Official Title: A Phase 1-2 Study of Combination Therapy With INCMGA00012 (Anti–PD-1), INCAGN02385 (Anti–LAG-3), and INCAGN02390 (Anti–TIM-3) in Participants With Select Advanced Malignancies

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Clinical Study Protocol

INCAGN 2385-201

A Phase 1-2 Study of Combination Therapy With INCMGA00012 (Anti–PD-1), INCAGN02385 (Anti–LAG-3), and INCAGN02390 (Anti–TIM-3) in Participants With Select Advanced Malignancies

Product:	**INCAGN02385; INCAGN02390; INCMGA00012**
IND Number:	**147,539**
Phase of Study:	**Phase 1-2**
Sponsor:	**Incyte Biosciences International Sàrl** **Route de la Corniche 1** **1066 Epalinges, Switzerland**
Original Protocol:	**27 FEB 2020**
Amendment 1:	**07 APR 2020**
Amendment 2:	**02 JUN 2021**
Amendment 3:	**12 MAY 2022**
Amendment 4:	**02 MAR 2023**

INVESTIGATOR'S AGREEMENT

I have read the INCAGN 2385-201 Protocol Amendment 4 (dated 02 MAR 2023) 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
ACTH	adrenocorticotropic hormone
ADA	antidrug antibody
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activate partial thromboplastin time
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the steady-state plasma or serum concentration
$AUC_{0-\infty}$	area under the single-dose plasma or serum concentration-time curve extrapolated to time of infinity
AUC_{0-t}	area under the plasma or serum concentration-time curve from time = 0 to the last measurable concentration at time = t
BOIN	Bayesian optimal interval
cfDNA	circulating free deoxyribonucleic acid
CFR	Code of Federal Regulations
CL	total systemic clearance
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 steady-state plasma or serum concentration over the dose interval
CNS	central nervous system
COVID-19	coronavirus disease 2019
CPI	checkpoint inhibitor(s)
CR	complete response
CrCl	creatinine clearance
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DCR	disease control rate
DLT	dose-limiting toxicity
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group

Abbreviations and Special Terms	Definition
eCRF	electronic case report form
EDC	electronic data capture
EOI	end of infusion
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30
EOT	end of treatment
EQ-5D-5L	Descriptive system of health-related quality of life states consisting of 5 dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression), each of which can take one of 5 responses
ESMO	European Society for Medical Oncology
ET	early termination
FACT-G	Functional Assessment of Cancer Therapy – General
FACT-M	Functional Assessment of Cancer Therapy – Melanoma
FAS	full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HDL	high-density lipoprotein
HIPAA	Health Insurance Portability and Accountability Act of 1996
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICI	immune checkpoint inhibitor
iCPD	immune confirmed progressive disease
iCR	immune complete response
IEC	independent ethics committee
INR	international normalized ratio
iPR	immune partial response
irAE	immune-related adverse event
IRB	institutional review board

Abbreviations and Special Terms	Definition
iRECIST	immune Response Evaluation Criteria in Solid Tumors
IRT	interactive response technology
iSD	immune stable disease
iUPD	immune unconfirmed progressive disease
LAG-3	lymphocyte-activation gene 3
LDL	low-density lipoprotein
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NSAID	nonsteroidal anti-inflammatory drug
NSCLC	non–small cell lung cancer
ORR	objective response rate
PBMC	peripheral blood mononuclear cell
PD	progressive disease
PD-1	programmed cell death protein 1
PD-L1	programmed cell death ligand 1
PFS	progression-free survival
PK	pharmacokinetic(s)
PO	orally
PP	per protocol
PR	partial response
PRO	patient reported outcome
PT	prothrombin time
PTT	prothromboplastin time
Q2W	once every 2 weeks
Q3W	once every 3 weeks
Q4W	once every 4 weeks
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
RO	receptor occupancy
RP2D	recommended Phase 2 dose
RSI	Reference Safety Information
SAE	serious adverse event

Abbreviations and Special Terms	Definition
SARS-CoV2	severe acute respiratory syndrome coronavirus 2
SD	stable disease
SJS	Stevens-Johnson syndrome
SoA	schedule of activities
SoC	standard of care
SOP	standard operating procedure
$t_{½}$	apparent terminal-phase disposition half-life
TEAE	treatment-emergent adverse event, AEs reported for the first time or worsening of a pre-existing event after first dose of study treatment
TEN	toxic epidermal necrolysis
TIM-3	T-cell immunoglobulin and mucin-domain containing-3
TnI	troponin I
TnT	troponin T
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
WBC	white blood cell

1. PROTOCOL SUMMARY

Protocol Title: A Phase 1-2 Study of Combination Therapy With INCMGA00012 (Anti–PD-1), INCAGN02385 (Anti–LAG-3), and INCAGN02390 (Anti–TIM-3) in Participants With Select Advanced Malignancies

Protocol Number: INCAGN 2385-201

Objectives and Endpoints:

Table 1 presents the primary endpoints and objectives.

