 2017).

Safety data from 15 participants receiving INCMGA00012 375 mg Q3W show that 93% reported any TEAE. Overall, 60% of participants had a TEAE that was considered at least possibly related to study treatment, and 47% of participants had TEAEs ≥ Grade 3. Serious TEAEs were reported for 40% of participants, with none considered related to study treatment. No events resulted in study drug withdrawal and no events had a fatal outcome. Immune-related adverse events were reported in this dose group. The TEAEs (any grade) reported in > 10% of participants included alkaline phosphatase increased (n = 3; 20%), tumor pain (n = 3; 20%), and anemia, gastritis, fatigue, influenza-like illness, AST increased, amylase increased, bilirubin increased, lymphocytes decreased, hypomagnesaemia, pain in extremity, tumor flare, cough, dyspnea, and pruritus (n = 2 each; 13% each).

The 375 mg Q3W flat dose regimen was selected in order to maintain steady-state trough serum concentration ≥ 21 µg/mL as well as to provide additional flexibility in combinations (eg, with chemotherapy). Pharmacokinetic data were obtained from 14 participants with samples who received INCMGA00012 375 mg Q3W in the cohort expansion portion of Study INCMGA 0012-101. Following a first dose of 375 mg Q3W, INCMGA00012 had $t_{½}$ (11.5 days) and CL (14.8 mL/minute) values comparable to those of the 500 mg Q4W and 750 mg Q4W doses. Furthermore, simulated $C_{min,ss}$ PK following a 375 mg Q3W infusion was 24,300 ng/mL with the accumulation ratio at approximately 1.4, making this a comparable dose to 500 mg Q4W.

Based on these observations, both 500 mg Q4W and 375 mg Q3W were selected as flat dose regimens for further development for the INCMGA00012 program.

2.2.4. Rationale for the Use of Placebo

The use of placebo in combination with standard chemotherapy will ensure the objectivity of investigator-assessed progression as well as any decisions to interrupt/discontinue therapy. Since randomization and placebo use can be a perceived barrier to participant enrollment, a 2:1 randomization in favor of the active arm will be used to increase the likelihood that participants will be assigned to the active arm and therefore enhance participant accrual. Participants assigned to INCMGA00012 placebo will also have the opportunity to receive INCMGA00012 monotherapy upon verified progression if protocol-defined conditions are met.

2.2.5. Benefit/Risk Assessment

Antibodies targeting the PD-1 pathway have proven efficacy against a wide variety of cancer types (Song et al 2020), and the available preclinical and clinical data from trial participants suggest that the pharmacologic and clinical profile of INCMGA00012 should be consistent with experience with other drugs in this class. Based on these observations, the benefit/risk for INCMGA00012 should also be favorable, provided efficacy objectives in the proposed study are met. The investigational nature of INCMGA00012 is clearly described in the ICF, which also notes that participants would be asked to forego treatment alternatives including some for which

a survival benefit has been established. However, access to approved important new therapies is not universal due to reimbursement obstacles, and questions remain regarding optimization of therapy for patients with lower levels of PD-L1 expression (ASCO 2017, da Veiga et al 2018, NCCN 2019).

Treatment with INCMGA00012 in early clinical studies has been generally well tolerated. Results from the dose-escalation portion of the first-in-human monotherapy study of INCMGA00012 in participants with advanced cancer (Study INCMGA 0012-101) have been presented (Lakhani et al 2017, Mehnert et al 2018). INCMGA00012 demonstrated acceptable tolerability at all dose levels tested with preliminary signals of efficacy in several expansion cohorts. The safety profiles of anti–PD-1 therapies and platinum-based chemotherapy are not expected to overlap; therefore, the tolerability of this combination is not expected to be significantly worse than either agent alone.

The combination of PD-(L)1 monoclonal antibodies and taxanes (such as paclitaxel and nab-paclitaxel) have been investigated in clinical studies that show a toxicity profile consistent with the known safety profile of each of these drugs (Paz-Ares et al 2018, Schmid et al 2018). In the KEYNOTE-407 study, pembrolizumab was combined with carboplatin and paclitaxel or nab-paclitaxel in participants with squamous NSCLC and compared with placebo in combination with carboplatin and paclitaxel or nab-paclitaxel. A total of 69.8% of the pembrolizumab group and 68.2% of the placebo group had AEs ≥ Grade 3. The discontinuation of study treatment due to AEs was more frequent in the pembrolizumab group than in the placebo group (13.3% vs 6.4%, respectively; Paz-Ares et al 2018). In the KEYNOTE-189 study, AEs ≥ Grade 3 occurred in 67.2% of the participants in the pembrolizumab-combination group and in 65.8% of those in the placebo-combination group. Discontinuation of all study drugs because of AEs occurred in 13.8% of the participants in the pembrolizumab combination group and in 7.9% of those in the placebo-combination group; discontinuation rates of pembrolizumab and placebo were 20.2% and 10.4%, respectively. The rates of AEs were similar in participants who received carboplatin and cisplatin (Gandhi et al 2018).

Atezolizumab was combined with nab-paclitaxel in participants with triple-negative breast cancer in the IMpassion 130 study. Similar to KEYNOTE-407, in this study, the discontinuation of study treatment due to AEs was higher in the atezolizumab group, with 15.9% of participants discontinuing study treatment due to an AE in the atezolizumab group compared with 8.2% in the placebo group (Schmid et al 2018).

Oversight of study conduct will be provided by an eDMC. Additionally, irAEs will be monitored throughout the study with appropriate guidance provided to investigators for their assessment and management. The eDMC will perform a safety review after approximately 45 participants have been randomized and completed at least 1 cycle of study treatment. The eDMC will continue to review safety data throughout the duration of the study, including review of irAEs as described in the eDMC Charter.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of INCMGA00012 may be found in the IB. More detailed information about the known and expected benefits and risks of the chemotherapy regimens to be used may be found in the approved labels.

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

In 2020, the 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 or enough; 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. Cancer therapy with immune checkpoint inhibitors does not confer additional mortality risks in the setting of active COVID-19 (Goldman et al 2022).

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 versus 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).

Patients with lung cancer have a high risk of complications and death due to COVID-19 and would derive substantial benefit from efforts such as vaccination against SARS-CoV-2 (Passaro et al 2020). As an at-risk population, there is a need for vaccinating these patients to avoid excess morbidity and mortality during the SARS-CoV2 pandemic (NCCN 2021b). 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 has provided an increased chance for patients with advanced cancer to be protected from or have less severe cases of COVID-19 (Ribas et al 2021, Cohn et al 2021, Tenforde et al 2021, Malek et al 2021, Sharafeldin 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 highly recommends that potential participants with NSCLC are vaccinated before entering the study or become fully vaccinated during the study, and/or receive booster doses according to country or local guidelines as available. The efficacy of COVID-19 vaccination is high in patients undergoing therapy with immune checkpoint inhibitors (Goldman et al 2022). This recommendation, 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, Goldman et al 2022, 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 G). 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 required primary endpoint study procedures in order to determine whether it is in the best interests of the potential participant to enroll and participate in 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 or local requirements may be followed with regard to COVID-19 testing frequency, diagnosis, and treatment. 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 G.

3. OBJECTIVES AND ENDPOINTS

Table 6 represents the objectives and endpoints.

Table 6: Objectives and Endpoints

Objectives	Endpoints
Primary	
To compare the OS of the combinations of INCMGA00012 and chemotherapy versus placebo and chemotherapy.	OS, defined as the time from randomization until death due to any cause.
Secondary	
To compare the PFS of the combinations of INCMGA00012 and chemotherapy versus placebo and chemotherapy.	PFS, defined as the time from randomization until disease progression by RECIST v1.1 as determined by BICR or death due to any cause.
To compare the ORR of the combinations of INCMGA00012 and chemotherapy versus placebo and chemotherapy.	ORR, defined as the proportion of participants who have a confirmed CR or PR per RECIST v1.1 based on BICR.
To compare the DOR of the combinations of INCMGA00012 and chemotherapy versus placebo and chemotherapy.	DOR, defined as the time from the earliest date of documented response until earliest date of disease progression or death from any cause, whichever comes first, per RECIST v1.1 based on BICR.
To evaluate the safety and tolerability of the combination of INCMGA00012 and chemotherapy and the combination of placebo and chemotherapy.	Number of participants experiencing AEs and number of participants discontinuing study drug due to AEs.
To evaluate the PK of INCMGA00012 375 mg Q3W when administered with chemotherapy.	Population PK parameters (including C_{max}, AUC) will be summarized.
[redacted]	

4. STUDY DESIGN

4.1. Overall Design

This is a global, randomized, double-blind, study of IV INCMGA00012 or placebo combined with platinum-based chemotherapy in participants with metastatic squamous or nonsquamous NSCLC who have not previously received systemic therapy for advanced disease and who do not have sensitizing driver mutations or gene rearrangements such as EGFR, ALK, BRAF, or ROS1. Participants who received adjuvant/neoadjuvant therapy are permitted onto the study as long as therapy was completed at least 12 months before the diagnosis of metastatic disease.

The primary endpoint of the study is OS. Approximately 600 participants with NSCLC will be randomized 2:1 to either receive INCMGA00012 375 mg IV Q3W or placebo along with the standard of care platinum-based chemotherapy regimens as per below. The investigator will select 1 of the chemotherapy combination agents (eg, pemetrexed plus cisplatin or pemetrexed plus carboplatin for nonsquamous NSCLC) and document in IVRS prior to randomization.

- Participants with **nonsquamous** NSCLC will be randomized to receive 1 of the following:
  - INCMGA00012 375 mg IV (D1) Q3W with pemetrexed 500 mg/m^2 + cisplatin 75 mg/m^2 (D1) Q3W OR carboplatin AUC 5 (D1) Q3W for 4 cycles followed by INCMGA00012 375 mg IV plus pemetrexed 500 mg/m^2 Q3W until progression
  - Placebo IV (D1) Q3W with pemetrexed 500 mg/m^2 + cisplatin 75 mg/m^2 (D1) Q3W OR carboplatin AUC 5 (D1) Q3W for 4 cycles followed by placebo IV plus pemetrexed 500 mg/m^2 Q3W until progression
- Participants with **squamous** NSCLC will be randomized to receive 1 of the following:
  - INCMGA00012 375 mg IV (D1) Q3W with carboplatin AUC 6 (D1) plus paclitaxel 200 mg/m^2 (D1) OR nab-paclitaxel 100 mg/m^2 (D1, D8, D15) Q3W for 4 cycles followed by INCMGA00012 375 mg IV Q3W until progression
  - Placebo IV (D1) Q3W with carboplatin AUC 6 (D1) plus paclitaxel 200 mg/m^2 (D1) OR nab-paclitaxel 100 mg/m^2 (D1, D8, D15) Q3W for 4 cycles followed by placebo IV Q3W until progression

The study design schema for nonsquamous and squamous NSCLC participants is shown in Figure 1.

Treatment with INCMGA00012 or placebo can continue up to a total of 35 cycles, or approximately 2 years. Participants on pemetrexed who complete 35 cycles of INCMGA00012 or placebo may continue pemetrexed until reaching any other stopping criteria as per package insert/SmPc and local guidelines.

Participants randomized to placebo and chemotherapy who have verification of progressive disease by BICR and qualified for the crossover period will have the option to receive INCMGA00012 monotherapy 375 mg IV Q3W for up to approximately 2 years (or up to 35 cycles).

A formalin-fixed tumor tissue sample or a fresh tumor biopsy at screening is required for participation in the study, and will be used for central laboratory testing of PD-L1 status (TPS) using the commercial PD-L1 IHC 22C3 pharmDx (Dako) assay. Formalin-fixed specimens after the participant has been diagnosed with metastatic disease will be preferred for determination of PD-L1 status. Additionally, sites that were previously irradiated should not be used as material for a tumor tissue biopsy. The PD-L1 expression results determined centrally will be used for stratification.

Randomization will be stratified by PD-L1 TPS (ie, < 1%, ≥ 1% to 49%, ≥ 50%), site geographic region (ie, East Asia vs non–East Asia), and predominant tumor histology (ie, squamous vs nonsquamous).

Study conduct will be overseen by an eDMC. An initial safety evaluation will be performed after approximately 45 participants have completed the initial cycle of treatment. An interim analysis for OS is planned when approximately 60% of the targeted OS events are expected to have occurred. Details are described in Section 5.5 and Section 10.5.

Specific procedures to be performed during the study as well as their prescribed times and associated visit windows are outlined in Table 3 and Table 4. The SoA for the crossover period is in Table 5.

4.2. Number of Participants

Approximately 600 participants will be randomized into the study. Enrollment of participants with squamous histology will be limited to < 40% of the total study population in view of the differing prognoses between squamous and nonsquamous NSCLC. Similarly, enrollment of participants whose tumors have low PD-L1 expression (ie, TPS < 1%) will be capped at < 30% of the total. See Section 10.1 for more details.

4.3. Overall Study Duration

The study begins when the first participant signs the ICF. The end of the study is defined as the date of the last visit (last scheduled procedure shown in the SoA) of the last participant in the study globally or as the date the last participant withdraws from the study, or is lost to follow-up (ie, the participant is unable to be contacted by the investigator). In 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 multiregions by having complete follow-up data determined by the statistical hypotheses for the objectives established. Not using the global date could potentially jeopardize the study integrity and invalidate the study conclusions due to potential bias, thus potentially violating the statistical analysis assumptions described in Section 10.

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

If the study is not unblinded as a result of the interim analysis, blinding will be maintained to assess OS. If the primary objective results of OS at the interim analysis are positive, the study may be stopped early, in which case participants' study treatment assignment will be unblinded and INCMGA00012 monotherapy will offered to those still receiving placebo.

If the primary objective results of OS at final analysis are negative, all participants will be unblinded and removed from placebo (see Section 10.5 for details on interim analysis).

All IRBs/ECs and regulatory authorities will be notified first of the decision to unblind. At this time, remaining participants will be treated according to the site's standard of care and monitored as per usual standard of care; participants receiving INCMGA00012 may be switched to standard of care unless there is a clinical benefit as determined by the investigator. Efficacy results will not be collected in the clinical database and investigators will perform imaging as per local standard of care. Data collection will be limited in scope (eg, no central imaging, no survival follow-up period) and will be documented in the site monitoring plan including a reduced frequency of site monitoring. The investigator will be expected to report any SAEs and pregnancies as detailed in Section 9. The remaining participants are considered to be on study until a discontinuation criterion is met.

4.4. Study Termination

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

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

In addition, further recruitment in the study or at a particular study site(s) 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. Ability to comprehend and willingness to sign a written ICF for the study.

   Note: Vulnerable legal adults who are subject to a measure of legal protection, or are unable to provide expressed consent to participate, according to applicable local health codes and regulations, are excluded.

2. Is at least 18 years of age on the day of signing the ICF (or as applicable per local country requirements).
3. Has histologically or cytologically confirmed diagnosis of NSCLC (either nonsquamous or squamous) that is Stage IV (AJCC v8).
   a. Documentation for absence of driver mutations or gene rearrangements for EGFR, ALK, BRAF, and ROS1 if the tumor is of nonsquamous histology.

      Note: If documentation does not exist for all 4 driver mutations, then archived or fresh tumor tissue material must be tested locally, or centrally arranged by the sponsor. Detailed information is found in the Laboratory Manual.

   b. If participant's tumor is known to have a predominantly squamous histology, molecular testing for EGFR mutation, ALK, BRAF, and ROS1 translocations will not be required, as this is not part of current diagnostic guidelines.
   c. Tumor with mixed histology will be categorized by the predominant cell type; if small cell elements are present, the participant is ineligible. In cases where it is not completely known, testing must occur.
4. No prior systemic treatment for the advanced/metastatic NSCLC with the exception of neoadjuvant or adjuvant therapy that did not include a PD-(L)1 directed therapy and completed at least 12 months before the development of metastatic disease.

   Note: Only participants without access (due to inadequate reimbursement, labelling restrictions, or any other reason) to the best standard treatment options (eg, an approved PD-(L)1 inhibitor in combination with chemotherapy or monotherapy) that, according to the investigator, could benefit the participant more can be included in the study. If the best approved and reimbursed standard treatment options become available during the study, the participant may discontinue from study treatment if the investigator and the participant believe that the participant could benefit more by switching to the approved and reimbursed standard treatment.

5. Able to provide a formalin-fixed archival tumor tissue sample during screening, or a fresh tumor biopsy after a participant has been diagnosed with metastatic disease, for central confirmation of PD-L1 status.

   Note: Biopsy should be from a tumor site that has not been treated with radiation. Formalin-fixed archival specimens after the participant has been diagnosed with metastatic disease will be preferred for determination of PD-L1 status (and driver mutations if needed) prior to randomization.

6. Has measurable disease per RECIST v1.1 as determined by local site investigator/radiology assessment. Target lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.
7. Has an ECOG performance status of 0 or 1 at study entry.
8. Has a life expectancy of at least 3 months before signing the ICF.
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 180 days after the last dose of chemotherapy and 120 days after the last dose of INCMGA00012 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. A female participant is eligible to participate if she is not pregnant, not breastfeeding, and at least 1 of the following conditions applies:
      – Women of childbearing potential must have a negative pregnancy test at screening (within 72 hours of the first dose on Day 1). Women of childbearing potential must agree to take appropriate precautions to avoid pregnancy (with at least 99% certainty) from screening through 180 days after the last dose of chemotherapeutic agents and for at least 120 days after the last dose of INCMGA00012. Permitted methods that are at least 99% effective in preventing pregnancy (see Appendix A) should be communicated to the participants and their understanding confirmed.
      – Women of nonchildbearing potential (see Appendix A for definitions) are eligible.
10. Has adequate organ function as indicated by the laboratory values in Table 7. Specimens must be collected and reviewed within 10 days prior to the start of study treatment.

Table 7: Adequate Organ Function Laboratory Values

Laboratory Parameter		Laboratory Value
Hematologic		
a	Platelets	≥ 100 × 10^9/L
b	Hemoglobin	≥ 9 g/dL or ≥ 5.6 mmol/L
c	ANC	≥ 1.5 × 10^9/L
Hepatic		
d	ALT (SGPT)	≤ 2.5 × ULN OR ≤ 5 × ULN for participants with liver metastases
e	AST (SGOT)	≤ 2.5 × ULN OR ≤ 5 × ULN for participants with liver metastases
f	Total bilirubin	≤ 1.5 × ULN OR direct bilirubin ≤ ULN for participants with total bilirubin levels > 1.5 × ULN. If there is no institutional ULN, then direct bilirubin must be < 40% of total bilirubin to be eligible. Note: In no case can the total bilirubin exceed 3 × ULN.
Renal		
g	Calculated CrCl[a] (glomerular filtration rate can also be used in place of CrCl)	≥ 50 mL/min
Coagulation		
h	INR or PT	≤ 1.5 × ULN unless participant is receiving anticoagulant therapy and as long as PT or aPTT is within therapeutic range of intended use of anticoagulants.
i	aPTT or PTT	≤ 1.5 × ULN unless the participant is receiving anticoagulant therapy and as long as PT or aPTT is within therapeutic range of intended use of anticoagulants.

[a] Creatinine clearance should be calculated using the Cockcroft-Gault Method or as per institutional guidelines or standard (see Appendix C).

11. Has had an evaluation by the investigator regarding vaccination against SARS-CoV-2 before study entry.

    Note: Vaccination before study entry is a strong recommendation, not a requirement. Potential participants and the investigator should discuss up-to-date information according to national or local vaccination programs and/or oncology professional guidelines.

    Note: Refer to Appendix G for vaccination-related information.

5.2. Exclusion Criteria

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

1. Is currently participating and receiving investigational therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks of the first dose of treatment.
2. Received prior systemic cytotoxic chemotherapy, targeted or biological therapy for metastatic disease therapy with an anti–PD-1, anti–PD-L1, anti–PD-L2, anti-CD137, or anticytotoxic T-lymphocyte–associated antigen-4 antibody, or any other antibody or drug specifically targeting T-cell costimulation or checkpoint pathways.
3. Has clinically significant or impaired cardiac disease including acute myocardial infarction, unstable angina, or New York Heart Association Class III or IV congestive heart failure within 6 months before Day 1 of study drug administration. Has other clinically significant heart disease (ie, ≥ uncontrolled Grade 3 hypertension) before Day 1 of study drug administration. Medically controlled arrhythmia stable on medication for at least 14 days before Day 1 of study drug administration is permitted.
4. Had any major surgery within 3 weeks of the first dose of study treatment.
5. Received thoracic radiation therapy of > 30 Gy within 6 months of the first dose of study treatment.

   Note: Participants must have recovered from all radiation-related toxicities to Grade 1 or less, not require corticosteroids, and not have had radiation pneumonitis. A 1-week washout is permitted for palliative radiation (≤ 2 weeks of radiotherapy) to non-CNS disease.
6. Has a history of peripheral neuropathy ≥ Grade 2 CTCAE v5 for participants who may receive cisplatin, paclitaxel, or nab-paclitaxel.
7. Has untreated CNS metastases and/or carcinomatous meningitis identified either on the baseline brain imaging obtained during the screening period OR identified before signing the ICF (ie, without evidence of progression by imaging during screening).

   Note: Participants whose brain metastases have been treated may participate provided they show radiographic stability (defined as 2 brain images, same imaging modality, both of which are obtained after treatment to the brain metastases; these imaging scans should be obtained at least 4 weeks apart and show no evidence of intracranial progression). In addition, any neurologic symptoms that developed either as a result of the brain metastases or their treatment must have returned to baseline or resolved. Any steroids administered as part of this therapy must be completed at least 3 days before study treatment.
8. Evidence of interstitial lung disease or history of interstitial lung disease, or has history of noninfectious pneumonitis that required systemic steroids or has active pneumonitis.

9. Has an active infection requiring IV systemic therapy or active tuberculosis.

   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 retesting result is negative and clinical recovery is obtained.

10. Has symptomatic ascites or pleural effusion. A participant who is clinically stable following treatment for these conditions (including therapeutic thoraco- or paracentesis) is eligible.

11. Has known active HBV or HCV defined as follows (testing must be performed to determine eligibility):

    a. HBV DNA must be undetectable and HBsAg negative at screening visit.
    b. Active HCV is defined as a positive HCV antibody result and quantitative HCV-RNA results greater than the lower limits of detection of the assay.

    Note: Participants who have had definitive treatment for HCV are permitted if HCV-RNA is undetectable.

12. Has a known history of HIV infection. HIV testing is not required unless mandated by the local health authority, or local regulations.

    Note: HIV testing is required in Czech Republic and South Africa.

13. Has a known history of an additional malignancy, except if the participant has undergone potentially curative therapy with no evidence of that disease recurrence for 3 years since initiation of that therapy.

    Note: The time requirement for no evidence of disease for 3 years does not apply to the NSCLC for which a participant is enrolled in the study. The time requirement also does not apply to participants who underwent successful definitive resection of basal cell carcinoma of the skin, superficial bladder cancer, squamous cell carcinoma of the skin, in situ cervical cancer, other noninvasive or indolent malignancies, or other in situ cancers.

14. Has had an allogeneic tissue/solid organ transplant.

15. Previously had a severe hypersensitivity reaction to treatment with a monoclonal antibody or has a known sensitivity to any component of INCMGA00012 or as applicable, to carboplatin, cisplatin, paclitaxel, nab-paclitaxel, or pemetrexed.

16. Is unable to interrupt aspirin or other NSAIDS, other than an aspirin dose $\leq$ 1.3 g per day, for a 5-day period (8-day period for long acting agents such as piroxicam).

    Note: This exclusion is for potential participants with nonsquamous NSCLC.

17. Is unable or unwilling to take folic acid or vitamin B12 supplementation.

    Note: This exclusion is for potential participants with nonsquamous NSCLC.

18. Has an active autoimmune disease that has required systemic treatment in past 2 years (ie, with use of disease modifying agents, corticosteroids, or immunosuppressive drugs). Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is allowed.
19. Is receiving systemic antibiotics or steroid therapy ≤ 7 days prior to the first dose of study treatment or receiving any other form of immunosuppressive medication.
    a. Corticosteroid use after randomization is allowed for management of AEs, SAEs, as a premedication for IV contrast, or if considered necessary for a participant's welfare.
    b. Participants who receive daily steroid replacement therapy ≤ 10 mg prednisone or equivalent are exempt.
    c. Participants with asthma that requires intermittent use of bronchodilators, inhaled steroids, or local steroid injections may participate (are allowed to participate).
    d. Participants using topical, ocular, intra-articular, or intranasal steroids (with minimal systemic absorption) may participate.
20. Has received a live vaccine within 30 days before the first dose of study treatment (and until 90 days after last dose of study drug).
    a. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, BCG, and typhoid vaccine. Seasonal influenza vaccines that do not contain live virus vaccines are allowed.
21. Current use of any prohibited medication as described in Section 6.6.3.
22. Has a history or current evidence of any condition including psychiatric or substance abuse disorders, therapy, or laboratory abnormality that might confound the results of the study, interfere with the participant's ability to participate, or cooperate, for the full duration of the study, or is not in the best interest of the participant to participate, in the opinion of the treating investigator.

5.3. Lifestyle Considerations

No restrictions are required.

5.3.1. Meals and Dietary Restrictions

Participants should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea, or vomiting.

5.3.2. Use in Nursing Women

It is unknown whether INCMGA00012 is excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, participants who are breast-feeding are not eligible for enrollment.

5.3.3. Use in Pregnancy

If a female participant inadvertently becomes pregnant while on treatment in this study, the participant will be immediately removed from the study. Participants should be informed that taking the study treatment may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. The site will contact the participant frequently (ie, approximately monthly) to document the participant's status until the pregnancy has been completed or terminated, and until follow-up to the first well-baby visit to monitor the child's and mother's safety. For details and pregnancy reporting requirements, see Section 9.7.

5.4. Screen Failures

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

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened 1 time after consultation with the sponsor and will receive a new participant number. Participants who rescreen must reconsent if more than 42 days have elapsed from original consent date.

Tests with results that fail eligibility requirements may be repeated once during screening if the investigator believes the result to be in error. For screening visit procedures refer to Section 8.1.2.

5.5. External Data Monitoring Committee

This study will use an eDMC to monitor safety and efficacy at the planned analyses (see Section 10.5) and as needed throughout the duration of the study as specified in the eDMC charter. There will be 1 planned interim analysis of OS and a final analysis of OS. The voting members of the eDMC are external to the sponsor. The members of the eDMC will not be involved with the study in any other way and will have no competing interests that could affect their roles with respect to the study. The eDMC will assess the initial safety of the INCMGA00012 plus chemotherapy treatment arm vs the placebo plus chemotherapy treatment arm when approximately 45 participants have been randomized and received at least 1 cycle of study treatment, or after 6 months of enrollment, whichever occurs first.

Specific details regarding composition, responsibilities, and governance, including the roles and responsibilities of the various members and the sponsor, and protocol team; and requirements for and proper documentation of eDMC reports, minutes, and recommendations will be described in the eDMC charter.

5.6. Replacement of Participants

A participant who discontinues from study treatment or withdraws from the study will not be replaced at any time during this study.

6. STUDY TREATMENT

6.1. Study Treatments Administered

Table 8 presents the study drug and study treatment information.

INCMGA00012 or placebo will be provided centrally by the sponsor, and commercial and local supply of chemotherapy agents will be used as permissible per regulatory requirements, or centrally by the sponsor.

Table 8: Study Drug and Treatment Information

Study Drug/ Treatment Name:	INCMGA00012/ placebo[a]	Carboplatin[b]	Cisplatin[b]	Pemetrexed[b]	Nab-paclitaxel[b]	Paclitaxel[b]
Dose Formulation(s):	Solution, 25 mg/mL in a glass vial for single use	Solution	Solution	Solution Powder for infusion	Powder for infusion	Solution
Source:	Sponsor	Locally by the study site, or designee as permissible per regulatory requirements, or centrally by the sponsor				
Dose Frequency:	375 mg Q3W	For nonsquamous: AUC 5 mg/mL × min Q3W For squamous: AUC 6 mg/mL × min Q3W	75 mg/m^2 Q3W	500 mg/m^2 Q3W	100 mg/m^2 Q1W	200 mg/m^2 Q3W
Use:	Experimental	Part of treatment of cancer/SOC	Part of treatment of cancer/SOC	Part of treatment of cancer/SOC	Part of treatment of cancer/SOC	Part of treatment of cancer/SOC
Route of Administration:	IV infusion	IV infusion	IV infusion	IV infusion	IV infusion	IV infusion
Study Treatment Period:	Day 1 of each 21-day cycle for up to 35 cycles	Day 1 of each 21-day cycle for 4 cycles	Day 1 of each 21-day cycle for 4 cycles	Day 1 of each 21-day cycle	Days 1, 8, and 15 of each 21-day cycle for 4 cycles	Day 1 of each 21-day cycle for 4 cycles

[a] Study drug (INCMGA00012/placebo) to be administered before chemotherapy in the blinded period of the study.
[b] Study treatment (INCMGA00012/placebo plus chemotherapy)

For any commercially available product that is provided by the study site, or designee, every attempt will be made to source these supplies from a single lot/batch number. The study site is responsible for recording the lot number or equivalent identifier, manufacturer, and expiry date for any locally purchased product as per local guidelines unless otherwise instructed by the sponsor. Minimally, the lot number or equivalent identifier will be collected in the clinical database.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, and distribution and usage of study treatments in accordance with the Protocol and any applicable laws and regulations.

6.1.1. Timing of Dose Administration

Study treatment should be administered on Day 1 of each cycle after all procedures have been completed. For participants who receive nab-paclitaxel, study treatment should be administered on Days 1, 8 (± 1 day), and 15 (± 1 day) of each cycle after all procedures have been completed. Study treatment can be administered ± 3 days of the targeted Day 1 for each cycle except Cycle 1 where study treatment can only be administered + 3 days of the targeted Day 1.

6.1.1.1. INCMGA00012/Placebo

INCMGA00012 or placebo will be administered in a blinded fashion by IV infusion over 30 minutes (ie, 25 to 45 minutes) on Day 1 of each 21-day cycle. INCMGA00012 or placebo infusion should precede that of chemotherapy.

For the first 4 cycles, after infusion of INCMGA00012, administration of combination doublet chemotherapy will follow. As with any monoclonal antibody, the risk of IRRs is greatest with the first few infusions. For the first 4 cycles, participants will be observed in the clinic for several hours since the 2 chemotherapy agents will be given after INCMGA00012/placebo is administered. The recommended postinfusion observation period for the first cycles provides sufficient time for monitoring of IRRs in this study. Premedication with antipyretics and/or histamine 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 2 years (or 35 administrations of INCMGA00012/placebo) until unacceptable toxicity, disease progression, investigator's decision, pregnancy, withdrawal of consent, or study termination.

Details on excipients, preparation, storage, and administration of the INCMGA00012/placebo infusion are provided in the Pharmacy Manual and the IB.

6.1.2. For Participants With Nonsquamous Non–Small Cell Lung Cancer

6.1.2.1. Carboplatin

Carboplatin AUC 5 mg/mL × minute will be administered as an IV infusion over 15-60 minutes for the first 4 cycles immediately after pemetrexed as per local practice and labels. Time windows for infusion may be modified based on local labels/SmPCs or institutional guidelines.

Carboplatin dose is not to exceed 750 mg. The carboplatin dose should be calculated using the Calvert formula as follows:

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

The CrCl used in the Calvert formula should not exceed 125 mL/minute.

Maximum dose (mg) = target AUC 5 (mg · min/mL) × (125 + 25) = 5 × 150 mL/min = 750 mg.

6.1.2.2. Cisplatin

Cisplatin 75 mg/m^2 should be infused approximately 30 minutes after the pemetrexed infusion for the first 4 cycles and should be immediately preceded and followed by hydration procedures and administered according to local practice and labels. Time windows for infusion may be modified based on local labels/SmPCs or institutional guidelines.

6.1.2.3. Pemetrexed

Pemetrexed 500 mg/m^2 will be administered as an IV infusion over 10 minutes on Day 1 of each cycle until progression or unacceptable toxicity. All participants should receive the appropriate supplementation of vitamin B12 and folic acid and corticosteroid prophylaxis as listed below:

- Folic acid 400-1000 µg orally: at least 5 doses of folic acid must be taken during the 7 days preceding the first dose of pemetrexed, and folic acid dosing must continue during the full course of therapy and for 21 days after the last dose of pemetrexed.
- Vitamin B12 1000 µg intramuscular injection in the week preceding the first dose of pemetrexed and once every 3 cycles thereafter. Subsequent vitamin B12 injections may be given the same day as pemetrexed administration.
- Dexamethasone prophylaxis 4 mg orally BID (or equivalent) must be taken the day before, day of, and day after pemetrexed administration. Higher or additional doses are permitted for antiemetic prophylaxis during Cycles 1 through 4 but are not to exceed doses in MASCC/ESMO guidelines (Rolia et al 2016; see Appendix B).

6.1.3. For Participants With Squamous Non–Small Cell Lung Cancer

6.1.3.1. Paclitaxel

Paclitaxel 200 mg/m^2 will be administered as an IV infusion over 3 hours on Day 1 for the first 4 cycles as per local practice and labels. All participants should be premedicated with oral or IV steroids and histamine blockers according to the approved label and/or standard practice. Time windows for infusion may be modified based on local labels/SmPCs or institutional guidelines.

Additional premedications should be administered as per standard practice. Paclitaxel should be completely administered before initiating the carboplatin dose.

6.1.3.2. Nab-Paclitaxel

Nab-paclitaxel (investigator's choice of either paclitaxel or nab-paclitaxel) 100 mg/m^2 will be administered as an IV infusion over 30 minutes on Days 1, 8, and 15 for the first 4 cycles as per local practice and approved labels. Time windows for infusion may be modified based on local

labels/SmPCs or institutional guidelines. Nab-paclitaxel should be completely administered before initiating the carboplatin dose.

6.1.3.3. Carboplatin

Carboplatin AUC 6 mg/mL × minute will be administered as an IV infusion over 15 to 60 minutes on Day 1 for the first 4 cycles immediately after paclitaxel or nab-paclitaxel as per local practice and labels. Time windows for infusion may be modified based on local labels/SmPCs or institutional guidelines. The carboplatin dose should not exceed 900 mg. The carboplatin dose should be calculated using the Calvert formula as follows:

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

The CrCl used in the Calvert formula should not exceed 125 mL/minute.

Maximum dose (mg) = target AUC 6 (mg · min/mL) × (125 + 25) = 6 × 150 mL/min = 900 mg.

6.1.3.4. Antiemetic Therapy for Nonsquamous Non–Small Cell Lung Cancer

Antiemetic therapy should follow MASCC/ESMO guidelines and should for the first 4 cycles include a 5-HT3 receptor antagonist, dexamethasone (or equivalent), and/or aprepitant (or equivalent) as per MASCC/ESMO Antiemetic Guidelines (Rolia et al 2016; see Appendix B).

6.2. Preparation, Handling, and Accountability

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

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

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

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

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

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

Relevant information on the handling and storage of the study drug information is provided in the Pharmacy Manual.

Standard chemotherapeutic agents (cisplatin, carboplatin, pemetrexed, paclitaxel, or nab-paclitaxel) will be prepared and administered as per the approved product label.

6.3. Measures to Minimize Bias: Randomization and Blinding

All participants will be centrally assigned to study treatment using an IRT/IVRS. Full details will be provided in the IRT/IVRS Manual.

Study treatment will be dispensed at the study visits summarized in the SoA (see Table 3 through Table 5).

Centralized randomization numbers within each stratum will be created for treatment assignment. Participants will be assigned to study treatment in accordance with the randomization schedule. Participants, investigators, the sponsor, and the study team will be blinded to treatment assignment. See emergency unblinding procedures in Section 9.6.

6.4. Study Treatment Compliance

The site personnel must emphasize compliance with all study-related treatments to the participant. Appropriate steps should be taken to optimize compliance during the study. Compliance with each study drug will be calculated by the sponsor based on the study treatment infusion records and monitored by the sponsor/designee.

6.5. Dose Modifications

6.5.1. Dose Modifications for Immune-Related Toxicity

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. INCMGA00012/placebo treatment may be interrupted or discontinued due to toxicity. Dose modification of INCMGA00012/placebo is not allowed. Instructions for management in the event of irAEs are outlined in Table 9.

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.

Should an irAE be suspected, efforts should be made to rule out neoplastic, infectious, metabolic, toxins, or other etiologies before attributing the irAE to an immune-related response. An irAE can occur shortly after the first dose or several months after the last dose of treatment.

Algorithms for 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).

If a dose interruption is necessary for management of treatment-related TEAEs, INCMGA00012/placebo will be reinitiated at the dose at which it was interrupted. INCMGA00012/placebo may be interrupted for a maximum of 12 weeks from the last infusion. Decisions regarding these dose interruptions and restarts will be made according to Table 9 and, when needed, jointly by the investigator and medical monitor on a case-by-case basis.

INCMGA00012/placebo may be interrupted for situations other than treatment related AEs such as medical surgical events (eg, planned hip surgery) or logistical reasons not related to study treatment. Participants should be back on study treatment within 3 weeks of the scheduled interruption, unless otherwise discussed with the sponsor. The reason for interruption should be documented in the participant's medical records and eCRFs.

Table 9: Dose Modifications for Adverse Events of INCMGA00012/Placebo and Toxicity Management Guidelines for Immune-Related Adverse Events

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

Table 9: Dose Modifications for Adverse Events of INCMGA00012/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 Study Drug	AE Management With Corticosteroid and/or Other Supportive Care[a] Therapies
Endocrinopathies • Adrenal insufficiency • Hypothyroidism • Hyperthyroidism • Type 1 diabetes mellitus • Hyperglycemia	Grade 1 adrenal insufficiency	No action.	None.
	Grade 2 adrenal insufficiency	Withhold until ≤ Grade 1 or otherwise clinically stable.	Initiate treatment with hormone replacement as clinically indicated.
	Grades 3 or 4 adrenal insufficiency	Withhold until ≤ Grade 1 after corticosteroid taper to ≤ 10 mg/day prednisone or equivalent or is otherwise clinically stable.	Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper and hormone replacement as clinically indicated.
	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 or 4 type 1 diabetes mellitus (or hyperglycemia)	Withhold until ≤ Grade 1 or is otherwise clinically stable.	Initiate treatment with antihyperglycemics or insulin as clinically indicated.
Endocrinopathies (continued) • Hypophysitis	Grade 1	No action.	None.
	Grade 2 (asymptomatic)	Withhold until ≤ Grade 1. May restart study drug treatment after controlled by hormone replacement therapy.	Administer hormonal replacement
	Grade 2 (symptomatic; eg, headaches, visual disturbances)	Withhold until ≤ Grade 1. May restart study drug after controlled with hormone replacement therapy, 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 replacement as clinically indicated. • Consult with endocrinologist as needed.

Table 9: Dose Modifications for Adverse Events of INCMGA00012/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 Study Drug	AE Management With Corticosteroid and/or Other Supportive Care[a] Therapies
Endocrinopathies (continued) • Hypophysitis (continued)	Grade 3 or 4 (symptomatic)	• Permanent discontinuation should occur if after withholding study drug, the toxicity does not resolve to ≤ Grade 1 within 12 weeks after last dose of study drug, or if corticosteroid dose cannot be reduced to ≤ 10 mg prednisone or equivalent per day within 12 weeks. • Permanent discontinuation of study drug 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 replacement as clinically indicated. • Consult with endocrinologist as needed.
Nephritis and renal dysfunction	Grade 1	No action.	None.
	Grade 2 or 3 increased blood creatinine	Withhold until ≤ Grade 1.	Administer corticosteroids per local practice followed by taper.
	Grade 4 increased blood creatinine	Permanently discontinue.	
Skin (eg, SJS, TEN)	Grade 1	No action.	None.
	Grade 2	No action.	Manage with topical steroids with or without drug interruption.
	Grade 3[b] or persistent Grade 2 (≥ 2 weeks) or suspected SJS[c]	Withhold until ≤ Grade 1 after corticosteroid taper to ≤ 10 mg/day prednisone or equivalent.	• Administer corticosteroids per local practice followed by taper. Additionally, oral histamine blocker such as diphenhydramine or famotidine (per institutional preference) may be utilized as needed. • Refer timely to dermatology consult if no resolution with these measures. • Refer timely to dermatology consult if SJS or TEN is suspected.
	Grade 4 or confirmed SJS[c] or TEN[d]	Permanently discontinue.	• Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper. • Refer timely to dermatology consult.