Table 1: Primary Objectives and Endpoints

Objectives	Endpoints
Primary	
Phase 1	
To determine RP2Ds for all study drugs to be used in the following regimens: Part 1 (Q2W): INCAGN02385 + INCAGN02390 Part 2 (Q2W): INCAGN02385 + INCAGN02390 + INCMGA00012 Part 3 (Q3W): INCAGN02385, INCAGN02390, INCAGN02385 + INCMGA00012 and INCAGN02390 + INCMGA00012 Part 4 (Q4W): INCAGN02385 + INCAGN02390 + INCMGA00012	• Safety and tolerability as assessed by monitoring the frequency and severity of AEs.
Phase 2	
To determine the preliminary efficacy of INCAGN02385 + INCAGN02390 + INCMGA00012 in Cohorts A and B. Cohort A: Participants with advanced melanoma who have progressed or relapsed on or after anti–PD-(L)1 therapy Cohort B: Participants with advanced melanoma naïve to systemic therapy (first line)	• ORR, defined as the percentage of participants having a CR or PR, will be determined by investigator assessment of radiographic disease assessments per RECIST v1.1. • DOR, defined as the time from earliest date of disease response (CR or PR) until earliest date of disease progression, will be determined by investigator assessment of radiographic disease per RECIST v1.1, or death from any cause, if occurring sooner than progression. • DCR, defined as percentage of participants having CR, PR, or SD as best on-study response. • PFS, defined as the time from date of first dose of study treatment until the earliest date of disease progression, as determined by investigator assessment of objective radiographic disease per RECIST v1.1, or death due to any cause.
To determine the safety of INCAGN02385 + INCAGN02390 + INCMGA00012.	• Safety and tolerability as assessed by monitoring the frequency and severity of AEs.

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 1-2
Clinical Indication	Advanced solid tumors
Population	Male and female participants at least 18 years of age. Phase 1: Participants with advanced malignancies who have received prior treatment with therapy directed toward PD-1/PD-L1. Phase 2: PD-1/PDL-1 refractory (Cohort A) and systemic therapy naïve (Cohort B) advanced melanoma.
Number of Participants	Approximately 146 participants will be enrolled in the study. Phase 1 will include approximately 52 participants. Phase 2 will include up to 94 participants. Dose for Phase 2 will be determined based on pharmacodynamics (including RO), safety, and preliminary efficacy in Phase 1.
Study Design	Phase 1 is an open-label, safety evaluation of INCAGN02385 and INCAGN02390 given both as monotherapy as well as combinations with INCMGA00012 at multiple doses on Q2W, Q3W, and Q4W schedules. Phase 2 is an open-label cohort expansion testing the combination of INCAGN02385 + INCAGN02390 + INCMGA00012 given on Q2W and Q3W schedules in participants with PD-(L)1 refractory (Cohort A) and systemic therapy naïve (Cohort B) advanced melanoma, respectively.
Estimated Duration of Study Participation	Individuals will participate for up to 24 months. It is estimated that average participation will be for approximately 6 months for Phase 1 and Phase 2 Cohort A and 10 months for Phase 2 Cohort B.
DMC	Yes, independent, internal DMC
Coordinating Principal Investigator	[redacted]

Treatment Groups and Duration:

This is an open-label, nonrandomized, Phase 1-2 study to determine the safety, tolerability, and preliminary efficacy of INCAGN02385 and INCAGN02390 given both as monotherapy as well as in combination with INCMGA00012 (ie, doublets and triplets) at multiple doses on Q2W, Q3W, and Q4W schedules.

- **Phase 1** is to determine safe combination doses given on various schedules. Combination doses for further study will be chosen based on safety.