Table 9: Dose Modifications for Adverse Events of INCMGA00012/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 Study Drug	AE Management With Corticosteroid and/or Other Supportive Care[a] Therapies
Myocarditis	Grade 2	• Depending on severity of symptoms, withhold until symptoms fully resolve and management with corticosteroids is complete. • Permanent discontinuation of study drug may take place earlier at the investigator's discretion.	• Treatment with systemic corticosteroids should be initiated (initial dose of 1-2 mg/kg/day of prednisone or equivalent). Taper as appropriate. • Refer timely to cardiology consult. • Management of 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/day of prednisone or equivalent). Taper as appropriate. • For Grade 2 transverse myelitis, consider permanent discontinuation. • Manage symptoms according to standard of care and with guidance from neurology.
	Grades 3 or 4	Permanently discontinue.	
All other irAEs	Grades 2 or 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 Grades 2 or 3	Permanently discontinue.	
	Grade 4[e] (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 last dose of study drug, or if corticosteroid dosing 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 steroids. Other immunosuppressive treatment should begin if irAEs are not controlled by corticosteroids.

[b] Participants with Grade 3 rash in the absence of desquamation, with no mucosal involvement, not requiring systemic steroids, and resolving or improving to ≤ Grade 1 within 14 days do not have to interrupt study drug.

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

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

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

6.5.1.1. Guidelines for Management of Suspected Infusion Reactions

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

Toxicity management guidelines for suspected infusion reactions are provided in Table 10.

Table 10: Guidelines for Management of Suspected Infusion Reactions

Grade	Description[a]	Treatment	Subsequent Infusions
1	Mild reaction; Interrupt or slow the rate of infusion; intervention not indicated.	Monitor vital signs closely until medically stable.	Premedication with an antipyretic (acetaminophen/paracetamol or equivalent) and a histamine blocker should be considered for participants who have had previous systemic reactions to protein product infusions or when recommended by institutional policy. Prophylaxis with an antipyretic and a histamine blocker is recommended in subsequent INCMGA00012 or placebo treatment cycles if the participant develops an IRR in a prior cycle.
2	Requires infusion interruption but responds promptly to symptomatic treatment (eg, histamine blocker, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hours.	**First occurrence:** Stop infusion and initiate appropriate medical measures (eg, IV fluids, histamine blocker, NSAIDS, antipyretics, 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 study treatment.	Premedicate at least 30 minutes before infusion with histamine blocker (diphenhydramine 50 mg PO or equivalent) and an antipyretic (acetaminophen or equivalent). Additional supportive measures may be acceptable (per institutional preference) and may 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, histamine blocker, NSAIDS, antipyretics, narcotics, oxygen, pressors, epinephrine, corticosteroids, per institutional preferences). Monitor vital signs frequently until medically stable. Hospitalization may be indicated.	Permanently discontinue study treatment. Note for NCI CTCAE (v5.0) Grade 3 IRR: 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 treatment administration.

6.5.2. Dose Modifications for Nonimmune (Chemotherapy-Related) Toxicity

Dose levels for modifications of chemotherapy agents used for participants with nonsquamous and squamous NSCLC are summarized in Table 11.

Table 11: Dose Levels for Carboplatin, Cisplatin, Pemetrexed, Paclitaxel, and Carboplatin

For Nonsquamous NSCLC	Dose Level 0	Dose Level -1	Dose Level -2	Dose Level -3
Cisplatin	75 mg/m^2	56 mg/m^2 (25% decrease)	38 mg/m^2 (25% decrease)	Discontinue
Carboplatin	AUC[a] 5 maximum dose 750 mg	AUC[a] 3.75 maximum dose (25% decrease)	AUC[a] 2.5 maximum dose (25% decrease)	Discontinue
Pemetrexed	500 mg/m^2	375 mg/m^2 (25% decrease)	250 mg/m^2 (25% decrease)	Discontinue
For Squamous NSCLC	**Dose Level 0**	**Dose Level -1**	**Dose Level -2**	**Dose Level -3**
Paclitaxel	200 mg/m^2	160 mg/m^2 (20% decrease)	120 mg/m^2 (20% decrease)	Discontinue
Carboplatin	AUC[a] 6 maximum dose 900 mg	AUC[a] 4.5 maximum dose (25% decrease)	AUC[a] 3 maximum dose (25% decrease)	Discontinue

[a] Area under the curve, mg × min/mL.

6.5.2.1. Chemotherapy Dose Modification for Hematological and Nonhematological Toxicities

Main chemotherapy hematological and nonhematological toxicities are described below in Table 12 through Table 15 for recommended dose modification. These recommendations are a guide and do not replace the investigator's judgment when applicable local label recommendations are not fully described, or when there are immediate local label updates available. 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).

Table 12: Recommended Dose Modifications of Pemetrexed, Cisplatin, and Carboplatin Chemotherapy Agents for Hematological Toxicity

Platelets	ANC	Pemetrexed	Cisplatin	Carboplatin
		Dose level from Table 11		
≥ 50,000/µL AND	≥ 500/µL	DL0	DL0	DL0
≥ 50,000/µL AND	< 500/µL	DL-1	DL-1	DL-1
< 50,000/µL without bleeding AND	ANY	DL-1	DL-1	DL-1
< 50,000/µL with Grade ≥ 2 bleeding AND	ANY	DL-2	DL-2	DL-2
ANY AND	< 1,000/µL + fever ≥ 38.5°C (101°F)	DL-1	DL-1	DL-1

Table 13: Recommended Dose Modifications of Pemetrexed, Cisplatin, and Carboplatin Chemotherapy Agents for Nonhematological Toxicity

Event	CTCAE Grade	Pemetrexed	Cisplatin	Carboplatin
		Dose level from Table 11		
Nausea or vomiting	Grade 3 or 4	DL0	DL0	DL0
Diarrhea	Grade 3 or 4	DL-1	DL-1	DL0
Mucositis	Grade 3 or 4	DL-2	DL0	DL0
Neurotoxicity	Grade 2	DL0	DL-2	DL0
	Grade 3 or 4	Discontinue	Discontinue	DL-1
Transaminase elevation	Grade 3	DL-1	DL-1	DL-1
	Grade 4	Discontinue	Discontinue	Discontinue
Other nonhematological toxicity	Grade 3 or 4	DL-1	DL-1	DL-1

If nab-paclitaxel is offered to eligible participants, the following is recommended. Participants should be administered nab-paclitaxel on Day 1 of a cycle with an ANC ≥ 1500 cells/mm^3 and a platelet count of ≥ 100,000 cells/mm^3. In participants who develop severe neutropenia or thrombocytopenia, withhold treatment until counts recover to an ANC of ≥ 1500 cells/mm^3 and a platelet count of ≥ 100,000 cells/mm^3 on Day 1. For each subsequent weekly dose, withhold treatment until counts recover to an ANC of ≥ 500 cells/mm^3 and a platelet count of ≥ 50,000 cells/mm^3 on Days 8 or 15 of the cycle or the dose is to be withheld until counts recover.

Upon restarting dosing, permanently reduce nab-paclitaxel and carboplatin doses as shown in Table 14.

Table 14: Dose Reductions for Hematologic Adverse Drug Reactions for Nab-Paclitaxel

Adverse Drug Reaction	Occurrence	Weekly Nab-Paclitaxel Dose (mg/m^2)[a]	Every 3 Week Carboplatin Dose (AUC mg/mL × min)[a]
Neutropenic Fever (ANC < $500/mm^3$ with fever > 38°C) OR Delay of next cycle by more than 7 days for ANC < $1500/mm^3$ OR ANC < $500/mm^3$ for more than 7 days	First	75	4.5
	Second	50	3
	Third	Discontinue	
Platelet count < $50,000/mm^3$	First	75	4.5
	Second	Discontinue	

[a] On Day 1 of the 21-day cycle reduce the dose of nab-paclitaxel and carboplatin simultaneously. On Days 8 or 15 of the 21-day cycle reduce the dose of nab-paclitaxel; reduce the dose of carboplatin in the subsequent cycle.

For Grade 2 or 3 cutaneous toxicity, Grade 3 diarrhea, or Grade 3 mucositis, interrupt treatment until the toxicity improves to ≤ Grade 1, then restart treatment according to the guidelines in Table 15. For ≥ Grade 3 peripheral neuropathy, withhold treatment until resolution to ≤ Grade 1. Treatment may be resumed at the next lower dose level in subsequent cycles according to the guidelines in Table 15. For any other Grade 3 or 4 nonhematologic toxicity, interrupt treatment until the toxicity improves to ≤ Grade 2, then restart treatment according to the guidelines in Table 15.

Table 15: Dose Reductions for Nonhematologic Toxicities for Nab-Paclitaxel

Nonhematologic Toxicity	Occurrence	Weekly Nab-Paclitaxel Dose (mg/m^2)[a]	Every 3 Week Carboplatin Dose (AUC mg/mL × min)[a]
Grade 2 or 3 cutaneous toxicity Grade 3 diarrhea Grade 3 mucositis ≥ Grade 3 peripheral neuropathy Any other Grade 3 or 4 nonhematologic toxicity	First	75	4.5
	Second	50	3.0
	Third	Discontinue	
Grade 4 cutaneous toxicity, diarrhea, or mucositis	First	Discontinue	

[a] On Day 1 of the 21-day cycle reduce the dose of nab-paclitaxel and carboplatin simultaneously. On Days 8 or 15 of the 21-day cycle reduce the dose of nab-paclitaxel; reduce the dose of carboplatin in the subsequent cycle.

Toxicity may be attributed to individual chemotherapy agents or INCMGA00012 alone or in combination. Dose modification must be based on maximum toxicity experienced during a cycle. 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 components of study treatment 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 any particular component will have that agent discontinued.

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 treatments. If, in the opinion of the investigator, the toxicity is related to the combination of 2 chemotherapy agents, both drugs should be reduced according to recommended dose modifications. If the toxicity is related to the combination of 3 agents, all 3 study treatment agents should be reduced (if applicable), interrupted, or discontinued according to the recommend dose modifications.

Participants may have chemotherapy discontinued and continue on INCMGA00012/placebo alone. Similarly, participants may discontinue INCMGA00012/placebo and continue on chemotherapy alone during the first 4 cycles if appropriate.

Chemotherapy may be interrupted for a maximum of 6 weeks; INCMGA00012/placebo may be interrupted for a maximum of 12 weeks as mentioned above.

These recommendations are a guide and do not replace investigator's judgment when applicable local label recommendations are not fully described, or when there are immediate local label updates available.

All dose modifications should be based on the AE requiring the greatest dose modification.

6.5.2.2. Modifications Due to Creatinine Clearance

Creatinine clearance will be based on the original weight-based Cockcroft and Gault formula (see Appendix C), or as per institutional method guideline, or based on GFR if that was used originally to determine eligibility (see Table 7). Creatinine clearance must be ≥ 45 mL/minute before the administration of subsequent chemotherapy. Pemetrexed and/or platinum-based chemotherapy may be delayed for up to 42 days to allow the participant time to recover from the toxicity. If a participant's CrCl value has not returned to ≥ 45 mL/minute within 42 days after the previous dose, platinum and/or pemetrexed must be discontinued.

6.5.3. Criteria for Permanent Discontinuation of Study Drug

The occurrence of unacceptable toxicity not caused by the underlying disease will require that the study drug (ie, INCMGA00012/placebo) be permanently discontinued. Unacceptable toxicity is defined as follows:

- Occurrence of an AE that is related to study drug that, in the judgment of the investigator or the sponsor's medical monitor, compromises the participant's ability to continue study-specific procedures or is considered to not be in the participant's best interest.
- An irAE that has not resolved within 12 weeks from the last infusion.
- Any AE defined in the dose modification guidelines requiring that study drug be discontinued.

See Section 7 for discontinuation procedures. See Section 6.5 for study drug and study treatment discontinuation/modifications.

6.6. Concomitant Medications and Procedures

All concomitant medications and treatments (including over-the-counter or prescription medicines, vitamins, vaccines, herbal supplements, prophylaxis for chemotherapy, and/or rescue medications for toxicities) must be recorded in the eCRF. Also the following will be recorded during the study:

- any prior medication received up to 28 days before the first dose of study treatment through the safety follow-up visit or until the participant begins a new anticancer therapy, whichever occurs first.
- any addition, deletion, or change in the dose of these medications.
- any treatments/procedures that are required to manage a participant's medical condition.
- concomitant medications administered after 30 days after the last dose of study treatment should be recorded for SAEs as defined in Section 9.2.

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.6.1. Permitted Medications and Procedures

For full details of prophylaxis medication recommendations for chemotherapy agents refer to approved drug product labels and updates.

Permitted medications and procedures include the following:

- Before administration of INCMGA00012/placebo, premedication with acetaminophen/paracetamol and a histamine blocker should be considered for participants who have had previous systemic reactions to protein product infusions or when recommended by institutional policy as described in Section 6.5.1.1.
- Premedications before administration of chemotherapy agents should be given in accordance with prescribing information and standard practice.
  - Examples include leucovorin for pemetrexed-related toxicity for treatment of CTCAE Grade 4 leukopenia or Grade 4 neutropenia lasting more than 3 days, beginning on the third day of Grade 4 myelosuppression; or immediately for treatment of Grade 4 thrombocytopenia, bleeding associated with Grade 3 thrombocytopenia, or Grade 3 or 4 mucositis.
- Anemia: Transfusions and/or erythropoietin may be utilized as clinically indicated for the treatment of anemia, and the information will be collected. Consider a potential immunologic etiology.
- Thrombocytopenia: Transfusion of platelets may be used if clinically indicated and the information will be collected. Immune thrombocytopenia should be ruled out before initiation of platelet transfusion.

- The use of corticosteroids is permitted in the following situations:
  - Acute treatment for an AE.
  - Physiologic corticosteroid replacement therapy at doses ≤ 10 mg/day of prednisone or equivalent for adrenal or pituitary insufficiency and in the absence of autoimmune disease.
  - Participants with asthma who require intermittent use of bronchodilators, inhaled steroids, or local steroid injections.
  - Topical, ocular, intra-articular, or intranasal steroids (with minimal systemic absorption)
  - Brief course of corticosteroids for prophylaxis (eg, < 3 weeks for contrast dye allergy), study-treatment related premedication as described above, chronic obstructive pulmonary disease exacerbation, or for treatment of nonautoimmune conditions (eg, delayed-type hypersensitivity reaction cause by a contact allergen).
- Palliative and supportive care is permitted during the course of the study for underlying medical conditions and management of symptoms.
- The high intraindividual variability of the coagulation status during disease and the possibility of interaction between oral anticoagulants and anticancer chemotherapy require increased frequency of INR monitoring, if it is decided to treat the participant with oral anticoagulants.
- SARS-CoV-2 vaccines (or vaccines for other viral diseases). See note regarding live vaccines in Section 6.6.3.
- 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. Restricted Medications and Procedures

When needed, ASCO guideline updates on the use of hematopoietic colony-stimulating factors should be followed for participants (Smith et al 2015). Consider a potential immunologic etiology.

For participants receiving pemetrexed, the following concomitant use should be taken into consideration:

- As per the approved pemetrexed label, participants taking NSAIDs or salicylates with mild to moderate renal insufficiency (creatinine clearance from 45 to 79 mL/minute) will not take the NSAID or salicylate (other than an aspirin dose ≤ 1.3 grams per day) for 2 days before, the day of, and 2 days after receiving premetrexed. Participants taking NSAIDs or salicylates with a long half-life (eg, naproxen, piroxicam, diflunisal, nabumetone) will not take the NSAIDs or salicylates for 5 days before, the day of, and 2 days after premetrexed.

For participants receiving carboplatin, the following concomitant use should be taken into consideration:

- Cyclosporine (and by extrapolation tacrolimus and sirolimus): excessive immunosuppression with risk of lymphoproliferation.
- Concurrent therapy with nephrotoxic drugs or ototoxic drugs such as aminoglycosides, vancomycin, capreomycin, and diuretics may increase or exacerbate toxicity due to carboplatin induced changes in renal clearance.
- Aminoglycosides: the concomitant use of carboplatin with aminoglycosides antibiotics should be approached with caution due to the cumulative nephrotoxicity and ototoxicity.
- Loop diuretics: the concomitant use of carboplatin with loop diuretic should be approached with caution due to the cumulative nephrotoxicity and ototoxicity.
- Phenytoin, fosphenytoin: risk of exacerbation of convulsions (resulting from the decrease of phenytoin digestive absorption by the cytotoxic drug) or risk of toxicity enhancement or loss of efficacy of the cytotoxic drug (due to increased hepatic metabolism by phenytoin). Thus, concomitant use is usually not recommended.

For participants receiving cisplatin, the following concomitant use should be taken into consideration:

- Phenytoin, fosphenytoin: risk of exacerbation of convulsions (resulting from the decrease of phenytoin digestive absorption by the cytotoxic drug) or risk of toxicity enhancement or loss of efficacy of the cytotoxic drug (due to increased hepatic metabolism by phenytoin). Plasma levels of anticonvulsant agents should be checked as warranted, as they may become subtherapeutic during cisplatin therapy.
- Aminoglycoside antibiotics when used concurrently with cisplatin can cause nephrotoxicity and thus they are not recommended for use.

For participants receiving nab-paclitaxel or paclitaxel, use caution when concomitantly administering nab-paclitaxel with inhibitors of either CYP2C8 or CYP3A4 (eg, ketoconazole and other imidazole antifungals, erythromycin, fluoxetine, gemfibrozil, clopidogrel, cimetidine, ritonavir, saquinavir, indinavir, nelfinavir) because toxicity of nab-paclitaxel/paclitaxel may be increased due to higher paclitaxel exposure.

For additional use of any restricted medications or for concomitant medications that must be used only in rare medical situations concurrently with the chemotherapy agents used in this study, or for any updates, refer to the local package inserts or prescribing information.

6.6.3. Prohibited Medications and Procedures

Medications or vaccinations specifically prohibited in the exclusion criteria (see Section 5.2) are not allowed during the study. If there is a clinical indication for one of these medications or vaccinations specifically prohibited during the study, discontinuation from study treatment may be required. The medical monitor should be consulted.

Participants are prohibited from receiving the following therapies during the screening and treatment period of this study:

- Antineoplastic systemic chemotherapy or biological therapy not specified in this Protocol.
- Immunotherapy not specified in this Protocol.
- Investigational agents other than INCMGA00012.
- Radiation therapy.
  - Surgery or radiotherapy for tumor control is not permitted during the study
- Live vaccines within 30 days before the first dose of study treatment, while participating in the study, and until 90 days after last dose of study drug. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/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 are live attenuated vaccines and are not allowed.
- The use of probiotic dietary supplements.

Participants who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the study. Participants may receive other medications that the investigator deems to be medically necessary.

6.7. Crossover Study Drug Treatment and Criteria

Participants who experience documented PD by RECIST v1.1 verified by the BICR and who were randomized to placebo and chemotherapy will have the opportunity to receive INCMGA00012 open-label monotherapy in the crossover period. These participants with verified PD will have treatment assignment unblinded (system-based through IRT **only** after sponsor-granted clinical approval of the request made for crossover) and be able to receive INCMGA00012 monotherapy for up to 35 cycles or approximately 2 years.

Medical emergency unblinding procedures should not be used for the purposes of determining eligibility for crossover. Refer to the IRT Manual for details on how to make a crossover request.

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:

- Documentation of PD will be defined as BICR assessment.
- Adverse events (except alopecia and peripheral neuropathy) due to therapy must have improved to CTCAE v5.0 $\leq$ Grade 1.
- If a participant is unstable as a result of a new or progressing brain metastasis(es), the participant will not be eligible for crossover.
- Participant must have an ECOG performance status of 0 to 1.

- Participant has not received any other systemic anticancer therapies other than the chemotherapy administered during the study treatment period.
- If required, the participant must have completed palliative radiotherapy (30 Gy or less) ≥ 7 days before the first dose of crossover study drug.
- Participant has adequate organ function as indicated by the laboratory values in Table 7.

For imaging required and the SoA in the crossover period, see Section 8.3.5 and Table 5, respectively. For the follow-up survival period, see Section 8.12.3.

6.8. Treatment After the End of the Study

Participants may receive approximately 2 years (or up to 35 cycles) of treatment with INCMGA00012/placebo. Participants receiving treatment with pemetrexed may continue to receive pemetrexed beyond 2 years as per approved product label if believed appropriate by the investigator (it may occur off-study after primary analysis is performed).

7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Treatment

7.1.1. Reasons for Discontinuation

In this study, a participant may discontinue from treatment but continue to participate in the Protocol-scheduled activities, as long as the participant does not withdraw consent. The discontinuation from the study treatment is permanent.

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

- Consent is withdrawn.

  Note: Consent withdrawn means that the participant has explicitly indicated that they do not want to be followed any longer; in this case, no further data, except data in public domain, may be solicited from or collected on the participant. Participants may choose to discontinue study treatment and remain in the study to be followed for progression and survival.

- Lost to follow-up.

  Note: As OS is a primary objective, documented multiple (ie, at least 2) efforts must be made to avoid lost to follow up.

- Further participation would be injurious to the participant's health or well-being, in the investigator's medical judgment.
- Unacceptable toxicity as noted in Section 6.5.
- Intercurrent illness that prevents further administration of treatment.
- Completed 35 cycles of INCMGA00012/placebo.

  Note: The number of cycles is calculated starting with the first dose.

- Verified radiologic disease progression.

  Note: If a participant has progression of disease verified by central radiological review using RECIST v1.1, a request may take place to move to the crossover period (through a system-based IRT-only process after sponsor-granted clinical approval of the request made for crossover as per Section 6.7). If a participant was receiving placebo and meets all crossover criteria defined in Section 6.7, they will have the opportunity to cross over to receive open-label INCMGA00012 monotherapy. Refer to the IRT Manual for details on how to make a crossover request.

- Any progression or recurrence of any malignancy, or any occurrence of another malignancy that requires other anticancer treatment.
- Intercurrent illness other than another malignancy as noted above that prevents further administration of study treatment.
- A confirmed positive serum pregnancy test.

- Investigator's decision to withdraw the participant from study treatment.
- The study is terminated by the sponsor or due to negative results so experimental study treatment may not be administered.
- The study is terminated by the local health authority, IRB, or IEC.

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

- 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 treatment.
- If a participant is noncompliant with study procedures or study drug/treatment administration in the investigator's opinion, the sponsor should be consulted for instruction on handling the participant.

Chemotherapy may be discontinued when a participant has received the maximum number of cycles permitted by the local regulatory authority/local label.

7.1.2. Discontinuation Procedures

In the event that the decision is made to permanently discontinue the study treatment, each participant will be followed for 90 days for AE monitoring following cessation of study treatment, or 30 days following cessation of treatment if new anticancer therapy is initiated as described in Section 9. Serious AEs will be collected for up to 90 days following cessation of study treatment, or 30 days following cessation of treatment if the participant initiates new anticancer therapy, whichever is earlier. Participants will have post-treatment follow-up for disease status until disease progression, initiating a nonstudy cancer treatment, withdrawing consent, or becoming lost to follow-up. After documented disease progression, each participant will be followed for OS until death or withdrawal of consent. These visits are described in Table 3 through Table 5, as applicable.

The last date of the last dose of study drug/treatment and the reason for discontinuation of study treatment will be recorded in the eCRF.

If a participant is discontinued from study treatment:

- The reason(s) for discontinuation must be documented in the participant's medical record and the primary reason for discontinuation must be included in the eCRF.
- The EOT visit should be performed.
- The status of the participant should be updated in IRT.
- Participants must be followed for safety until the time of the follow-up visit or until study drug/treatment–related toxicities resolve, return to baseline, or are deemed irreversible, whichever is longest.
- Participants will enter the survival follow-up period. See Section 8.12.3 for full survival follow-up requirements.

If the participant discontinues study treatment and actively withdraws consent for collection of follow-up data (safety follow-up or disease assessment), then no additional data collection

should occur; however, participants will have the option of withdrawing consent for study treatment but continuing in the follow-up period of the study for safety/efficacy assessments (eg, survival follow-up).

7.2. Participant Withdrawal From the Study

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

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

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

See Table 3 through Table 5 for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

7.3. Lost to Follow-Up

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

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make multiple (ie, at least 2) efforts to regain contact with the participant. These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Administrative and General Procedures

8.1.1. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
  - Informed consent must be obtained before any study-related procedures are conducted, unless otherwise specified by the Protocol.
  - Informed consent must be obtained using the IRB/IEC-approved version in a language that is native and understandable to the participant. A template will be provided by the sponsor or its designee. The sponsor or its designee must review and acknowledge the site-specific changes to the ICF template. The ICF must include a statement that the sponsor or its designee and regulatory authorities have direct access to participant records.
  - The ICF must contain all required elements and describe the nature, scope, and possible consequences of the study in a form understandable to the study participant.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the applicable requirements and regulations for the countries in which the study is being conducted as well as the IRB/IEC or study center.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection laws. The level of disclosure must also be explained to the participant.
  - The medical record of a potential participant may be first reviewed during the site's internal oncology multidisciplinary meetings, or as required by local regulations, in order to discuss the best treatment to be provided to a potential participant. If potential participant consents, the study doctor may contact participant's general practitioner to collect additional medical information. If participant does not want his/her referring physician to be informed, he/she must tell his study doctor.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

- Participants must provide consent to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.
- A participant who is rescreened is not required to sign another ICF if the rescreening occurs within 42 days from the previous ICF signature date.

8.1.2. Screening Procedures

Screening is the interval between signing the ICF and the day the participant is randomized in the study (Cycle 1 Day 1). Screening may not exceed 28 days. A time window of up to 3 days exists from randomization to study treatment administration in Cycle 1 Day 1.

Procedures conducted as part of the participant's routine clinical management (eg, blood count, imaging study) and obtained before signing of informed consent may be used for screening or baseline purposes provided the procedure meets the Protocol-defined criteria and has been performed in the timeframe of the study (ie, within 10 days of Cycle 1 Day 1). Screening laboratory assessments must be performed within 28 days of Cycle 1 Day 1. If chemistry and hematology laboratory assessments were performed more than 10 days before Cycle 1 Day 1, then the tests must be repeated and eligibility confirmed before study treatment administration on Cycle 1 Day 1.

For potential participants with cancer and HBV infection who need cancer treatment that lowers the immune system such as chemotherapy, there is a risk that an inactive, or latent, infection with hepatitis B can become active again. This situation could lead to serious liver problems and may complicate cancer treatment. Participants with active hepatitis will be excluded. Hepatitis B surface antigen, HBV-DNA, HCV antibody and HCV-RNA (or just HCV antibody if HCV-RNA is not the local standard of care) will be tested. If the hepatitis testing panel is conducted per standard of care within 60 days before randomization, testing does not need to be repeated. Additional tests at screening for hepatitis may be performed if clinically indicated.

As per Section 5.2, active HCV is defined as a positive HCV antibody result and quantitative HCV-RNA results greater than the lower limits of detection of the assay. In some countries, however, a qualitative HCV-RNA result may be used instead of the quantitative HCV-RNA result. If positive, these participants will be excluded. Hepatitis C antibody testing is allowed only for screening purposes in countries where HCV-RNA is not part of standard of care. In these cases, HCV antibody–positive participants will be excluded.

Results of a test performed before the participant signs consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified timeframe. For participants who are randomized, 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 before randomization or the administration of study drug/treatment. Laboratory results must be known before dosing. Tests with results that fail eligibility requirements may be repeated once during screening if the investigator believes the results to be in error. For screening assessments that are repeated, the most recent available result before randomization will be used to determine

eligibility. See Section 8.3.2 for imaging tests at screening and Section 5.4 for information regarding screen failures.

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 treatment assignment. The investigator or designee will select the assigned treatments that correspond to the number provided by the IRT, record the unique identifiers in the eCRF, and administer the treatment to the participant. Additionally, the IRT will be contacted at each regular study visit to update the study drug supply. Additional details are provided in the IRT Manual.

8.1.4. Assignment of Treatment/Randomization Number

All eligible participants will be randomly allocated and will receive a treatment/randomization number via IRT. The treatment/randomization number identifies the participant for all procedures occurring after treatment allocation/randomization. Once a treatment/randomization number is assigned to a participant, it can never be reassigned to another participant.

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

8.1.5. Distribution of Reminder Cards

Participants will be provided with a reminder card at each visit. The reminder card will indicate the date/time of the next visit.

All participants will be given a Participant Identification Card identifying them as participants in a research study. The card will contain study 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 immediately after the participant provides written informed consent. At the time of treatment allocation/randomization, site personnel will add the treatment/randomization number to the Participant Identification Card.

8.1.6. COVID-19

For Protocol procedures and tests that require additional time window allowances (due to the COVID-19 pandemic or temporary lockdowns) from what are permitted in Table 3 through Table 5, refer to Appendix G.

Prior vaccination (eg, primary dose or booster) against SARS-CoV-2 is not required to participate in the study (see Section 5.1), but it is highly recommended.

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 the 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 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, race, ethnicity, 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.

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. A complete history of the participant's treatment of NSCLC (if any) will be recorded separately and not listed as a prior medication.

8.1.8. Prior and Concomitant Medications Review

8.1.8.1. Prior Medications

The investigator or qualified designee will record medication, if any, taken by the participant during the study through the safety follow-up visit. In addition, new medications started during the crossover period through safety follow-up visit should be recorded.

8.1.8.2. Concomitant Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the participant within 28 days before the first dose of study treatment. Antibiotics use and type is to be collected 2 months before first study treatment.

8.2. Treatment Administration

Administration of IV study treatment (INCMGA00012/placebo and chemotherapy) will be witnessed by the investigator and/or study staff.

Study treatment should begin on the day of treatment allocation/randomization or as close as possible to the date on which the participant is allocated/assigned but within 3 days after the date of randomization.

8.2.1. Timing of Dose Administration

Depending on the treatment arm and investigator's choice of chemotherapy, study treatments will generally be administered in the following order: INCMGA00012/placebo, paclitaxel/nab-paclitaxel or pemetrexed, and carboplatin or cisplatin. Details of administering the individual components are discussed in Section 6.

8.3. Efficacy Assessments

Objective assessment of disease status is required, using the evaluations by RECIST v1.1 (Eisenhauer et al 2009) by the BICR and the investigator. The investigator's assessment will be recorded in the eCRF.

8.3.1. 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. Computed tomography is the highly preferred method for tumor imaging. Imaging should include the chest, abdomen, and pelvis. For the abdomen and pelvis, contrast-enhanced MRI may be used when CT with iodinated contrast is contraindicated or when local practice mandates it. The same imaging technique 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. The strongly preferred modality for imaging the brain is MRI.

Local site investigator/radiology assessment based on RECIST v1.1 will be used to determine participant eligibility. Although RECIST v1.1 references to a maximum of 5 target lesions in total and 2 per organ, the sponsor allows a maximum of 10 target lesions in total and 5 per organ. All scheduled images for all study participants from the sites will be submitted to the central imaging vendor. In addition, images (including via other modalities) that are obtained at an unscheduled time point to determine disease progression, and imaging obtained for other reasons that demonstrate radiologic progression, should also be submitted to the central imaging vendor. Note: If a study participant is hospitalized due to a medical emergency during the study, the participant must still undergo the Protocol tumor imaging procedures as in Table 3 through Table 5 as soon as the participant is recovered or stable.

The central imaging vendor will expedite the verification of PD upon request following local site investigator-assessed radiologic evidence of PD. Verification of progression by BICR (not by investigator's assessment) is 1 of the qualification criteria for the crossover period. Expedited verification of radiologic PD by the central imaging vendor will be communicated to the study site and sponsor. Treatment continues in a blinded fashion until PD has been verified by BICR, and images continue to be submitted to the central imaging vendor. Additionally, if the investigator considers the participant has progressed, but elects to implement iRECIST, the investigator will assess for confirmation of progression by iRECIST at subsequent timepoints. Images should continue to be submitted to the central imaging vendor.

8.3.2. Initial Tumor Imaging

Initial tumor imaging at screening must be performed within 28 days before the date of randomization. The site study team must review screening images 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.

Scans including PET-CT scans performed as part of routine clinical management are acceptable for use as screening tumor imaging if they are of **diagnostic** quality, performed within 28 days before the date of randomization, and can be assessed by the central imaging vendor.

Baseline brain imaging per the local standard of care is required if there are signs or symptoms suggesting that the participant has disease involvement in the CNS. Postbaseline brain imaging will be performed only if the screening brain imaging was positive or as clinically indicated; if indicated, brain scans should occur at the same time as other disease assessment scans. Brain imaging using MRI is strongly preferred. If MRI is medically contraindicated, CT with contrast is an acceptable alternative.

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 3 days before study initiation as per local site assessment. This exception does not include carcinomatous meningitis, as participants with carcinomatous meningitis are excluded regardless of clinical stability.

8.3.3. Tumor Imaging During the Study

The on-study treatment assessments should be performed every 6 weeks (42 days ± 7 days) for the first 24 weeks, then every 9 weeks (± 7 days) for the next 27 weeks, and subsequently every 12 weeks (± 14 days) until PD is verified by BICR from the date of randomization. Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts. Imaging should continue to be performed until disease progression verified by central imaging vendor (unless site investigator elects to continue treatment and follow iRECIST), the start of new anticancer treatment, withdrawal of consent, or death, whichever occurs first. All supplemental imaging must be submitted to the central imaging vendor. If the investigator elects to continue treatment and follow iRECIST after initial radiographic PD, imaging should continue after the participant is reconsented, and images should be submitted to the central imaging vendor.

Participants who have unconfirmed disease progression may continue on treatment at the discretion of the site investigator until progression is confirmed by the site provided they have met the conditions detailed in Section 8.3.7. Participants who have confirmed disease progression as assessed by the site will discontinue the treatment.

For participants who are eligible to enter the crossover period, refer to Section 8.3.5.

8.3.4. End of Study Treatment and Follow-Up of Tumor Imaging

In participants who discontinue study treatment, tumor imaging should be performed at the time of treatment discontinuation (± 4-week window). The imaging assessment should be performed even if the participant has clinical symptoms of deterioration or clinical progression in order to avoid censoring events. If a previous scan was obtained within 4 weeks before the date of discontinuation, then a scan at treatment discontinuation is not mandatory. In participants who discontinue study treatment due to documented disease progression, this is the final required tumor imaging.

Once a participant stops imaging assessments (eg, PD or starting a new anticancer therapy) the participant moves into the survival follow up period.

In participants who discontinue study treatment without documented disease progression, tumor imaging using the same imaging schedule used while on treatment to monitor disease status until (1) the start of new anticancer treatment, (2) disease progression, (3) death, or (4) the end of the study, whichever occurs first, should be used. The timing of follow-up visits should be scheduled to coincide with the participant's follow-up imaging. Once imaging is complete (eg, BICR-verified PD, new antineoplastic therapy), the participant enters into survival follow-up.

If a participant receives subsequent or new anticancer therapy after documentation of PD on or after study treatment, the imaging schedule should follow the recommendation in Section 8.12.3.1.

8.3.5. Crossover Tumor Imaging

A scan must be performed within 4 weeks before starting treatment with the first cycle of INCMGA00012 monotherapy in this period.

Then, the first on-study imaging assessment should be performed at 12 weeks (84 days ± 14 days) from the start of INCMGA00012 study drug treatment or more frequently if clinically indicated. Per RECIST v1.1, partial or complete response should be confirmed by a repeat tumor imaging assessment not less than 4 weeks from the date the response was first documented.

The tumor imaging for confirmation of response may be performed at the earliest 4 weeks after the first indication of response, or at the next scheduled scan, whichever is clinically indicated. Participants will then return to regular scheduled imaging every 12 weeks (84 days ± 14 days), starting with the next scheduled imaging timepoint. Participants who obtain a confirmation scan do not need to undergo scheduled tumor imaging if it is < 4 weeks later and may wait until the next scheduled imaging timepoint.

Imaging should continue to be performed until second PD, the start of new anticancer treatment, withdrawal of consent, death, or notification by the sponsor, whichever occurs first.

In participants who discontinue study treatment, tumor imaging should be performed at the time of treatment discontinuation (± 4-week window). If a previous scan was obtained within 4 weeks prior to the date of discontinuation, then a scan at treatment discontinuation is not mandatory. In participants who discontinue study treatment due to documented disease progression, this is the final required tumor imaging.

In participants who discontinue study treatment without documented disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging every 12 weeks until (1) the start of new anticancer treatment, (2) disease progression, (3) death, or (4) the end of the study, whichever occurs first.

8.3.6. RECIST Version 1.1 Assessment of Disease

RECIST v1.1 will be applied by the central imaging vendor as the primary measure for assessment of tumor response, date of PD, and as a basis for all Protocol guidelines related to disease status (eg, discontinuation of study therapy). Initial tumor imaging showing site-assessed PD should be submitted to the central imaging vendor immediately for confirmation regardless if the investigator intends to cross over without hesitation to INCMGA00012 monotherapy. The site will be notified if the central imaging vendor verifies PD using RECIST v1.1.

8.3.7. iRECIST Assessment of Disease

Immunotherapeutic agents may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents and can manifest as a clinical response after an initial increase in tumor burden or the appearance of new lesions. iRECIST is not an exploratory objective. The investigator may use iRECIST to make treatment decisions after PD is verified by BICR by RECIST v1.1 for assessing tumor response and progression if participants consent and are clinically stable (Seymour et al 2017).

These disease assessments for clinically stable participants will be performed by the study site, and participants will need to have an opportunity to be reconsented. Participants may receive study treatment 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.
- 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 F.

8.4. Health Economics

Not applicable.

8.5. Health Care Resource Utilization

Not applicable.

8.7. Safety Assessments

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

8.7.1. Adverse Events

Adverse events will be monitored from the time the participant signs the ICF until at least 90 days after the last dose of study drug/treatment, or 30 days following cessation of study drug/treatment if new anticancer therapy is initiated. Serious adverse events will be collected for up to 90 days following cessation of study drug/treatment, or 30 days following cessation of drug/treatment if the participant initiates new anticancer therapy. Refer to Section 9.4 for Reporting of Serious Adverse Events.

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

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

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs 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.

8.7.2. Physical Examinations

At the screening and safety follow-up visits, a comprehensive physical examination should be conducted. The comprehensive physical examination will include height (at screening or before dose administration on Cycle 1 only) and body weight and assessment(s) of the following organ or body systems: skin; head, eyes, ears, nose, and throat; thyroid; lungs; cardiovascular system; abdomen (liver, spleen); extremities; and lymph nodes; as well as a brief neurological examination. For chemotherapy agents, additional testing may be necessary. For example, since ototoxicity of cisplatin is cumulative, audiometric testing may be performed prior to initiating therapy and prior to each subsequent dose of drug. Refer to approved product label information for each chemotherapy agent used as part of study treatment and perform additional tests as clinically indicated and as recommended in the approved labels.

During the study, targeted examination as indicated in Table 3 through Table 5 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 study treatment constitute an AE if they are considered clinically meaningful, induce clinical signs or symptoms, require concomitant therapy, or require changes in study treatment.

8.7.3. Vital Signs

Vital sign measurements include blood pressure, pulse, respiratory rate (where it is part of standard of care), and body temperature and are to be taken as specified in Table 3 through Table 5. Blood pressure and pulse will be taken preferably 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 study treatment.

8.7.4. Electrocardiograms

Baseline ECGs (local) will be obtained at screening, with additional ECGs obtained at the safety follow-up visit, and as clinically indicated for all participants (see Table 3 and Table 4). Single 12-lead ECGs will be obtained locally using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. All 12-lead ECGs will be performed with the participant in a recumbent or semirecumbent position after 5 minutes of rest. No ECGs are required in the crossover period (see Table 5) unless clinically indicated.

Additional 12-lead ECGs may be performed as clinically indicated to manage participant safety. The decision to include or withdraw a participant from the study 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 and recorded in the eCRF.

8.7.5. Eastern Cooperative Oncology Group Performance Status

Eastern Cooperative Oncology Group performance status will be assessed as indicated in Table 3 through Table 5 and according to the criteria in Appendix E.