[redacted]

  - **Part 1:** Part 1 will use a BOIN design and will determine whether the doses selected for further study from the respective monotherapy studies (Q2W INCAGN02385 dose is 350 mg and INCAGN02390 dose is 400 mg) are safe when used in the combination of INCAGN02385 and INCAGN02390 ($n \leq 9$). If the safety of doses tested cannot be established, then the dose level will be reduced 1 level from doses tested in monotherapy studies (ie, 250 mg Q2W for INCAGN02385 and 200 mg Q2W for INCAGN02390).
  - **Part 2:** Following confirmation of the safety of the doublet, the safety of the triple combination of INCAGN02385 (350 mg Q2W) + INCAGN02390 (400 mg Q2W) + INCMGA00012 (500 mg Q4W) will be tested ($n \leq 9$). If safety of doses tested in the triplet cannot be established, the dose levels for INCAGN02385 and INCAGN02390 will be dropped 1 level from doses tested in monotherapy studies (ie, 250 mg Q2W for INCAGN02385 and 200 mg Q2W for INCAGN02390).
  - **Part 3:** Once safety for the Q2W schedule has been established for the PD-1-free doublet (INCAGN02385 + INCAGN02390) and the triplet (INCAGN02385 + INCAGN02390 + INCMGA00012), a Q3W schedule will be evaluated in a stepwise manner.
    - Q3W schedule validation will better accommodate the combination of INCAGN02385 and INCAGN02390 with INCMGA00012 (at the established RP2D of 375 mg Q3W) and limit the number of visits for participants.
    - [redacted]
    - Two doses of INCAGN02385, 450 mg Q3W and 750 mg Q3W, will be administered to participants (n = 6 each) as monotherapy for 2 21-day cycles. Following 2 monotherapy cycles, these same participants will then remain on their current dose of INCAGN02385 and be given INCMGA00012 (375 mg Q3W) in combination. Concurrently, 2 doses of INCAGN02390, 500 mg Q3W and 1000 mg Q3W, will be administered to participants (n = 6 each) as monotherapy for 2 21-day cycles. Following 2 monotherapy cycles, these same participants will then remain on their current dose of INCAGN02390 and be given INCMGA00012 (375 mg Q3W) in combination.

- Participants in Part 3 will be evaluated for safety and occurrence of DLTs from first dose until Day 21. After 21 days, the DMC will review safety data and if the DMC determines the doses to be tolerable, will make a recommendation to the study team that Phase 2 Cohort B should be opened to evaluate the Q3W schedule of INCMGA0012 + INCAGN02385 + INCAGN02390 utilizing doses tested in Phase 1 Part 3.
- [redacted]
- Additional doses and schedules may be evaluated based on data from Phase 1 Part 3.

– **Part 4:** Q4W schedule will be evaluated as alternative schedule to accommodate future combinations with other agents of interest and in a stepwise manner. [redacted]

- **Phase 2** will further assess safety and determine preliminary efficacy for the combination of INCAGN02385 + INCAGN02390 + INCMGA00012.

– **Cohort A:** A population of participants with unresectable/metastatic or adjuvant-treated melanoma (n = 15) who progressed or relapsed on or after prior anti–PD-(L)1 therapy will receive INCAGN02385 + INCAGN02390 + INCMGA00012 Q2W at doses selected in Part 2. If a sufficient number of responses are seen (≥ 1/15 responses), the population will be expanded to include additional participants (+ n = 15) in a Simon 2-stage expansion to further evaluate safety and efficacy.

Cohort B: Following DMC review of Phase 1 Part 3, a population of participants with advanced melanoma naïve to systemic therapy (1L) will receive INCAGN02385 + INCAGN02390 + INCMGA00012 Q3W at the doses selected in Phase 1 Part 3 (n = 32 for each dose level). Initially, 14 participants will be enrolled in Cohort B. If a sufficient efficacy signal is seen (eg, ≥ 6/14 in a nonbinding analysis) in Stage 1, additional participants (+ n = 18) will be enrolled. Cohort B is designed with 1-sided $\alpha = 0.09$ with an approximate 98% power to observe at least 17 responses in the total population enrolled (N = 32) using a Bayesian predicted probability.

See Figure 1 represents the study design schema, and Table 3 and Table 6 present the SoA.