8.7.6. Laboratory Assessments

See Appendix D for the list of clinical laboratory tests to be performed at the site (locally), and see Table 3 and Table 4 (during the study treatment) and Table 5 (during the crossover period) for the timing and frequency. All Protocol-required laboratory assessments must be conducted in accordance with these SoAs.

Additional testing may be required by the sponsor based on emerging safety data, as clinically indicated as per the investigator, or due to COVID-19 (see Section 8.1.6). Laboratory results must be known and reviewed before dosing. The laboratory reports must be filed with the source documents. Information regarding collection, processing, and shipping of laboratory assessments is provided in the Laboratory Manual.

If laboratory values from non–Protocol specified laboratory assessments performed at the institution's local laboratory require a change in study participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the appropriate eCRF.

Screening laboratory assessments must be performed within 28 days of Cycle 1 Day 1. If assessments for blood chemistries and hematology are performed more than 10 days before Cycle 1 Day 1, then the tests must be repeated and eligibility confirmed before study treatment administration on Cycle 1 Day 1. Laboratory samples collected on study Day 1 must be performed before study treatment administration. After Cycle 1, predose laboratory procedures can be conducted up to 72 hours before study treatment administration (within the 3-day study window), and results should be reviewed by the investigator or qualified designee and found to be acceptable before a new cycle of treatment is initiated.

Endocrine function laboratory tests are to be performed on Cycle 2 Day 1 and Cycle 4 Day 1 and then repeated every other cycle beginning with Cycle 6 for both nonsquamous and squamous participants. For the thyroid function tests (ie, T3 or FT3, FT4, and TSH), participants may be dosed in subsequent cycles after Cycle 1 Day 1 while thyroid function tests are pending.

In some regions, lipase and/or amylase laboratory results may not be immediately available for investigator review before study treatment. In those situations, participants may be administered study treatment while the results are pending. Investigators are required to review the results once available and take prompt action as appropriate (eg, following up with the participants by telephone in between visits if warranted).

Participants with active tuberculosis are excluded from the study as per Section 5.2. For participants who have a known history of active tuberculosis (eg, cured before study entry), tuberculosis testing approximately 6 months or as per standard of care in a particular country or region (eg, South Africa) where tuberculosis prevalence is high is recommended. Investigators can also test as clinically indicated, regardless of the history before study entry, if suspected during the study.

Hematology laboratory tests for Cycle 1 through Cycle 4, Days 8 and 15 apply only to participants receiving nab-paclitaxel.

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 laboratory tests with values considered clinically significantly abnormal during participation in the study or within 90 days after the last dose of study treatment (or until the start of new anticancer therapy) should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

A certified laboratory local to the investigative site will perform all clinical laboratory assessments for safety (ie, blood chemistries, hematology assessments, coagulation tests, endocrine function, and urinalysis). The investigative site will enter the laboratory results and laboratory normal ranges into the eCRF. Additional tests may also be performed if clinically indicated.

See Section 9.1 for information regarding laboratory abnormalities that should be recorded as an AE in the eCRF.

8.7.7. Pregnancy Testing

See Table 3 through Table 5 for timepoints and frequency of pregnancy testing. A serum pregnancy test (within 72 hours of Cycle 1 Day 1) for female participants of childbearing potential is required at screening and safety follow-up visits. At EOT, the test can be from urine or serum. Women of childbearing potential are defined in Appendix A. During the study, including the crossover period, if a urine pregnancy test is positive, the results should be confirmed with a serum pregnancy test. Pregnancy testing should be conducted before each cycle, and additionally as per local regulations, where applicable.

Participants who are WOCBP are asked in the ICF before consenting to the study if they are willing to take appropriate precautions to avoid pregnancy after cessation of study treatment (through 180 days after the last dose of chemotherapeutic agents, and for at least 120 days after the last dose of INCMGA00012). Permitted methods that are at least 99% effective in preventing pregnancy (see Appendix A) should be communicated to the participants and their understanding confirmed. A WOCBP must agree to follow the contraceptive guidance in Appendix A during the treatment period and up to 180 days after last dose of chemotherapeutic agents and for at least 120 days after the last dose of INCMGA00012. If a urine test is positive or not evaluable, a serum test will be required. Participants must be excluded/discontinued from the study in the event of a positive test result.

8.8. Pharmacokinetic [redacted] Assessments

Blood PK [redacted] samples will be obtained from all participants to measure PK of INCMGA00012. Blood samples for measurement of serum concentrations of INCMGA00012 [redacted] will be collected for participants at the timepoints specified in Table 3, Table 4, and Table 16.

The actual date and time (24-hour clock time) of each sample will be recorded in the eCRF. Instructions for the sample preparation, storage, and shipping will be provided in the Laboratory Manual.

The INCMGA00012 serum C_{max} and C_{min} at planned visits and times will be summarized. Pharmacokinetic data will also be analyzed using nonlinear mixed effects modeling. Based on PK data obtained in this study as well as PK data obtained from other studies, a population PK analysis will be performed to characterize PK parameters and to further support proposed dosing regimen. Samples will be analyzed by the sponsor or sponsor's designee.

Pharmacokinetic data will also be used to explore the exposure-response relationships for INCMGA00012 antitumor activity/efficacy as well as safety in the proposed patient population, if feasible.

No PK [redacted] samples are collected during the crossover period.

Analyses of PK [redacted] will be performed after the study is unblinded and only on samples from participants who received INCMGA00012.

Table 16: Pharmacokinetic [redacted] Blood (Serum) Sample Timing

Study Visit	Timing of Sample for PK
Cycle 1 Day 1	• Predose within 60 minutes (± 5 min) before the start of infusion • Immediately after the end of INCMGA00012/placebo infusion (+ 10 min). Sample must be collected before dose/infusion of other agents
Cycle 2 Day 1	Within 24 hours before the start of infusion
Cycle 4 Day 1	• Within 24 hours before the start of infusion • Immediately after INCMGA00012/ placebo infusion (+ 10 min). Sample must be collected before dose/infusion of other agents
Cycle 6 Day 1	Within 24 hours before the start of infusion
Cycle 8 Day 1, and every 4 cycles thereafter	Within 24 hours before the start of infusion
EOT	At the time of the visit
Safety follow-up	At the time of the visit

[redacted]

8.9. [redacted]

[redacted]

[redacted]

8.9.1. Tumor Tissue Biopsies

Tumor tissue will be collected during screening to conduct PD-L1 assessment centrally. 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 PD-L1 IHC 22C3 pharmDx (Dako) assay. Fine-needle aspirates are not acceptable for use in this assay. Adequate tumor sample must be available at the time of screening for PD-L1 assessment; results from a central laboratory are required before randomization and stratification.

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 specimens after the participant has been diagnosed with metastatic disease 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.

If the investigator needs assistance to conduct testing of specific sensitizing driver mutations or gene rearrangement due to lack of documentation demonstrating eligibility criteria and cannot do the testing locally, the sponsor can arrange to have samples sent to its central laboratory.

If there are a sufficient number of representative samples, including those after the Protocol-required screening/baseline testing, any remaining sample from screening will be used for baseline characterization of RNA expression and possible association with clinical outcomes. This potential testing will not apply to participants enrolled in China.

8.10. Unscheduled Visits

Unscheduled study visits may occur at any time if medically warranted, including scheduled cycle visits where a study treatment hold is indicated for toxicity purposes. Any assessments performed at those visits should be recorded in the eCRF.

8.11. End of Treatment and/or Early Termination

Once a participant permanently discontinues all study treatments, the EOT visit should be conducted. Further, once a participant has permanently discontinued all study treatments, even if prematurely, or once they have received the last dose of study treatment defined per Protocol, have verified disease progression by BICR, or start a new anticancer therapy, they move into the survival follow-up period. See Section 8.12.3 for full survival follow-up requirements.

If the EOT visit coincides with a regular study visit, the EOT evaluations will supersede those of that scheduled visit, and the data should be entered in the EOT visit in the eCRF.

All EOT assessments should be completed within 3 days of the decision to discontinue study treatment. Should EOT occur ≤ 21 days after the final dose of study treatment, a separate 30-day safety follow-up visit is required and should be conducted according to Table 3 through Table 5. The participant should be encouraged to return for the safety follow-up visit. If the EOT visit occurs > 21 days after the last study treatment, only a single EOT/30-day safety follow-up visit is required, and all unique assessments for the EOT and 30-day follow-up visit will be performed once.

8.12. Follow-Up

8.12.1. Safety Follow-Up

The safety follow-up period starts once the participant discontinues study treatment. Approximately 30 days (± 7 days) after the EOT, participants are to attend a clinic visit for safety evaluation. Adverse events and SAEs must be reported until 1) at least 90 days after the last dose of study drug/treatment, or 30 days following cessation of study drug/treatment if new anticancer therapy is initiated. Serious AEs will be collected for up to 90 days after the last dose of study drug/treatment, or 30 days following cessation of drug/treatment if the participant initiates new anticancer therapy or 2) until toxicities resolve, return to baseline, or are deemed irreversible, whichever is longer.

Reasonable efforts should be made to have the participant return for the follow-up visit and report any AEs that may occur during this period. If the participant cannot return to the site for the safety follow-up visit, the participant should be contacted by telephone, or other methods of communication, for assessment of any AEs; this contact should be documented in source.

If a participant is scheduled to begin a new anticancer therapy before the planned 30-day safety follow-up visit, the safety follow-up visit should be performed before a new anticancer therapy is started. Once a new anticancer therapy has been initiated, the participant will move into the survival follow-up period.

8.12.2. Post-Treatment Disease Follow-Up

Participants who discontinue study treatment for a reason other than PD will move into the disease status follow-up period and should be assessed every 12 weeks (± 14 days) by radiologic imaging to monitor disease status. Every effort should be made to collect disease status information via study imaging assessments until:

- The start of new anticancer therapy
- PD (verified by BICR)
- Death
- The end of the study
- Withdrawal of consent
- Pregnancy
- Lost to follow-up

Information regarding poststudy anticancer treatment will be collected if new treatment is initiated.

See Section 8.12.3.1 for subsequent PD after initiation of new anticancer therapy as applicable.

8.12.3. Survival Follow-Up

Survival is the primary objective of the study, thus multiple (ie, at least 2) documented efforts should be made to collect this information per the SoA until the study has been completed unless participants have permanently withdrawn their consent for follow-up.

Once a participant has received the last dose of study drug/treatment, has confirmed disease progression, or starts a new anticancer therapy, the participant moves into the survival follow-up period. The participant should be contacted by telephone, email, or visit at least every 12 weeks (± 14 days) to assess for survival status until death, withdrawal of consent, the end of the study, or the participant is lost to follow-up, whichever occurs first.

For participants who do not intend to return to the study investigator for their ongoing care, follow-up should be maintained by phone contact, patient records, and public records/databases at intervals of no longer than 12 weeks (± 14 days). Also, participants may be contacted for survival status at any time during the course of the study to support planned survival analyses.

Participants may withdraw their consent at any time from any or all portions or periods of the study. Participants who withdraw consent for treatment and/or imaging are encouraged to remain on the noninvasive survival follow-up portion of the study. The procedures associated with this phase may be only telephone contacts to assess survival status and the current state of the participant's metastatic NSCLC. The noninvasive nature and societal benefit of survival follow-up should be explained to the participant by the site staff, particularly when discontinuing treatment and imaging.

[redacted]

8.12.4. Survival Status Monitoring

To ensure current and complete survival data is available at the time of database locks, updated survival status may be requested during the course of the study by the sponsor. For example, updated survival status may be requested before but not limited to an eDMC review, interim and/or final analysis. Upon sponsor notification, all participants who do not/will not have a scheduled study visit or study contact during the sponsor's defined time period will be contacted for their survival status (excluding participants who have a previously recorded death event in the clinical database).

8.13. Crossover Period

Eligible participants who had verified PD by BICR review (RECIST v1.1) first and who were on placebo plus chemotherapy arm after randomization will have the opportunity to receive monotherapy INCMGA00012 in this crossover period (see Section 6.7). Participants who permanently discontinue chemotherapy due to an AE, withdraw consent, or for any reason other than PD will not be eligible for crossover. Eligible crossover period participants may receive open label monotherapy INCMGA00012 for up to 35 cycles.

In this crossover period, the imaging schedule is every 12 weeks (± 14 days). Table 5 shows the schedule of activities to be performed in the crossover period including the entry criteria. Crossover period participants must not initiate treatment any earlier than 3 weeks (21 days ± 3 days) after their last dose of chemotherapy regardless of the time of progression. Screening procedures need to be completed within 28 days of verified PD by BICR (or up to 42 days from last dose if recovering from an AE). All procedures and assessments completed at the time of withdrawal from the main study (blinded period) may be used as appropriate for the start of the crossover period of the study.

The tumor image used to determine PD can be used as the new baseline image for the crossover period if 1) the image was within 30 days before receiving the first dose of INCMGA00012 monotherapy and 2) no study treatment was administered between the image and the first dose of INCMGA00012 monotherapy; otherwise, a new baseline image must be performed before INCMGA00012 monotherapy treatment.

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

9.1. Definition of Adverse Event

Adverse Event Definition

- An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related.
- An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study treatment.

Events Meeting the Adverse Event Definition

- Any safety assessments (eg, ECG, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease).
- Abnormal laboratory test results constitute an AE if they are considered clinically meaningful, induce clinical signs or symptoms, require concomitant therapy, or require changes in study drug. Whenever possible, a diagnosis (eg, anemia, thrombocytopenia) should be recorded in the eCRF rather than the abnormal lab result (eg, low hemoglobin, platelet count decreased).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study treatment administration even though they may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. **Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent.** Such overdoses should be reported regardless of sequelae.
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT Meeting the Adverse Event Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition or considered to be treatment-related by the investigator.
- Efficacy endpoints as outlined in Section 3 will not be reported as AE/SAEs, specifically, any event that is related to disease progression of the cancer under study. All efforts must be made to not record worsening of an AE due to disease progression as an AE but rather the AE itself (eg, "worsening of congestive heart failure" versus "worsening of congestive heart failure due to disease progression") followed by the causality due to disease progression. Unblinded aggregated efficacy endpoint events and safety data will be monitored to ensure the safety of the participants in the study. Any suspected endpoint that upon review is not progression of the cancer under study will be forwarded to Incyte Pharmacovigilance as a SAE within 24 hours of determination that the event is not progression of the cancer under study.

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE if it occurred after signing informed consent. If present before entering the study, the condition should be captured as medical history.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

9.2. Definition of Serious Adverse Event

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

A serious adverse event is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

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

c. Requires inpatient hospitalization or prolongation of existing hospitalization

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

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

d. Results in persistent or significant disability/incapacity

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

e. Is a congenital anomaly/birth defect

f. Other situations (Important Medical Event)

An event that may not result in death, be immediately life-threatening, or require hospitalization, but may be considered serious when, based on appropriate medical judgment, the event may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in the above definition. Examples of such events include new invasive or malignant cancers (excluding the disease 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 as serious adverse events.

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

Adverse Event and Serious Adverse Event Recording

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

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

- The severity grade (CTCAE Grade 1 to 5). See below for further instructions on the assessment of intensity.
- Whether there is at least a reasonable possibility that the AE is related to the study treatment (including study drug): suspected (yes) or not suspected (no). See below for further instructions on the assessment of causality.
- The start and end dates, unless unresolved at final follow-up.
- The action taken with regard to study drug as a result of the AE/SAE(s) and/or reference therapy.
- 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 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 treatment 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/reference therapy 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 treatment administration, will be considered and investigated.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- With regard to assessing causality of SAEs:
  - There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report. However, the causality assessment is one of the criteria used when determining regulatory reporting requirements. **Therefore, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE.**
  - The investigator may change his/her opinion of causality in light of follow-up information and send a follow-up SAE report with the updated causality assessment.

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

9.4. Reporting of Serious Adverse Events

Regardless of suspected causality (eg, relationship to study treatment or study procedures), all SAEs occurring after the participant has signed the ICF through 90 days after the last dose of study treatment or until 30 days following cessation of study drug/treatment if new anticancer therapy is initiated must be reported to the sponsor (or designee). The reporting of SAEs must be within 24 hours of learning of its occurrence, unless otherwise specified by the Protocol. The investigator will submit any updated SAE data to the sponsor (or designee) immediately without undue delay but no later than within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE information after conclusion of the study participation. However, if the investigator learns of any SAE, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must notify the sponsor (or designee) immediately without undue delay but no later than within 24 hours of obtaining knowledge of its occurrence unless otherwise specified by the Protocol.

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

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

If the SAE is not documented in the IB for the study drug (new occurrence) and is thought to be related to the sponsor's study drug, the sponsor or its designee may urgently require further information from the investigator for reporting to health authorities. The sponsor or its designee may need to issue an Investigator Notification to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions will be collected and reported to the competent authorities and relevant ethics

committees in accordance with Directive 2001/20/EC, or as per national regulatory requirements in participating countries.

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

Investigator safety reports must be prepared for suspected unexpected 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 Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

Serious Adverse Event Reporting

- Information about all SAEs is collected and recorded on the Adverse Event Form in the eCRF.
- The investigator must report within 24 hours of learning of its occurrence any SAE via the EDC system (primary method).
- In circumstances in which 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 and Submitting the Serious Adverse Event Report Form. The contact information for Incyte Pharmacovigilance by email/fax is listed in the Incyte Reference Guide for Completing the Serious Adverse Event 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 for details).
- Follow-up information is recorded through EDC (or on an amended or new Serious Adverse Event Report Form if the EDC system is not available with an indication that it is follow-up to the previously reported SAE and the date of the original report). Refer to the eCRF guidelines for more information. The follow-up report should include information that was not provided on the previous Serious Adverse Event Report Form, such as the outcome of the event (eg, resolved or ongoing), treatment provided, action taken with study drug because of the SAE (eg, dose reduced, interrupted, or discontinued), or participant disposition (eg, continued or withdrew from study participation). Each recurrence, complication, or progression of the original event should be reported as follow-up to that event, regardless of when it occurs.

9.5. Adverse Events of Special Interest

No specific AEs are expected to be sent to the sponsor within an expedited manner outside the AEs that meet the seriousness category as described in Section 9. Adverse events of special interest will include irAEs that will be coded according to MedDRA along with all other adverse events. Immune response AEs will be tabulated by preferred term and system organ class, and by events of Grade 3 or higher.

9.6. Emergency Unblinding of Treatment Assignment

In a medical emergency, if knowledge of the treatment assignment is necessary to determine optimal medical management of the participant, the procedure for emergency unblinding is provided in the IRT. This option may be used *only* if the participant's well-being requires the investigator to be aware of the participant's treatment assignment. If a participant's treatment assignment is unblinded, the sponsor or its designee must be notified immediately by telephone.

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

9.7. Pregnancy

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

- The study treatment and study drug must be discontinued immediately (female participants only).
- The investigator must complete and submit the Sponsor Clinical Trial Pregnancy Form to the sponsor or its designee within 24 hours of learning of the pregnancy.

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

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

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

9.8. Warnings and Precautions

Special warnings or precautions for the study drug, derived from safety information collected by the sponsor or its designee, are presented in the IB. Special warnings or precautions to the chemotherapy agents used are found in Section 6.5 and Section 6.6 and are further detailed in the approved labels.

Additional safety information regarding INCMGA00012 collected between IB updates will be communicated in the form of Investigator Notifications. Any important new safety information should be discussed with the participant during the study, as necessary. If new significant risks are identified, they will be added to the ICF.

9.9. Product Complaints

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

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

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

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

9.10. Treatment of Overdose

For this study, any dose of INCMGA00012 ≥ 1500 mg (4 times the 375 mg dose) 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 9.3.
- 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

The study has a primary endpoint of OS with PFS as a secondary endpoint. The overall population consists of participants with both nonsquamous and squamous NSCLC.

Assumptions such as for HRs for PFS and OS from current clinical study results with pembrolizumab, atezolizumab, and nivolumab in combination with chemotherapy in the first line metastatic NSCLC setting were reviewed. The HR of PFS varies from 0.48 to 0.64 in nonsquamous NSCLC participants and 0.56 to 0.71 in squamous NSCLC participants, while the HR of OS varies from 0.56 to 0.81 in the nonsquamous population and from 0.64 to 0.92 in the squamous population, respectively (Gandhi et al 2018, Hellmann et al 2019, Paz-Ares et al 2018, Socinski et al 2018).

The study plans to enroll < 40% squamous NSCLC participants, which represents the prevalence of this histology in NSCLC and provides an adequate population from both disease groups (Mok et al 2019, NCI 2019). Additionally, participants with tumors with PD-L1 TPS < 1% will be limited to < 30% for the same reason (Gandhi et al 2018, Mok et al 2019, Paz-Ares et al 2018). This capping is required 1) as the HR estimates were calculated based on previous clinical trials with similar distribution of the squamous and nonsquamous histologies and PD-L1 status of the tumors and 2) for study rigor and integrity.

Combining the above median PFS and OS estimates in both nonsquamous and squamous disease, it is reasonable to assume the median PFS = 5 months in the chemotherapy arm and the target HR = 0.63 in the overall population. Similarly, it is reasonable to assume the median OS = 14 months in the chemotherapy arm and the target HR = 0.7 in the overall population.

For OS analysis, a target of 341 OS events will provide 87% power to detect an HR of 0.7 at a 1-sided 2.5% significance level.

For PFS analysis, a target of 222 PFS events will provide 90% power to detect an HR of 0.63 at a 1-sided 2.5% significance level.

The study design assumptions are based on randomization of approximately 530 participants in a 2:1 ratio for INCMGA00012 plus chemotherapy arm and placebo plus chemotherapy arm, respectively. The sample size estimation considers a recruitment period of 34 months at a uniform rate of 18 participants per month with a 6-month ramp-up period, a monthly withdrawal rate of 2% for PFS and 1% for OS from exponential distribution, and a follow-up period of 20 months after the last participant is enrolled. Due to potential early censoring attributable to the COVID-19 pandemic and/or disruptions in Ukraine, approximately 600 participants will be enrolled to ensure enough number of events will be observed within reasonable follow-up time. The sample size calculation is by East® v6.5.

10.2. Populations for Analysis

The populations to be analyzed are defined in Table 17.

Table 17: Populations for Analysis

Population	Description
FAS	The full analysis set comprises all participants to whom study treatment has been assigned by randomization. Participants will be analyzed according to ITT principle (ie, according to the treatment and strata they have been assigned to during the randomization procedure). The FAS will be used for the summary of demographics, baseline characteristics, and participant disposition and for analyses of all efficacy data.
PPS	The PPS comprises all participants in the FAS who are considered compliant with the Protocol. Sensitivity analyses of OS may be performed using the PPS when the primary endpoint is statistically significant.
Safety	The safety population comprises all participants who received at least 1 dose of study treatment. Treatment groups for this population will be determined by the actual treatment that the participant received regardless of treatment assignment at randomization. The actual treatment received corresponds to: • The randomized treatment if the participant took at least 1 dose of that treatment. • The first treatment received if the randomized treatment was never received. All safety analyses will be conducted by safety population.
PK	The PK evaluable population comprises all participants who received at least 1 dose of INCMGA00012 and have provided at least 1 PK postdose sample.
[redacted]	

10.3. Level of Significance

The level of significance for the primary endpoint of OS and secondary endpoint PFS is strongly controlled at 1-sided 2.5% through gate-keeping procedure. For the OS endpoint, the Type I error will be controlled by a 1-sided, 2-look, group-sequential design with Lan-DemMets (O'Brien and Fleming 1979) alpha spending function. If the OS test indicates statistical significance, PFS by RECIST v1.1 (via BICR) will be tested in an alpha-controlled manner. The ORR by RECIST v1.1 (via BICR) will be tested at 2.5% if PFS is statistically significant.

10.4. Statistical Analyses

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

10.4.1. Primary Analysis

Overall survival is defined as the time from the date of randomization to the date of death due to any cause. The primary 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 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. Kaplan-Meier curves, medians, and 95% CIs of the median OS will be presented for each treatment group.

The HR for OS will be calculated, along with its 95% CI, 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.

In order to adjust for cross over effect in placebo arm, rank preserving structural failure time model and inverse probability of censoring weighting method may be used to analyze the OS endpoint as supportive analysis. Sensitivity analyses may be performed according to regulatory guidelines (EMA 2012, EMA 2022, FDA 2015) and will be detailed in the SAP.

As a sensitivity analysis, an unstratified log-rank test may be considered for OS. In addition, study discontinuation due to clinical progression, death, or documented progression by BICR after 2 missed scheduled tumor assessment may be considered as events for PFS in sensitivity analysis. In addition, sensitivity analyses may be conducted to evaluate potential impacts of the COVID-19 pandemic (ie, deaths) and/or organizational disruptions in Ukraine (ie, conflict conditions in Ukraine).

10.4.2. Subgroup Analyses

To determine whether the treatment effect is consistent across various subgroups, the estimate of the between-group treatment effect (with a nominal 95% CI) for the OS and PFS endpoints will be estimated and plotted within each category of the following classification variables:

- Age category (≤ 65 vs > 65 years, ≤ 75 vs > 75 years, and ≤ 85 vs > 85 years)
- Sex (female, male)
- Race (White, Chinese, other Asian, Other)
- Brain metastasis (presence vs absence)
- Smoking status (never vs former/current smoker)
- Investigator's choice of chemotherapy (for nonsquamous NSCLC vs squamous NSCLC)
- PD-L1 TPS (< 1%, ≥ 1% to 49%, ≥ 50%)
- Site geographic region (East Asia vs non-East Asia)
- Country enrollment (eg, China, Ukraine, and any countries with ≥ 100 participants randomized vs all other countries combined)
- Predominant tumor histology (squamous vs nonsquamous)

10.4.3. Secondary Analyses

10.4.3.1. Progression-Free Survival

Progression-free survival is defined as the time from the date of randomization to the date of the first documented progression or death due to any cause. Progression-free survival will be assessed via BICR according to RECIST v1.1 (Eisenhauer et al 2009). 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. Censoring for PFS will follow the algorithm outlined in Table 18. Progression-free survival as assessed via investigator may be used for supportive analysis of the primary endpoint.

Table 18: Evaluation and Censoring of Progression-Free Survival

Situation	Outcome	Date of Progression or Censoring
No baseline tumor assessments	Censored	Date of randomization
Progression documented between scheduled visits	Progressed	Date of first disease assessment of PD
No progression	Censored	Date of last valid radiologic assessment (not NE and not missing)
Study discontinuation for undocumented progression	Censored	Date of last valid radiologic assessment (not NE and not missing)
New anticancer treatment started	Censored	Date of last valid radiologic assessment (not NE and not missing) before new anticancer treatment
Death before first progressive disease assessment	Progressed	Date of death
Death between adequate assessment visits	Progressed	Date of death
Death after 1 missed assessment	Progressed	Date of death
Progression after 1 missed assessment	Progressed	Date of first objective response of PD
Death or progression after more than 1 missed assessment	Censored	Date of last valid radiologic assessment (not NE and not missing)

If the OS endpoint is tested as statistically significant, 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% CIs will be presented by treatment group.

A stratified Cox regression with Efron's method for tie-handling will be used to estimate the HR of PFS, along with 95% CIs, using the same strata information assigned at randomization. The analysis of PFS will be conducted at the time of the OS interim analysis. The p-value will be a nominal p-value if OS is not statistically significant at the time of interim analysis.

10.4.3.2. Objective Response Rate

Objective response rate is defined as the proportion of participants with best objective response of CR or PR according to RECIST v1.1 by BICR. Objective response rate by iRECIST is not an endpoint; iRECIST is used for participant's disease management. Objective response rate will be calculated based on the FAS according to the ITT principle. Objective response rate will be presented by treatment group along with approximate 95% CI. The Cochran-Mantel-Haenszel chi-square test (stratum based on the baseline stratification factor) will be used to compare the 2 treatment groups with respect to the ORR at a 1-sided 2.5% level of significance if OS and PFS are both statistically significant. As a supportive analysis, ORR as assessed by the investigator will be calculated by treatment group and presented along with the approximate 95% CI.

10.4.3.3. Duration of Response

For participants who demonstrate CR or PR, DOR is defined as the time from first documented evidence of CR or PR until disease progression or death due to any cause, whichever occurs first. Censoring rules for DOR are summarized in Table 19. Duration of response will be assessed using RECIST v1.1 by BICR. The distribution of DOR will be estimated using the Kaplan-Meier method. The median DOR along with 95% CIs will be presented by treatment group.

For each DOR analysis, a corresponding summary of the reasons responding participants are censored will also be provided. Responses in participants who are alive, have not progressed, have not initiated new anticancer treatment, and have not been determined to be lost to follow-up are considered ongoing at the time of analysis. If a participant meets multiple criteria for censoring, the censoring criterion that occurs earliest will be applied.

Table 19: Evaluation and Censoring of Duration of Response

Situation	Outcome	Date of Progression or Censoring
No progression or death, new anticancer treatment not started	Censored	Date of last valid radiologic assessment (not NE and not missing)
No progression or death, new anticancer treatment started	Censored	Date of last valid radiologic assessment (not NE and not missing) before new anticancer treatment
Death or progression after ≥ 2 consecutive missed assessments	Censored	Date of last valid radiologic assessment (not NE and not missing) before ≥ 2 missing assessments
Death or progression after ≤ 1 missed adequate assessments	Progressed	Date of first objective response of progressive disease or death

10.4.4. Safety Analyses

Safety analyses will be conducted for the safety population by treatment group and by histology.

10.4.4.1. Adverse Events

A TEAE is any AE either reported for the first time or worsening of a pre-existing event after first dose of study treatment, up to 90 days after last dose of study treatment, and prior to start of new anticancer therapy. Analysis of AEs will be limited to TEAEs, but data listings will include all AEs regardless of their timing to study treatment administration.

Adverse events will be tabulated by MedDRA system organ class and preferred term. Severity of AEs will be based on the NCI CTCAE v5.0 using Grades 1 through 5. The subset of AEs considered by the investigator to have a relationship to study treatment will be considered to be treatment-related AEs. If the investigator does not specify the relationship of the AE to study treatment, the AE will be considered treatment-related.

Number (%) of participants reporting any TEAEs, any SAEs, any Grade 3 or higher TEAEs, irAEs, clinically diagnosed Hy's Law AEs, any treatment-related TEAEs, any treatment-related SAEs, any treatment-related Grade 3 or higher TEAEs, any fatal TEAE, and any TEAEs leading to treatment interruption/dose reduction/discontinuation will be tabulated by MedDRA system organ class and preferred term.

10.4.4.2. 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. Potential DILIs will be listed. The criteria for determining potential DILIs will be provided in the Statistical Analysis Plan.

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 classification based on laboratory reference ranges.

10.4.4.3. 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.

10.4.4.4. Electrocardiograms

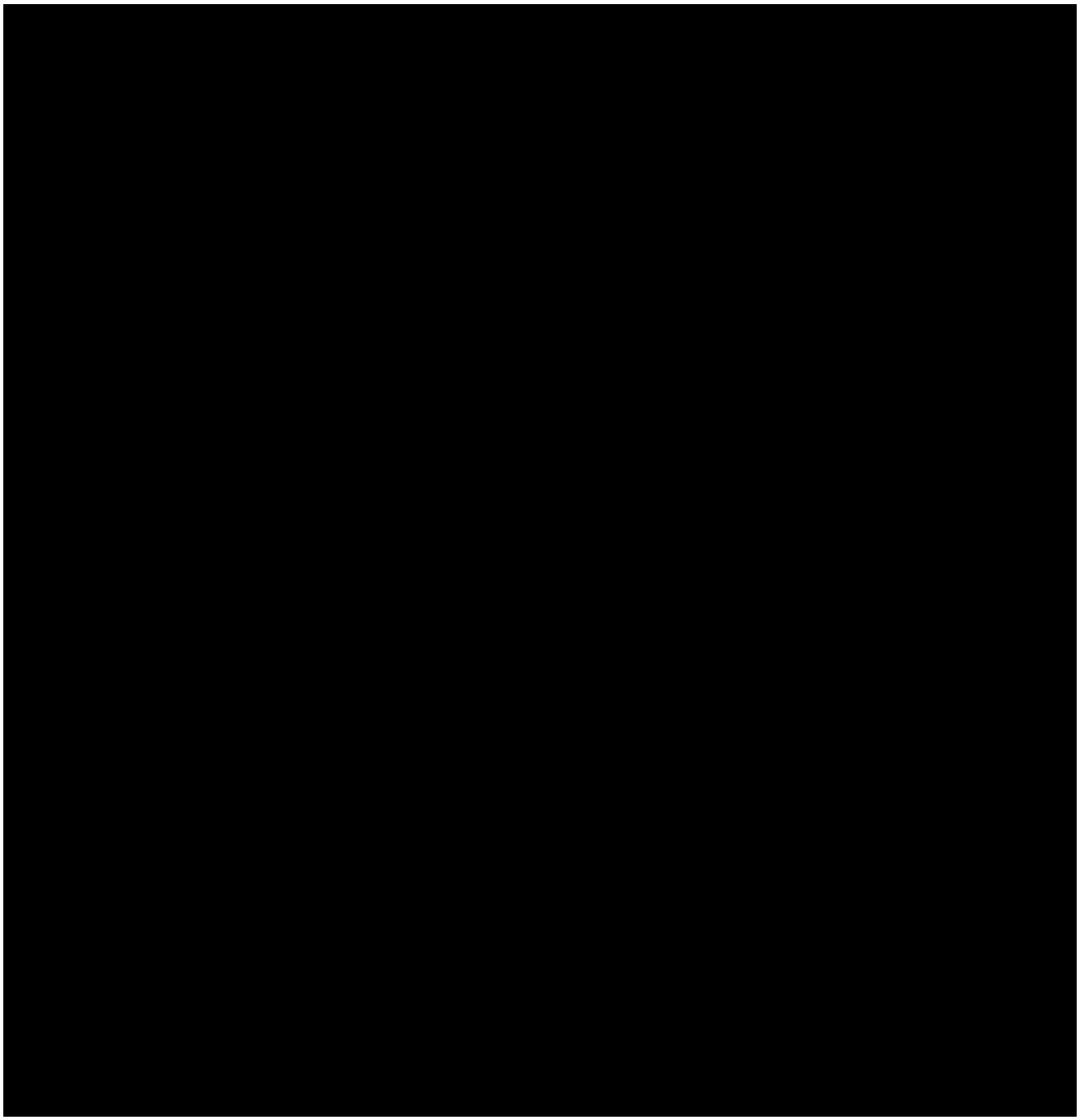
Descriptive statistics and mean change from baseline will be determined for each ECG parameter at each assessment time.

10.4.4.5. Dose Exposure

Measures of exposure (eg, days of exposure, dose intensity) of INCMGA00012 and chemotherapy by histology and by treatment group will be summarized by means of summary statistics.

10.4.4.6. Pharmacokinetics

The INCMGA00012 PK will be described using a population PK modeling approach software (eg, NONMEM) following unblinding of the study. If there is not sufficient data, data from this study will be pooled with data from other studies for a population PK analysis.



10.5. Interim Analysis

An interim analysis for OS is planned when approximately 60% of the targeted OS events are expected. Under the assumption of 14-month median OS in the placebo plus chemotherapy arm, it is expected that treatment with INCMGA00012 plus chemotherapy will result in a 30% reduction in HR (corresponding to an increase in median OS from 14 months to 20 months under exponential model assumption). If the true HR is 0.7 (under alternative hypothesis), a total of 341 OS events are required to have 87% power at a 1-sided overall 2.5% level of significance to reject the null hypothesis (HR = 1) using a log-rank test and a 2-look group sequential design with Lan-DeMets (O'Brien and Fleming 1979) alpha spending function to determine efficacy stopping boundary. Considering a recruitment period of 34 months at a uniform rate of 18 participants/month with a 6-month ramp-up period and 20-month minimum follow-up, approximately 530 participants were planned for randomization in a 2:1 ratio. Due to potential early censoring from Ukraine participants, approximately 600 participants will be enrolled to ensure enough number of events will be observed within reasonable follow-up time.

The primary intent of the interim analysis is to stop early for outstanding efficacy.

Table 20 presents stopping boundary at a 1-sided 2.5% level of significance based on current projection. The boundary will be recalculated at the time of interim analysis if some assumptions are violated.

Table 20: Guidelines for Decisions in Overall Survival Endpoint

	Interim Analysis		Final Analysis	
Number of events[a]	205		341	
Decision outcome	**Continue With Sponsor Blinded**	**Continue With Sponsor Unblinded**	**Futility**	**Efficacy**
One-sided p-value	> 0.004	< 0.004	> 0.024	≤ 0.024
Estimated hazard rate reduction	< 32.7%	> 32.7%	< 20.4%	≥ 20.4%
Estimated median improvement (month)	< 6.8	> 6.8	< 3.6	≥ 3.6

Note: Estimates are based on randomized participants and on original exponential assumptions in which median OS is 14 months on control and 20 months on INCMGA00012 with the analysis. Enrollment is projected as 18 participants per month.

[a] Total number of events in participants from both control and INCMGA00012 arms.

Preplanned analyses of safety and efficacy will be provided to an eDMC as specified in the eDMC Charter. See Section 5.5 for details on the eDMC role, their review of data, eDMC meetings, and composition.

The SAP will describe all planned analyses and safety data reviews in greater detail.

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.
- 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 approval from both health authorities and the IRB/IEC before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
  - Providing oversight of the conduct of the study at the site and adherence to GCP, IRB/IEC requirements, institutional requirements, and applicable laws and country-specific regulations.
- Adhering to the Protocol as described in this document and agreeing that changes to the Protocol procedures, with the exception of medical emergencies, must be discussed and approved, first, by the sponsor or its designee and, second, by the IRB/IEC. Each investigator is responsible for enrolling participants who have met the specified eligibility criteria.
- Retaining records in accordance with all local, national, and regulatory laws but for a minimum period of at least 2 years after the last marketing application approval in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or if not approved, 2 years after the termination of the test article for investigation to ensure the availability of study documentation should it become necessary for the sponsor or a regulatory authority to review.
  - The investigator must not destroy any records associated with the study 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.

11.1.1. Identification of the Coordinating Principal Investigator

A coordinating principal investigator will be appointed by the sponsor before the end of the study. As part of their 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, or study charters, or [redacted] 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, [redacted] data, photographs, diary data), or as otherwise specified in the Protocol.

- Maintaining adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial 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 trial necessary for the reconstruction and evaluation of the trial. 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 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 trial).
  - 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.
  - As required by privacy and data protection regulations and Incyte's privacy policies, if any photographs of participants are to be taken, the photographs must be limited to the area of the face or the body that is strictly necessary and the photographs should be masked (ie, identifying features such as eyes, mouth, scars, tattoos, or unique markings or features should be either obscured with a black bar or digitally pixelated so as to not permit the reidentification of the participants and preserve their confidentiality) by a specially designated photography vendor prior to sending the photographs to Incyte or any other third-party vendors for analysis or further processing.

- 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 Quality Assurance

The sponsor assumes accountability for actions delegated to other individuals (eg, contract research organizations). The sponsor or designee is responsible for the data management of this study, including quality checking of the data. Further, monitoring details describing strategy, including definition of study-critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues, Protocol deviations, and monitoring techniques (eg, central, remote, or on-site monitoring) are provided in the monitoring plan or equivalent.

Quality tolerance limits will be predefined in the operational manual or equivalent to identify systematic issues that can impact participant's safety, efficacy results and analysis, and/or reliability of study results. These predefined parameters will be monitored during the study and can be adjusted during the study upon data review. Important deviations from the quality tolerance limits and remedial actions taken, including reporting to IRBs/IECs and health authorities if applicable, will be summarized in the CSR.

11.4. 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 sensitive personal information is handled in accordance with local data protection laws (including but not limited to HIPAA and GDPR) as applicable, and the sponsor operates comprehensive data privacy and data security programs that are applicable to this study. Appropriate notice, or notice and consent (as may be required by each applicable jurisdiction),

for collection, use, disclosure, and/or transfer (if applicable) of personal information must be obtained in accordance with local data protection laws. Appropriate data protection terms that comply with applicable laws will be included in relevant study agreements.

To ensure confidentiality of records and protect personal data, participant names will not be supplied to the sponsor or its designee. Only the participant number will be recorded in the eCRF; if the participant's name appears on any other document (eg, laboratory report), it must be obliterated on the copy of the document to be supplied to the sponsor or its designee. Study findings stored on a computer will be stored in accordance with appropriate technical and organizational measures as required by local data protection laws.