Figure 1: Study Design Schema

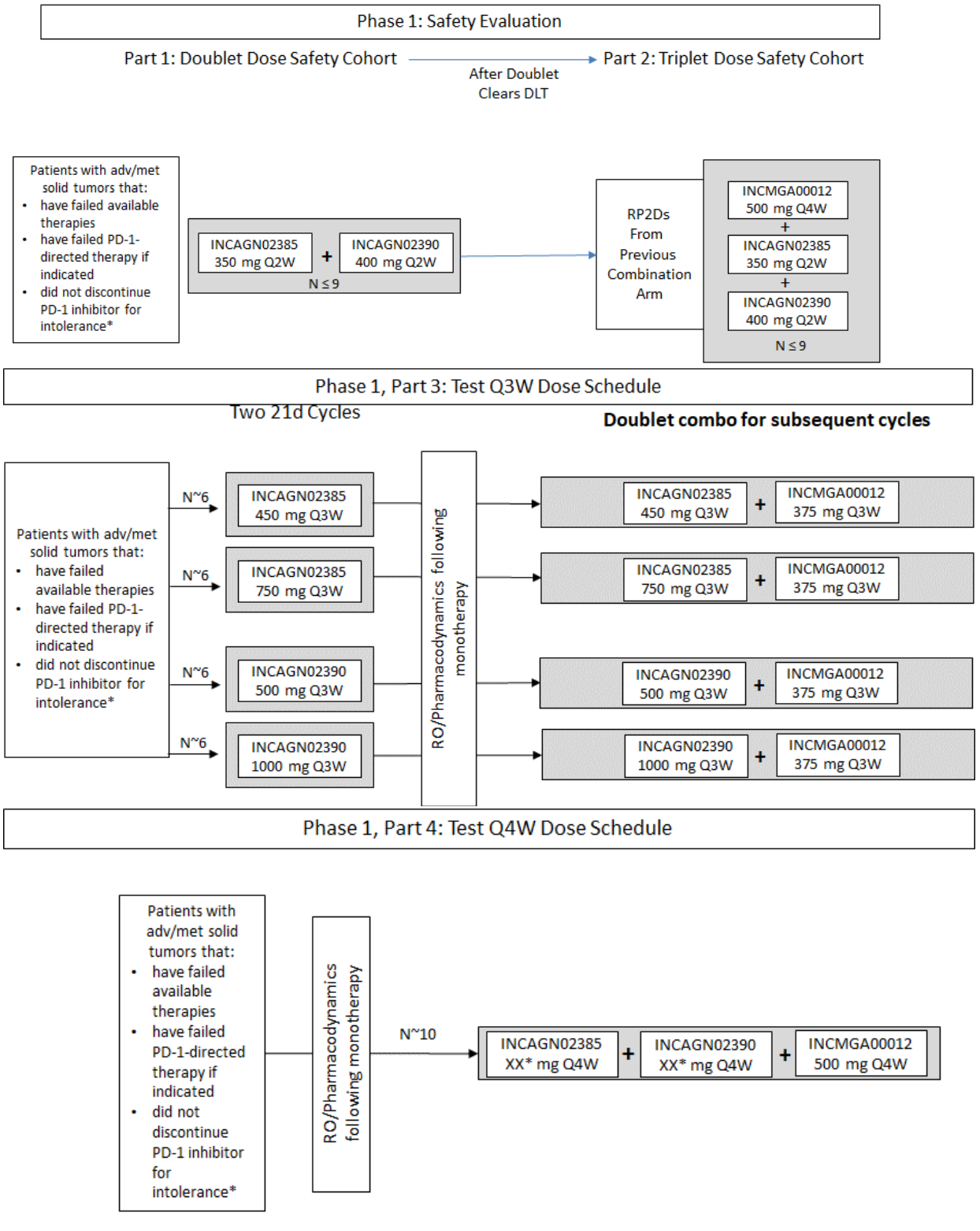
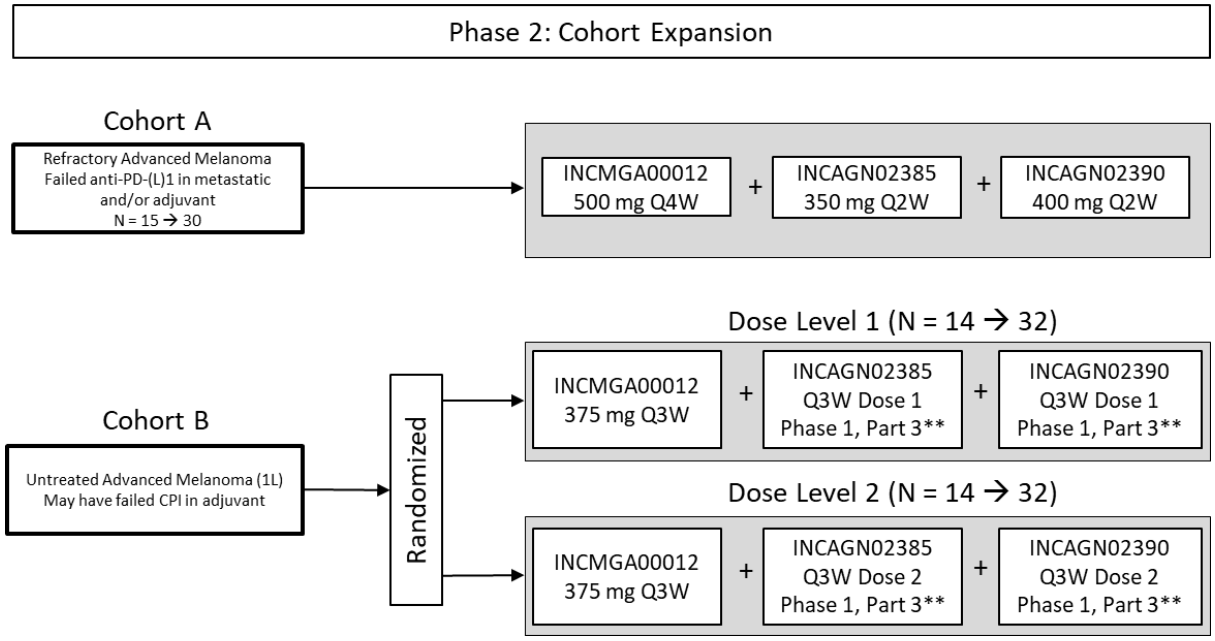