Biological samples will be stored under secured conditions (ie, locked with limited access by authorized individuals at a laboratory facility designated by the sponsor) for up to 10 years from the first clinical study report publication. After this storage period, remaining samples will be destroyed according to most recent biospecimen guidance at that facility. Only researchers at the study site or a laboratory designated by the sponsor will have access to and use of biological samples. [redacted]

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.

11.5. 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.

11.6. 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.

11.7. Compliance With Trial Registration and Results Posting Requirements

The sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to clinicaltrials.gov, clinicaltrialsregister.eu, or other local and/or national registries. The results of the study endpoints will be posted for the public and participants in national and local clinical trial registries such as clinicaltrials.gov as per current requirements and format from registries. Information posted will allow participants to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information. These websites will not include information that can identify participants. [redacted]

11.8. Study and Site Closure

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

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

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

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

12. REFERENCES

[redacted]

American Society of Clinical Oncology. The state of cancer care in America, 2017: a report by the American Society of Clinical Oncology. J Oncol Pract 2017;13:e353-e394.

American Society of Clinical Oncology. COVID-19 vaccines & patients with cancer. Accessed December 7, 2021. https://www.asco.org/covid-resources/vaccines-patients-cancer

Bai S, Jorga K, Xin Y, et al. A guide to rational dosing of monoclonal antibodies. Clin Pharmacokinet 2012;51:119-135.

[redacted]

Borghaei H, Hellmann MD, Paz-Ares LG, et al. Nivolumab (nivo) + platinum-doublet chemotherapy (chemo) vs chemo as first-line (1L) treatment (Tx) for advanced non-small cell lung cancer (NSCLC) with <1% tumor PD-L1 expression: results from CheckMate 227. J Clin Oncol 2018;36:9001.

Borghaei H, Langer CJ, Gadgeel S, et al. 24-month overall survival from KEYNOTE-021 cohort G: pemetrexed and carboplatin with or without pembrolizumab as first-line therapy for advanced nonsquamous non-small cell lung cancer. J Thorac Oncol 2019;14:124-129.

Chen X, Wang P, Kaul S, Sumrow B, Yeleswaram S. Assessment of flat dosing strategy for INCMGA00012 in patients with advanced tumors. Presented at: AACR Annual Meeting 2019; March 29-April 3, 2019; Atlanta, GA. Abstract LB268.

Clinical Trials Facilitation and Coordination Group. Recommendations related to contraception and pregnancy testing in clinical trials. 2014.

Clinical Trials Facilitation and Coordination Group. Recommendations related to contraception and pregnancy testing in clinical trials. 2020.

Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16:31–41.

Cohn BA, Cirillo PM, Murphy CC, Krigbaum NY, Wallace AW. SARS-CoV-2 vaccine protection and deaths among US veterans during 2021 [published online ahead of print November 4, 2021]. Science. doi: 10.1126/science.abm0620.

Condamine T, Owens S, Feldman P, et al. Pharmacodynamic correlates in a Phase I study of INCMGA00012, a PD-1 antagonistic monoclonal antibody. Presented at: AACR Annual Meeting 2019; March 29-April 3, 2019; Atlanta, GA. Abstract CT085.

Curigliano G, Banerjee S, Cervantes A, et al. Managing cancer patients during the COVID-19 pandemic: an ESMO multidisciplinary expert consensus. Ann Oncol 2020;31:1320-1335.

da Veiga CRP, da Veiga CP, Drummond-Lage AP. Concern over cost of and access to cancer treatments: a meta-narrative review of nivolumab and pembrolizumab studies. Crit Rev Oncol Hematol 2018:129:133-145.

Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45:228-247.

European Medicines Agency: Appendix 1 to the guideline on the evaluation of anticancer medicinal products in man - Methodological consideration for using progression-free survival (PFS) or disease-free survival (DFS) in confirmatory trials. 2012.

European Medicines Agency. Points to consider on implications of Coronavirus disease (COVID-19) on methodological aspects of ongoing clinical trials. 2020.

European Medicines Agency. Guidance on the Management of Clinical Trials During the COVID-19 (Coronavirus) Pandemic. 2021.

European Medicines Agency. Points to consider on the impact of the war in Ukraine on methodological aspects of ongoing clinical trials. 2022.

European Society of Medical Oncology. ESMO statements for vaccination against COVID-19 in patients with cancer. Accessed December 7, 2021. https://www.esmo.org/covid-19-and-cancer/covid-19-vaccination

Food and Drug Administration. Guidance for Industry: Clinical Trial Endpoints for the Approval of Non–Small Cell Lung Cancer Drugs and Biologics. 2015. https://www.fda.gov/media/116860/download. Accessed November 8, 2019.

Freshwater T, Kondic A, Ahamadi M, et al. Evaluation of dosing strategy for pembrolizumab for oncology indications. J Immunother Cancer 2017;5:43.

Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. N Engl J Med 2018;378:2078-2092.

Goldman JD, Gonzalez MA, Rüthrich MM, Sharon E, von Lilienfeld-Toal M. COVID-19 and cancer: special considerations for patients receiving immunotherapy and immunosuppressive cancer therapies. Am Soc Clin Oncol Educ Book 2022;42:176-188.

Haanen JBAG, Carbonnel F, Robert C, et al. Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up [published correction appears in Ann Oncol. 2018 Oct 1;29(Suppl 4):iv264-iv266]. Ann Oncol 2017;28(suppl 4):iv119-iv142.

Hellmann MD, Paz-Ares L, Bernabe Caro R, et al. Nivolumab plus ipilimumab in advanced non–small-cell lung cancer [published online ahead of print September 28, 2019]. N Engl J Med. doi: 10.1056/NEJMoa1910231.

Herbst RS, Baas P, Kim DW, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. Lancet 2016;387:1540-1550.

Horn L, Whisenant J, Torri V, et al. Thoracic Cancers International COVID-19 Collaboration (TERAVOLT): impact of type of cancer therapy and COVID therapy on survival. J Clin Oncol 2020;39(suppl 18):Abstract LBA111.

INCMGA00012 Investigator's Brochure. Wilmington, DE: Incyte Corporation.

Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin 2011;61:69-90.

Jotte RM, Cappuzzo F, Vynnychenko I, et al. IMpower131: primary PFS and safety analysis of a randomized Phase III study of atezolizumab + carboplatin + paclitaxel or nab-paclitaxel vs carboplatin + nab-paclitaxel as 1L therapy in advanced squamous NSCLC. J Clin Oncol 2018;36(suppl):LBA9000.

Lakhani N, Mehnert JM, Rasco D, et al. A Phase 1 study of the safety, tolerability, and pharmacokinetics (PK) of MGA012 (anti-PD-1 antibody) in patients with advanced solid tumors. Poster presented at: 32nd Annual Meeting of the Society for Immunotherapy of Cancer; November 8-12, 2017; National Harbor, MD. Abstract P249.

Lee LY, Cazier JB, Angelis V, et al. COVID-19 mortality in patients with cancer on chemotherapy or other anticancer treatments: a prospective cohort study. Lancet 2020;395:1919-1926.

Lisberg A, Cummings A, Goldman JW, et al. A phase II study of pembrolizumab in EGFR-mutant, PD-L1+, tyrosine kinase inhibitor naïve patients with advanced NSCLC. J Thorac Oncol 2018;13:1138-1145.

Malek AE, Cornejo PP, Daoud N, Alam M. The mRNA COVID-19 vaccine in patients with cancer receiving checkpoint inhibitor therapy: what we know and what we don't [published online ahead of print November 8, 2021]. Immunotherapy. doi:10.2217/imt-2021-0235.

Mandala M, Lorigan P, De Luca M, et al. SARS-CoV-2 infection and adverse events in patients with cancer receiving immune checkpoint inhibitors: an observational prospective study. J Immunother Cancer 2021;9:e001694.

Maurer W, Bretz F. Multiple testing in group sequential trials using graphical approaches. Stat Biopharm Res 2013;5:311-320.

Mehnert J, Joshua A, Lakhani N, et al. First-in-human Phase 1 study of INCMGA00012 in patients with advanced solid tumors: interim results of the cohort expansion phase. Presented at: 33rd Annual Meeting of the Society for Immunotherapy of Cancer; November 7-11, 2018; Washington, DC. Abstract P669.

Mehnert JJ, Paz-Ares L, Pikiel J, et al. A Phase 1 study of INCMGA00012, a PD-1 inhibitor, in patients with advanced solid tumors: preliminary results for patients with advanced cervical cancer (POD1UM-101). Presented at the 34th Annual Meeting of The Society for Immunotherapy of Cancer. November 6-10, 2019; National Harbor, MD. Abstract P394.

Mok TSK, Wu, YL, Kudaba I, et al. Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, Phase 3 trial. Lancet 2019;393:1819-1830.

National Cancer Institute. Surveillance, Epidemiology, and End Results (SEER) Program. Cancer Stat Facts: Lung and Bronchus Cancer. 2019.

National Comprehensive Care Network. National Comprehensive Cancer Network Guidelines in Oncology: Non-Small Cell Lung Cancer Version 3.2019. 2019.

National Comprehensive Care Network. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology: Management of Immunotherapy Related Toxicities Version 3.2021. 2021a.

National Comprehensive Care Network. NCCN: Cancer and COVID-19 Vaccination. Recommendations of the National Comprehensive Cancer Network (NCCN) COVID-19 Vaccination Advisory Committee. Version 4.0. 2021b.

O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. Biometrics 1979;35:549-556.

Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649-655.

Passaro A, Bestvina C, Velez Velez M, Garassino MC, Garon E, Peters S. Severity of COVID-19 in patients with lung cancer: evidence and challenges. J Immunother Cancer 2021;9:e002266.

Paz-Ares L, Luft A, Vicente D, et al. Pembrolizumab plus chemotherapy for squamous non-small-cell lung cancer. N Engl J Med 2018;379:2040-2051.

Peters S, Gettinger S, Johnson ML, et al. Phase II trial of atezolizumab as first-line or subsequent therapy for patients with programmed death-ligand 1-selected advanced non–small-cell lung cancer (BIRCH). J Clin Oncol 2017;35:2781-2789.

Planchard D, Popat S, Kerr K, et al. Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2019;30:863-870.

Postmus PE, Kerr KM, Oudkerk M, et al. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2017;28(supp4):iv1-iv21.

Reck M, Rodríguez-Abreu D, Robinson AG, et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. N Engl J Med 2016;375:1823-1833.

Ribas A, Sengupta R, Locke T, et al. Priority COVID-19 vaccination for patients with cancer while vaccine supply is limited. Cancer Discov 2021;11:233-236.

Rolia F, Molassiotis A, Herrstedt J, et al. 2016 MASCC and ESMO guideline update for the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting and of nausea and vomiting in advanced cancer patients. Ann Oncol 2016;27(suppl5):v119-v133.

Schmid P, Adams S, Rugo HS, et al. Atezolizumab and nab-paclitaxel in advanced triple-negative breast cancer. N Engl J Med 2018;379:2108-2121.

Schneider BJ, Naidoo J, Santomasso BD, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: ASCO guideline update [published online ahead of print November 1, 2021]. J Clin Oncol. doi:10.1200/JCO.21.01440.

Seymour L, Bogaerts J, Perrone A, et al. iRECIST: guidelines for response criteria for use in trail testing immunotherapeutics. Lancet Oncol 2017;18:e143-e152.

Sharafeldin N, Bates B, Song Q, et al. Outcomes of Covid-19 in patients with cancer: report from the National COVID Cohort Collaborative (N3C). J Clin Oncol 2021;39:2232-2246.

Smith TJ, Bohle K, Lyman GH, et al. Recommendations for the use of WBC growth factors: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol 2015;33: 3199-3212.

Society for Immunotherapy of Cancer. SITC Statement on SARS-CoV-2 Vaccination and Cancer Immunotherapy. Accessed December 7, 2021. https://www.sitcancer.org/aboutsitc/press-releases/2020/sitc-statement-sars-cov-2-vaccination-cancer-immunotherapy

Socinski MA, Jotte RM, Cappuzzo F, et al. Atezolizumab for first-line treatment of metastatic nonsquamous NSCLC. N Engl J Med 2018;378:2288-2301.

Song P, Zhang D, Cui X, Zhang L. Meta-analysis of immune-related adverse events of immune checkpoint inhibitor therapy in cancer patients. Thorac Cancer 2020;11:2406-2430.

Tenforde, MW, Self WH, Adams K, et al. Association between mRNA vaccination and COVID-19 hospitalization and disease severity. JAMA 2021;326:2043-2054.

Wang DD, Zhang S, Zhao H, Men AY, Parivar K. Fixed dosing versus body size-based dosing of monoclonal antibodies in adult clinical trials. J Clin Pharmacol 2009;49:1012-1024.

APPENDIX A. IMPORTANT INFORMATION REGARDING EFFECTIVENESS OF CONTRACEPTIVE METHODS

For male participants in the study:

Male participants should use a condom from screening through 120 days after the end of systemic exposure for INCMGA00012 and 180 days after INCMGA00012 plus chemotherapy. If the male participant has a partner that is of childbearing potential, the partner should also use contraception through the same time period as noted above after the end of relevant systemic exposure. In addition, male participants must refrain from donating sperm.

Note: Males who have had a vasectomy qualify as having met the requirement for a highly effective birth control method if he has received medical assessment of the surgical success.

Contraception Requirements for Male Participants

Male participants with female partners of childbearing potential are eligible to participate if they agree to 1 of the following during the Protocol-defined time frame:

- 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. Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments/protocol-defined periods. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the participant.
- 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.
  - -The following are **not** acceptable methods of contraception:
    - Periodic abstinence (eg, calendar, symptothermal, post-ovulation methods), withdrawal (ie, coitus interruptus), spermicides only, and lactational amenorrhea method.
    - Male condom with cap, diaphragm or sponge with spermicide.
    - Male and female condom used together.

Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration.

For female participants in the study:

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

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

Woman of Childbearing Potential
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 FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with 2 FSH measurements in the postmenopausal range is required.

Note: Females on HRT 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.

[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 WOCBP study participant and that the vasectomized partner has received medical assessment of the surgical success.
[d] In the context of this guidance, sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments.
Source: Clinical Trials Facilitation and Coordination Group (2014 and 2020).

APPENDIX B. MASCC/ESMO ANTIEMETIC GUIDELINES

Dexamethasone[a]	**Dose and Schedule**	
High Risk	Acute emesis	20 mg once [12 mg when used with (fos)aprepitant or netupitant][b]
	Delayed emesis	8 mg BID for 3-4 days [8 mg once daily when used with (fos)aprepitant or netupitant]
Moderate risk	Acute emesis	8 mg once
	Delayed emesis	8 mg BID for 2-3 days (can also give the dose as 4 mg BID)
Low risk	Acute emesis	4-8 mg once

Note: Investigators may use local equivalents, and should check for most recent updates if available, at mascc.org

[a] While corticosteroids other than dexamethasone are effective antiemetics, the dose and schedule of dexamethasone coupled with its wide availability in various dose forms established it as the guideline agent of choice (Rolia et al 2016)

[b] 12 mg dose of dexamethasone is the only one tested with (fos)aprepitant/netupitant in large randomized trials.

APPENDIX C. CALCULATED CREATININE CLEARANCE

Original, Weight-Based Cockcroft and Gault Formula for Calculated CrCl for Men

For serum creatinine concentration in mg/dL:

$$\text{CrCl (mL/min)} = \frac{(140 - \text{age}^{a}) \times (\text{wt}^{b}) \times 1.0}{72 \times \text{serum creatinine (mg/dL)}}$$

For serum creatinine concentration in µmol/L:

$$\text{CrCl (mL/min)} = \frac{(140 - \text{age}^{a}) \times (\text{wt}^{b}) \times 1.0}{0.81 \times \text{serum creatinine (µmol/L)}}$$

Original, Weight-Based Cockcroft and Gault Formula for Calculated CrCl for Women

For serum creatinine concentration in mg/dL:

$$\text{CrCl (mL/min)} = \frac{(140 - \text{age}^{a}) \times (\text{wt}^{b}) \times 0.85}{72 \times \text{serum creatinine (mg/dL)}}$$

For serum creatinine concentration in µmol/L:

$$\text{CrCl (mL/min)} = \frac{(140 - \text{age}^{a}) \times (\text{wt}^{b}) \times 0.85}{0.81 \times \text{serum creatinine (µmol/L)}}$$

[a] Age in years.
[b] Weight in kilograms.
Source: Cockcroft and Gault 1976.

APPENDIX D. CLINICAL LOCAL LABORATORY TESTS

<table>
<tr><th>Blood Chemistries</th><th>Hematology</th><th>Urinalysis</th><th>Serology</th><th>Coagulation</th></tr>
<tr>
<td rowspan="2">Albumin
Alkaline phosphatase
ALT/SGPT
AST/SGOT
Amylase
Either bicarbonate or CO_2[a]
Blood urea nitrogen or urea
Calcium
Chloride
Creatinine
CrCl or GFR
Glucose
Lactate dehydrogenase
Lipase
Magnesium
Phosphate
Potassium
Sodium
Total bilirubin
Direct bilirubin (if total bilirubin is elevated above ULN)
Total protein</td>
<td rowspan="2">Complete blood count, including:
• Hemoglobin
• Hematocrit
• Platelet count
• Red blood cell count
• White blood cell count

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

Absolute values must be provided for:
• WBC differential laboratory results</td>
<td rowspan="2">• Specific gravity
• pH
• (Qualitative is allowed): glucose, protein, occult blood, ketones, bilirubin, urobilinogen, nitrite, leukocytes

Microscopic examination (if blood or protein is abnormal)</td>
<td><u>Hepatitis B tests</u>
• HBsAg
• HBV DNA
<u>Hepatitis C tests</u>
• HCV antibody
• HCV-RNA quantitative or qualitative
  • HCV antibody test alone (only) is acceptable[b] if HCV RNA test cannot be done additionally per local SOC
<u>HIV test</u>
• HIV RNA (only if required by local regulation or health authorities)</td>
<td>PT
PTT or aPTT
INR

(PTT may be performed if the local lab is unable to perform aPTT)</td>
</tr>
<tr>
<td>Endocrine Function

TSH, FT4, and T3 or FT3. Total T3 is preferred; if not available Free T3 may be tested.

SARS-CoV-2 Tests

SARS-CoV-2 tests (including types of approved tests) as per local clinical practice guidelines, standards, and/or evolving needs of the COVID-19 pandemic or variations.</td>
<td>Pregnancy Testing

Human chorionic gonadotropin</td>
</tr>
</table>

Notes: 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, tuberculosis) may be performed at any time during the study as determined necessary by the investigator or required by local regulations, or required by regions, or based on emerging safety data, or depending on the extent of COVID-19 pandemic. Amylase, lipase, and endocrine tests and other specific laboratory tests may be performed more frequently for management of irAE toxicities and can be sent for testing to the sponsor's central laboratory upon request if local site testing is not available.

[a] Perform if available as standard of care in your region (if these tests are not done as part of standard of care in your region then these tests do not need to be performed). Also, carbon dioxide may be either a measurement of CO_2 or bicarbonate as an electrolyte per institutional standard (it is not required to perform both of these laboratory tests).

[b] Both HCV antibody test and HCV-RNA tests are required to determine eligibility for Hepatitis C. In countries where HCV-RNA test cannot be done per local SOC, then HCV antibody test alone is acceptable to determine eligibility.

APPENDIX E. EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS

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

Source: Oken et al 1982.

APPENDIX F. TREATMENT AND IMAGING AFTER EVIDENCE OF PROGRESSIVE DISEASE WITH 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 in the table below. If PD is confirmed by iRECIST, participants will be discontinued from study treatment.

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 participant refusal or participant death), the initial date of unconfirmed progression will be considered the date of PD.