Figure 1: Study Design Schema (Continued)



Note: For Part 1 and 2, if safety of doses tested in either the doublet or the triplet cannot be established, the dose levels for INCAGN02385 and INCAGN02390 will be dropped 1 level from doses tested in monotherapy studies (ie, 250 mg Q2W for INCAGN02385 and 200 mg Q2W for INCAGN02390).
Note: For Part 4, dose(s) for the triple combination on Q4W schedule will be simulated based on PK, RO of monotherapy INCAGN02385 and INCAGN02390 in the Q3W dose evaluation in Part 3.
*See Section 5 for full inclusion and exclusion criteria
**Dose(s) for Phase 2 Cohort B will be based on Phase 1 Part 3. At least 2 doses may be tested for both INCAGN02385 and INCAGN02390. Cohort B will open as soon as Q3W doses are established in Phase 1.

Table 3: Schedule of Activities for Q2W Dosing (Phase 1 Parts 1 and 2 and Phase 2 Cohort A) and Q4W Dosing (Phase 1 Part 4)

A Cycle Is Defined as a 28-Day Period for Q2W and Q4W Schedules										
	Screening	Treatment							Safety Follow-Up	
		Cycle 1			Other Cycles		Every 8 Weeks			
Visit Day (Range)	Days –28 to –1	Day 1	Day 8 (± 2 d)	Day 15 (± 2 d)	Day 1 (± 3 d)	Day 15 (± 2 d)	(± 7 d)	EOT	EOT + 30, 60, & 90 d (± 7 d)	Notes
Administrative procedures										
Informed consent	X									
Contact IRT	X	X			X			X	X	
Inclusion/exclusion criteria	X									
General and disease medical history	X									
Prior/concomitant medications	X	X	X	X	X	X*		X	X	*Beyond C1D15, procedures are applicable to Q2W combinations only.
Administer INCMGA00012		X			X					Phase 1 Part 2 and Phase 2 Cohort A only.
Administer INCAGN02385		X		X	X	X*				*Beyond C1D15, procedures are applicable to Q2W combinations only.
Administer INCAGN02390		X		X*	X	X*				*Beyond C1D15, procedures are applicable to Q2W combinations only.
Safety assessments										
AE assessments	X	X	X	X	X	X*		X	X	Body systems with symptoms should be physically examined. *Beyond C1D15, procedures are applicable to Q2W combinations only.
Physical examination	X	X	X	X	X	X*		X	X	See Section 8.3.2 *Beyond C1D15, procedures are applicable to Q2W combinations only.
Vital signs/body weight/height	X	X	X	X	X	X*		X	X	Height at screening only. *Beyond C1D15, procedures are applicable to Q2W combinations only.

Table 3: Schedule of Activities for Q2W Dosing (Phase 1 Parts 1 and 2 and Phase 2 Cohort A) and Q4W Dosing (Phase 1 Part 4) (Continued)

A Cycle Is Defined as a 28-Day Period for Q2W and Q4W Schedules										
	Screening	**Treatment**							**Safety Follow-Up**	
		Cycle 1			**Other Cycles**		**Every 8 Weeks**			
Visit Day (Range)	**Days –28 to –1**	**Day 1**	**Day 8 (± 2 d)**	**Day 15 (± 2 d)**	**Day 1 (± 3 d)**	**Day 15 (± 2 d)**	**(± 7 d)**	**EOT**	**EOT + 30, 60, & 90 d (± 7 d)**	**Notes**
Safety assessments (continued)										
12-lead ECG	X	X*			X*			X		*ECG should be completed on Cycle 1 Day 1 (ONLY if not done at screening) and on Day 1 of Cycles 2, 3, and 4 only and then as indicated thereafter by the investigator and at EOT. ECG collection should occur within 10 minutes after the end of infusion on Cycle 1 Day 1 and Cycle 4 Day 1. All ECGs should be checked prior to dose administration (predose defined as within 3 calendar days prior to dose administration).
ECOG status	X	X	X	X	X	X*		X	X	*Beyond C1D15, procedures are applicable to Q2W combinations only.

Table 3: Schedule of Activities for Q2W Dosing (Phase 1 Parts 1 and 2 and Phase 2 Cohort A) and Q4W Dosing (Phase 1 Part 4) (Continued)

A Cycle Is Defined as a 28-Day Period for Q2W and Q4W Schedules										
	Screening	**Treatment**							**Safety Follow-Up**	
		Cycle 1			**Other Cycles**		**Every 8 Weeks**			
Visit Day (Range)	**Days –28 to –1**	**Day 1**	**Day 8 (± 2 d)**	**Day 15 (± 2 d)**	**Day 1 (± 3 d)**	**Day 15 (± 2 d)**	**(± 7 d)**	**EOT**	**EOT + 30, 60, & 90 d (± 7 d)**	**Notes**
Efficacy assessments										
Radiologic tumor assessments (CT of the chest and CT or MRI of the abdomen [pelvis is optional])	X*						X**	X***	X****	*Screening imaging will be performed within 28 days of the first dose. Screening imaging can be used for the purpose of PD confirmation following anti–PD(L)-1 therapy given as last line of treatment. **Imaging will be performed every 8 weeks (± 7 days) for the first 12 months, then every 12 weeks (± 7 days) thereafter. Imaging should not be adjusted for treatment delays. Participants with CR or PR require confirmatory assessment at least 4 weeks after criteria for response are first met. ***If scan is obtained within 4 weeks of discontinuation, then an EOT scan is not mandatory. ****For participants who discontinue for reasons other than PD, imaging should continue imaging every 8 weeks (± 7 days) for the first 12 months and then every 12 weeks (± 7 days) thereafter until 1) start of new therapy, 2) documented PD, 3) death, 4) withdrawal of consent, or 5) the end of the study, whichever occurs first.

Table 3: Schedule of Activities for Q2W Dosing (Phase 1 Parts 1 and 2 and Phase 2 Cohort A) and Q4W Dosing (Phase 1 Part 4) (Continued)

A Cycle Is Defined as a 28-Day Period for Q2W and Q4W Schedules										
	Screening	Treatment							Safety Follow-Up	
		Cycle 1			Other Cycles		Every 8 Weeks			
Visit Day (Range)	Days –28 to –1	Day 1	Day 8 (± 2 d)	Day 15 (± 2 d)	Day 1 (± 3 d)	Day 15 (± 2 d)	(± 7 d)	EOT	EOT + 30, 60, & 90 d (± 7 d)	Notes
Efficacy assessments (continued)										
Brain CT or MRI	X*									*Screening brain imaging should be performed on all participants who have previous history of CNS metastasis or as clinically indicated (eg, based on clinical symptoms). Repeated brain imaging will be performed only if the screening brain imaging was positive or as clinically indicated. If indicated, brain imaging should occur at approximately the same time (± 2 weeks) as disease assessment scans. Whenever feasible, contrast-enhanced brain MRI is preferred to CT.
[redacted]										

Table 4: Schedule of Laboratory Assessments for Q2W Dosing (Phase 1 Parts 1 and 2 and Phase 2 Cohort A) and Q4W Dosing (Phase 1 Part 4)