Table F1: Imaging and Treatment After Radiologic Evidence of Progressive Disease

	Clinically Stable		**Clinically Unstable**	
	Imaging	**Treatment**	**Imaging**	**Treatment**
Initial unconfirmed PD by RECIST v1.1 (iUPD) OR subsequent iUPD after iSD, iPR or iCR	Repeat imaging at ≥ 4 and ≤ 8 weeks to confirm PD.	May continue study treatment at the investigator's discretion while awaiting confirmatory scan.	Repeat imaging at ≥ 4 weeks and ≤ 8 weeks to confirm PD if possible.	Discontinue Treatment
Next evaluable scan confirms PD (iCPD)	No additional imaging required.	Discontinue treatment.	No additional imaging required.	Not applicable
Confirmation scan shows iUPD, iSD, iPR, or iCR[a]	Continue regularly scheduled imaging assessments every 8 weeks for the first 12 month after the start of treatment and then every 12 weeks (± 14 days) thereafter.	Continue study treatment at the investigator's discretion.	Continue regularly scheduled imaging assessments every 8 weeks for the first 12 month after the start of treatment and then every 12 weeks (± 14 days) thereafter.	May restart study treatment if condition has improved and/or is clinically stable per investigator's discretion.

[a] iSD, iPR, and iCR is based on baseline or nadir.

In determining whether the tumor burden has increased or decreased, investigators should consider all baseline and any new target lesions as well as baseline and any new nontarget lesions. Progressive disease (iCPD) is confirmed if further increase in tumor burden, compared to the last assessment, is seen as evidenced by 1 or more of the following:

- Continued increase in tumor burden (from iUPD) where RECIST v1.1 definitions of progression had been met (from nadir) in target, nontarget disease or new lesions
  - Progression in target disease worsens with an increase of at least 5 mm in the absolute value of the sum;
  - Continued unequivocal progression in nontarget disease with an increase in tumor burden;
  - Increase in size of previously identified new lesion(s) (an increase of at least 5 mm in the absolute value of the sum of those considered to be target new lesions) or additional new lesions
- RECIST v1.1 criteria are met in lesions types (target or nontarget or new lesions) where progression was not previously identified, including the appearance of additional new lesions.

If iUPD is not confirmed at the next assessment, then the appropriate response will be assigned (iUPD if the criteria are still met, but no worsening, or iSD, iPR, or iCR if those criteria are met compared to baseline). As can be seen in Table F1, the prior documentation of iUPD does not preclude assigning iCR, iPR, or iSD in subsequent timepoint assessments or as best overall response providing that iCPD is not documented at the next assessment after iUPD.

Source: Seymour et al 2017.

APPENDIX G. 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's 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 very dynamic nature of COVID-19 pandemic and flexibility required to manage the impact of the pandemic on ongoing clinical studies, clarifications specific to allowed ancillary local (country) medical tests, and/or additions may need to be added into 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 2.2.5.1.

Recommendations for COVID-19 Vaccination

If performed during the study, the guidelines of SARS-CoV-2 vaccination, timing, and precautions are listed below:

- Prophylactic vaccination with an approved vaccine against SARS-CoV-2 is not a study requirement (see Section 5.1). Participants may complete the vaccination process during the study. A "booster" vaccination dose if needed during the study is also acceptable.
- If given, 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.
- If given, the vaccination primary dose or doses, or boosters and manufacturer 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 the 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 $\leq$ 10 mg of prednisone equivalent.
- Any AEs resulting from the vaccination and medications for treating the AEs must be entered in the eCRFs.
- If a potential participant recovered from COVID-19 within approximately 6 months before signing the ICF, a negative test (PCR) may be performed.

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 8.7.6) and must be reviewed before dosing. During COVID-19 pandemic restrictions, when permissible as per national regulations*, 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.

  *Note: This clarification (see also Section 6.6.1 and Section 8.1.6) is for countries, for example, Bulgaria, that do not allow visits at a clinic, local medical laboratory, or hospital outside of the approved study site for procedures and tests in the Protocol sections referenced above. However, in Bulgaria, it is possible, if needed, to use the closest medical center or a medical laboratory for laboratory testing and ECGs. Procedures such as imaging and chest x-ray, for example, to supplement and monitor a COVID-19 diagnosis are not permissible at a local hospital outside the approved study site. Applicable minor modifications to the ICF under the COVID-19 subheading were consequently made to the Bulgarian ICF. Similar scenarios or information found or released for other countries will be managed outside the Protocol, including but not limited to changes to the study manual, by Dear Investigator Letter, and updates to ICFs.
- In order to minimize a participant's 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 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 drug/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 3, 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 (testing 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 study treatment, the participant should be afebrile for 72 hours and SARS-CoV2-related symptoms (if any) should have recovered 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 the 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 information on 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 H. PROTOCOL AMENDMENT SUMMARY OF CHANGES

Document	Date
Amendment 1	16 DEC 2021
Amendment 2	16 MAY 2022
Amendment 3	18 OCT 2022

Amendment 3 (18 OCT 2022)

Overall Rationale for the Amendment

The primary purpose of the amendment is to align with the US FDA's recommendation that OS should be the only primary endpoint in the study and to update COVID-19 guidance in view of the evolving pandemic. Additional changes are summarized below.

1. **Section 1, Protocol Summary (Table 1: Primary and Secondary Objectives and Endpoints; Table 2: Key Study Design Elements); Section 2.2.2, Scientific Rationale for Study Design; Section 3, Objectives and Endpoints (Table 6: Objectives and Endpoints); Section 4.1, Overall Design; Section 5.5, External Data Monitoring Committee; Section 10.1, Sample Size Determination; Section 10.2, Populations for Analysis (Table 17: Populations for Analysis); Section 10.3, Level of Significance; Section 10.4.1, Primary Analysis; Section 10.4.1.1, Multiplicity Adjustment (Figure 2: Multiplicity Graph for Type I Error Control); Section 10.4.3.1, Progression-Free Survival (Table 18: Evaluation and Censoring of Progression-Free Survival); Section 10.5, Interim Analysis (Table 20: Guidelines for Decisions in Overall Survival Endpoint)**

   Description of change: The dual primary objective of OS and PFS was changed to just OS. Progression-free survival was converted to a secondary objective. Consequently, for OS analysis, the same target of 341 OS events will provide 87% (from 85%) power to detect an HR of 0.7 at a 1-sided 2.5% (from 2.0%) significance level, and for PFS analysis, a target of 222 (from 314) PFS events will provide the same 90% power to detect an HR of 0.63 at a 1-sided 2.5% (from 0.5%) significance level.

   Rationale for change: Based on a recommendation made by the US FDA due to 2 considerations: 1) recent approvals granted by the FDA to first-line immunotherapy for metastatic lung cancer were based on statistically significant and formally tested improvements in OS and 2) due to the unclear impact on the analysis of PFS as a primary dual endpoint caused by disruptions in data collection and monitoring during the Ukrainian and Russian conflict.

2. **Section 1, Protocol Summary (Table 3: Schedule of Activities for Participants With Nonsquamous Non–Small Cell Lung Cancer); Section 2.2.5.1, Benefit/Risk Assessment During the COVID-19 Pandemic; Section 5.1, Inclusion Criteria (Criterion 11); Section 8.1.6, COVID-19; Appendix G, COVID-19 Pandemic Guidance**

   Description of change: An updated reference was added demonstrating that immunotherapy does not negatively affect participants with cancer who are SARS-CoV-2–positive. Participants' vaccination against SARS-CoV-2 was changed from mandatory to highly recommended. Local and/or country guidelines as available are recommended to be followed for primary vaccination and/or boosters. Potential participants are to be apprised with up-to-date information according to their country's vaccination program, local vaccination recommendations, or oncology societies' guidelines, as assessed by the investigator.

   Rationale for change: To continue to provide a balanced view with current studies on a positive benefit/risk assessment during the COVID-19 pandemic or endemic or its variants, and to show cancer immunotherapy with immune checkpoint inhibitors such as the one provided in this study does not confer additional mortality risks in the setting of active COVID-19. In view of the waxing and waning regional incidences of COVID-19, flexibility has been added to allow enrollment of participants who are not willing to receive vaccination and/or who have a contraindication to vaccination. Additionally, the recommendation will provide flexibility for participant management in regions where COVID-19 is no longer endemic.

3. **Section 7.1.1, Reasons for Discontinuation; Section 7.3, Lost to Follow-Up; Section 8.12.3, Survival Follow-Up**

   Description of change: Before a participant is deemed lost to follow-up multiple (ie, at least 2) documented efforts must be made to regain contact unless participants have permanently withdrawn their consent for follow-up.

   Rationale for change: Addition made since OS is the primary objective and to minimize loss to follow up.

4. **Section 10.2, Populations for Analysis (Table 17: Populations for Analysis); Section 10.4.1, Primary Analysis**

   Description of change: The FAS description was reverted to the original population for analysis with the following removed: For participants from Ukraine, all data will be censored by approximately 20 DEC 2021 due to potential concerns of not having critical data variables source verified.

   Rationale of change: The primary analysis of a primary endpoint in a randomized study is based on the ITT principle as per regulatory guidelines; therefore, the originally defined FAS that includes all randomized participants is maintained. As per the FDA's recommendation to the sponsor, the potential impact due to the Ukrainian and Russian conflict (eg, wartime disruption) will be evaluated through sensitivity analyses as described in the SAP.

5. **Appendix G, COVID-19 Pandemic Guidance**

   Description of change: Added note that visits at a clinic, local medical laboratory, or hospital outside of the approved study site for procedures and tests related to COVID-19 are not permissible for the conduct of the study in Bulgaria. Applicable minor modifications to the ICF under the COVID-19 subheading were consequently made.

   Rationale for change: As per clarification that was requested by the Bulgarian Drug Agency on 22 MAR 2022.

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

Amendment 2 (16 MAY 2022)

Overall Rationale for the Amendment:

The primary purpose of the amendment is to update the number of participants from approximately 530 to approximately 600. Ukraine has randomized 160 participants in the study. Participants' care and study operations have been partially or completely disrupted in many Ukrainian cities, and the overall impact cannot be determined with any degree of certainty at this time. The sponsor anticipates that many participants will be prematurely withdrawn or otherwise lost to follow-up prior to reaching the primary efficacy endpoints of PFS and OS, although an exact rate of attrition cannot be estimated from the available information. Additional changes are summarized below.

1. **Sections 1, Protocol Summary (Table 2: Key Study Design Elements); Section 4.1, Overall Design; Section 4.2, Number of Participants; Section 10.1, Sample Size Determination; Section 10.5, Interim Analysis**

   Description of change: An increase in study enrollment from approximately 530 participants to approximately 600 participants.

   Rationale for change: This increase in the number of participants does not change the number of target events for the PFS or OS endpoints in order to compensate for participants lost to follow-up or with less follow-up time than was anticipated due to conflict and national operational disruptions in Ukraine. Further, this increase is to ensure study integrity and that the study will provide interpretable findings to support a marketing application.

2. **Section 4.3, Overall Study Duration**

   Description of change: Added that in 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 EU). This will ensure the results are robust, meaningful, and representative of all multiregions by having complete follow-up data determined by the statistical hypotheses for the objectives established.

3. **Section 10.1, Sample Size Determination; Section 10.4.1, Primary Analysis; Section 10.5 Interim Analysis**

   Description of change: Added high-level description of sensitivity analysis for dual primary efficacy endpoints of PFS and OS (due to potential early censoring from Ukrainian participants, approximately 600 participants will be enrolled to ensure enough number of events will be observed within reasonable follow-up time).

   Rationale for change: Due to conflict and country organizational disruptions related issues in Ukraine, these changes are to ensure study integrity and to provide interpretable findings.

4. **Section 10.2, Population for Analysis (Table 17: Populations for Analysis)**

   Description of change: Updated definition of FAS to also include censored data for participants from Ukraine; all data will be censored by approximately 20 DEC 2021 due to potential concerns of not having critical data variables source-verified from that date forward.

   Rationale for change: Due to conflict and country organizational disruptions related issues in Ukraine, these changes are to ensure study integrity and to provide interpretable findings.

5. **Section 10.4.2, Subgroup Analyses**

   Description of change: Updated subgroup categories for age and ethnic group and added subgroup analysis by country enrollment.

   Rationale for change: Due to conflict and country organizational disruptions related issues in Ukraine, these changes are to ensure study integrity and to provide interpretable findings.

6. **Appendix G, COVID-19 Pandemic Guidance**

   Description of change: Corrected typographical error for type of a particular SARS-CoV-2 test and added that local (country) practices or regulations may dictate what may be able to be done at local hospitals outside the main investigational site as an ancillary diagnostic or supportive test, if needed, during the COVID-19 pandemic or regional resurges.

   Rationale for change: Editorial and minor clarification. Depending on the country, not all types of tests and/or procedures may be able or allowed to be performed at local hospitals, and proper planning is first warranted.

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

Amendment 1 (16 DEC 2021)

Overall Rationale for the Amendment:

The primary purpose of Amendment 1 is to update the management of suspected irAEs, incorporate changes requested by regulatory authorities, and provide guidance for participant management during the COVID-19 pandemic.

1. **Section 1, Protocol Summary (Table 3: Schedule of Activities for Participants With Nonsquamous Non-Small Cell Lung Cancer; Table 4: Schedule of Activities for Participants With Squamous Non-Small Cell Lung Cancer); Section 8.3.3, Tumor Imaging During the Study**

   Description of change: Added a note that the first on-study image will be performed at 6 weeks (± 7 days). Clarification regarding the imaging schedule was also provided in Section 8.3.3.

   Rationale for change: Clarification.

2. **Section 1, Protocol Summary (Table 3: Schedule of Activities for Participants With Nonsquamous Non-Small Cell Lung Cancer); Section 5.1, Inclusion Criteria (Criterion 11); Section 6.6.1, Permitted Medications and Procedures; Section 8.1.6, COVID-19**

   Description of change: Inclusion criterion was added to indicate that potential participants with NSCLC are to be fully vaccinated against SARS-CoV-2 before randomization or willing and able to be fully vaccinated during the study by starting the vaccination process during screening. SARS-CoV-2 vaccines and applicable ancillary procedures and tests were added to the list of permitted medications and procedures.

   Rationale for change: Due to expanding protection for potential participants in a research study, and as per recommendations by the main international worldwide oncology societies (eg, ASCO, ESMO), this new requirement was added as a safety precaution.

3. **Section 1, Protocol Summary (Table 4: Schedule of Activities for Participants With Squamous Non-Small Cell Lung Cancer)**

   Description of change: Added notes that Cycle 1 Day 8 and Cycle 1 Day 15 blood chemistries and hematology are applicable only to participants receiving nab-paclitaxel. Also, a note was added to indicate that the on-treatment pregnancy testing required at each cycle starts at Cycle 2 Day 1.

   Rationale for change: Clarification.

4. **Section 1, Protocol Summary (Table 4: Schedule of Activities for Participants With Squamous Non-Small Cell Lung Cancer)**

   Description of change: Removed the Cycle 1 Day 8 timepoint for PK [redacted] assessments.

   Rationale for change: To correct a typographical error and align with the sample timing presented in Table 16.

5. **Section 2.2.5.1, Benefit/Risk Assessment During the COVID-19 Pandemic; Appendix G, COVID-19 Pandemic Guidance**

   Description of change: New section was added to describe the sponsor's 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 study objectives in the context of the global COVID-19 pandemic.

   Rationale for change: To provide additional guidance to the investigators. This guidance is in line with regulatory guidance regarding clinical study execution during the pandemic.

6. **Section 4.3, Overall Study Duration**

   Description of change: Added clarification regarding treatment options for participants if the final analysis of OS is negative.

   Rationale for change: Requested by the EU health authorities.

7. **Section 5.1, Inclusion Criteria (Criterion 4)**

   Description of change: A note was added to clarify that only participants without access to the best standard treatment options can be included in the study and may discontinue study treatment if those options become available. This information was already fully described in the ICF.

   Rationale for change: Requested by the EU health authorities.

8. **Section 5.2, Exclusion Criteria (Criterion 9); Section 8.1.6, COVID-19; Appendix D, Clinical Local Laboratory Tests**

   Description of change: A note was added to indicate that participants may be tested for COVID-19 if required by country or local regulations, and 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.

9. **Section 5.2, Exclusion Criteria (Criterion 12)**

   Description of change: A note was added to specify that HIV testing is required in Czech Republic and South Africa.

   Rationale for change: To reflect known local regulatory requirements.

10. **Section 5.2, Exclusion Criteria, (Criterion 13)**

    Description of change: The note was updated to indicate that the 3-year time requirement of no evidence of disease prior to study participation is not required for noninvasive or indolent malignancies.

    Rationale for change: Clarification.

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

    Description of change: Added powder for infusion under pemetrexed.

    Rationale for change: To reflect both dose formulations available during the study.

12. **Section 6.1.1.1, INCMGA00012/Placebo**

    Description of change: Text was added to indicate that for the first 4 cycles, participants will be observed in the clinic for several hours after the infusion of INCMGA00012/placebo and chemotherapy administration.

    Rationale for change: Requested by the EU health authorities.

13. **Section 6.3, Measures to Minimize Bias: Randomization and Blinding**

    Description of change: An unblinded sponsor statistician will not be used to provide summary aggregated data by treatment group to the sponsor and/or the eDMC. An external/independent statistician who is not part of the study team or the sponsor will be utilized. Details are described in the in the eDMC charter.

    Rationale for change: Requested by the US FDA to avoid inadvertent unblinding of the study.

14. **Section 6.5.1, Dose Modifications for Immune-Related Toxicity (Table 9: Dose Modifications for Adverse Events of INCMGA00012/Placebo and Toxicity Management Guidelines for Immune-Related Adverse Events)**

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

    Rationale for change: To align with updated information available for irAEs known to be associated with INCMGA00012 and other PD-1 inhibitors (eg, pembrolizumab, nivolumab).

15. **Section 6.5.1.1, Guidelines for Management of Suspected Infusion Reactions (Table 10: Guidelines for Management of Suspected Infusion Reactions)**

    Description of change: The guidance for Grade 1 infusion reactions was revised to interrupt or slow the rate of infusion and to indicate when prophylaxis with an antipyretic and histamine blocker for subsequent cycles of INCMGA00012 or placebo administration are recommended. Clarification was also provided on guidance for subsequent infusions after Grade 3 or 4 infusion reactions with rapid response to intervention.

    Rationale for change: For clarification and to align with guidance based on the most recent information available for INCMGA00012 and other PD-1 inhibitors (eg, pembrolizumab, nivolumab) and with CTCAE v5.0.

16. **Section 8.1.2, Screening Procedures**

    Description of change: Wording regarding active HBV was clarified to match existing exclusion criteria.

    Rationale for change: Clarification.

17. **Section 8.7.6, Laboratory Assessments**

    Description of change: Information was added regarding tuberculosis testing and potentially delayed test results for amylase/lipase.

    Rationale for change: Clarification requested by South Africa's health authority; and to provide guidance in a situation in which regional specific laboratory test results may be delayed as part of local standard.

18. **Section 9.4, Reporting of Serious Adverse Events**

    Description of change: Text, while known to investigators and site staff before the first participant was randomized, was added to clarify that SAE reporting is via EDC as the primary avenue. Paper reporting is only when the EDC (ie, the clinical database) system may be temporarily down.

    Rationale for change: Added for clarification only.

19. **Section 10.4.1.1, Multiplicity Adjustment (Figure 2: Multiplicity Graph for Type I Error Control)**

    Description of change: Footnote was corrected to indicate ORR instead of OS.

    Rationale for change: Typographical error; requested by the EU health authorities.

20. **Section 10.5, Interim Analysis (Table 20: Guidelines for Decisions in Overall Survival Endpoint)**

    Description of change: The decision outcomes for the interim analysis were clarified to match existing text from overall section.

    Rationale for change: Clarification requested by the EU health authorities.

21. **Appendix D, Clinical Local Laboratory Tests**

    Description of change: Amylase was added to the blood chemistry test panel to occur more frequently, and the footnote was clarified such that amylase, lipase, endocrine, and other specific laboratory tests may be performed more frequently for the management of irAE toxicities.

    Text was also added to indicate both HCV RNA and HCV antibody tests are required to determine eligibility as previously indicated in other sections, but for countries in which HCV RNA testing cannot be done per SOC, an HCV antibody test is acceptable.

    Rationale for change: The addition of the amylase test was based on feedback by the EU health authorities. Changes regarding HCV testing were for clarification only.

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

Signature Page for VV-CLIN-001051 v4.0

Approval Task	[redacted] Approver [redacted]
Approval Task	[redacted] Document Preparer [redacted]
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