A Cycle Is Defined as a 28-Day Period for Q2W and Q4W Schedules								
	Screening	**Treatment**					**Safety Follow-Up**	
		Cycle 1		**Other Cycles**				
Procedure	**Days –28 to -1**	**Day 1**	**Day 15 (± 3 d)**	**Day 1 (± 3 d)**	**Day 15 (± 3 d)**	**EOT**	**EOT + 30, 60, & 90 d (± 7 d)**	**Notes**
Clinical laboratory assessments								Assessments will be performed by **local** laboratory.
Comprehensive serum chemistries	X	X*	X	X		X	X**	*Only required at Cycle 1 Day 1 if screening assessment was not performed within 7 days. **30-day visit only. Note: If liver chemistry tests are abnormal (eg, change in grade from baseline), monitoring should increase to once per week until resolved to baseline. Persistent low grade abnormalities do not need to be monitored indefinitely. Appropriate monitoring intervals should be discussed with the medical monitor.
Hematology with differential	X	X*	X	X		X	X**	*Only required at Cycle 1 Day 1 if screening assessment was not performed within 7 days. **30-day visit only.
Fasting lipid panel	X	X*		X**				*Only required at Cycle 1 Day 1 if screening assessment was not performed within 7 days. **Perform Q8W (Day 1 of every other cycle; C2, C4, etc).
Urinalysis	X	X*		X**				*Only required at Cycle 1 Day 1 if screening assessment was not performed within 7 days. **Perform Q8W (Day 1 of every other cycle; C2, C4, etc). Note: If blood is suspected in urine (see Table 17).
Coagulation panel	X	X*		X**				*Only required at Cycle 1 Day 1 if screening assessment was not performed within 7 days. **Perform Q8W (Day 1 of every other cycle; C2, C4, etc). Note: Participants may be administered study treatment in subsequent cycles after Cycle 1 Day 1 while thyroid test results are pending.

Table 4: Schedule of Laboratory Assessments for Q2W Dosing (Phase 1 Parts 1 and 2 and Phase 2 Cohort A) and Q4W Dosing (Phase 1 Part 4) (Continued)

A Cycle Is Defined as a 28-Day Period for Q2W and Q4W Schedules								
	Screening	Treatment					Safety Follow-Up	
		Cycle 1		Other Cycles				
Procedure	Days –28 to -1	Day 1	Day 15 (± 3 d)	Day 1 (± 3 d)	Day 15 (± 3 d)	EOT	EOT + 30, 60, & 90 d (± 7 d)	Notes
Endocrine panel (thyroid panel, ACTH, cortisol)	X	X*		X**		X		*Only required at Cycle 1 Day 1 if screening assessment was not performed within 7 days. **Perform Q8W (Day 1 of every other cycle; C2, C4, etc). Note: Nycthemeral cortisol levels variation should be considered, sample collection at fixed time such as early morning is advised.
Troponin I or T monitoring	X	X*	X	X**	X**	X		*Only required predose on Cycle 1 Day 1 if screening assessment was not performed. **To be performed predose on C2D1, C2D15, C3D1, C3D15, and C4D1 and EOT. Predose defined as within 3 calendar days prior to dose administration. All labs should be checked prior to dose administration. In case of high troponin, perform cardiac imaging via echocardiography or cardiac MRI.
Hepatitis screening	X							Results obtained within the last 3 months before Cycle 1 Day 1 are acceptable.
Pregnancy testing	X*	X**		X***		X*	X****	*Serum pregnancy test; only required for women of childbearing potential during screening and must be within 72 hours before the first dose of study treatment and at EOT (optional if participant is going to hospice). **Urine pregnancy test before first dose. ***Urine pregnancy testing on Day 1 of each cycle. ****Serum or urine pregnancy test will be performed monthly for 6 months after the last dose of study treatment.

Table 5: Schedule of Pharmacokinetic and Pharmacodynamic Assessments for Q2W Dosing (Phase 1 Parts 1 and 2 and Phase 2 Cohort A) and Q4W Dosing (Phase 1 Part 4)

A Cycle Is Defined as a 28-Day Period for Q2W and Q4W Schedules												
	Screening	Treatment									Safety Follow-Up	
		Cycle 1			Cycle 2 and 3		Cycle 4	Cycle 6			EOT + 30, 60, & 90 d (± 7 d)	
Procedure	Days –28 to –1	Day 1	Day 8 (± 1 d)	Day 15 (± 1 d)	Day 1 (± 1 d)	Day 15 (± 1 d)	Day 1 (± 1 d)	Day 1	Day 8	Day 15		Notes
[redacted]												

Table 5: Schedule of Pharmacokinetic and Pharmacodynamic Assessments for Q2W Dosing (Phase 1 Parts 1 and 2 and Phase 2 Cohort A) and Q4W Dosing (Phase 1 Part 4) (Continued)

A Cycle Is Defined as a 28-Day Period for Q2W and Q4W Schedules												
	Screening	**Treatment**									**Safety Follow-Up**	
		Cycle 1			**Cycle 2 and 3**		**Cycle 4**	**Cycle 6**				
Procedure	**Days –28 to –1**	**Day 1**	**Day 8 (± 1 d)**	**Day 15 (± 1 d)**	**Day 1 (± 1 d)**	**Day 15 (± 1 d)**	**Day 1 (± 1 d)**	**Day 1**	**Day 8**	**Day 15**	**EOT + 30, 60, & 90 d (± 7 d)**	**Notes**
Plasma correlative		X*	X	X**	X***	X**	X***	X***†				*Preinfusion, EOI, and 4 h after EOI for Q4W dose administration (Phase 1 Part 4). Preinfusion only for Q2W (Phase 1 Parts 1 and 2 and Phase 2 Cohort A). **Anytime for Q4W dose administration (Phase 1 Part 4). Preinfusion only for Q2W (Phase 1 Parts 1 and 2 and Phase 2 Cohort A). ***Preinfusion and EOI for Q4W dose administration (Phase 1 Part 4). Preinfusion only for Q2W (Phase 1 Parts 1 and 2 and Phase 2 Cohort A). †Q4W dose administration (Phase 1 Part 4) only.
Plasma cfDNA	X						X*					*One-time collection, preferentially during disease status assessment visit.

Table 5: Schedule of Pharmacokinetic and Pharmacodynamic Assessments for Q2W Dosing (Phase 1 Parts 1 and 2 and Phase 2 Cohort A) and Q4W Dosing (Phase 1 Part 4) (Continued)

A Cycle Is Defined as a 28-Day Period for Q2W and Q4W Schedules												
	Screening	Treatment									Safety Follow-Up	
		Cycle 1			Cycle 2 and 3		Cycle 4	Cycle 6			EOT + 30, 60, & 90 d (± 7 d)	
Procedure	Days –28 to –1	Day 1	Day 8 (± 1 d)	Day 15 (± 1 d)	Day 1 (± 1 d)	Day 15 (± 1 d)	Day 1 (± 1 d)	Day 1	Day 8	Day 15		Notes
Whole blood correlative for flow cytometry		X*	X	X**	X***	X**	X***	X***†				*Preinfusion, EOI, and 4 h after EOI for Q4W dose administration (Phase 1 Part 4). Preinfusion only for Q2W (Phase 1 Parts 1 and 2 and Phase 2 Cohort A). **Anytime for Q4W dose administration (Phase 1 Part 4). Preinfusion only for Q2W (Phase 1 Parts 1 and 2 and Phase 2 Cohort A). ***Preinfusion and EOI for Q4W dose administration (Phase 1 Part 4). Preinfusion only for Q2W (Phase 1 Parts 1 and 2 and Phase 2 Cohort A). †Q4W dose administration (Phase 1 Part 4) only.
Whole blood for PBMC	X		X	X*	X**		X**					*Preinfusion for Q2W (Phase 1 Parts 1 and 2 and Phase 2 Cohort A). Anytime for Q4W dose administration (Phase 1 Part 4). **Preinfusion only.
Whole blood DNA	X											Collected for Q2W (Phase 1 Parts 1 and 2 and Phase 2 Cohort A).

Table 5: Schedule of Pharmacokinetic and Pharmacodynamic Assessments for Q2W Dosing (Phase 1 Parts 1 and 2 and Phase 2 Cohort A) and Q4W Dosing (Phase 1 Part 4) (Continued)

A Cycle Is Defined as a 28-Day Period for Q2W and Q4W Schedules												
	Screening	Treatment									Safety Follow-Up	
		Cycle 1			Cycle 2 and 3		Cycle 4	Cycle 6				
Procedure	Days –28 to –1	Day 1	Day 8 (± 1 d)	Day 15 (± 1 d)	Day 1 (± 1 d)	Day 15 (± 1 d)	Day 1 (± 1 d)	Day 1	Day 8	Day 15	EOT + 30, 60, & 90 d (± 7 d)	Notes
Pretreatment tumor tissue collection	X*†											*Phase 1: Provide fresh or archival except with medical monitor approval (see Section 8.5.2). †Phase 2: Pretreatment fresh biopsy required at or following progression on/after prior PD-(L)1 therapy for melanoma Cohort A. This biopsy may serve for PD confirmation as per Section 5.1. A baseline biopsy obtained for other purposes (ie, not a Protocol-defined procedure) before signing consent may be used ONLY if the participant has not had any intervening systemic therapy from the time of the biopsy to the start of treatment (ie, Cycle 1 Day 1) and if sufficient tissue can be submitted.
Suitable archival tumor tissue collection	X											Whenever possible, provide archival tumor tissue collected before last anti–PD(L)-1 therapy.
Suitable on-treatment tissue collection					X*							*Optional biopsy once the participant meets the requirements for SD, response, or progression by radiographic disease assessment.

Table 6: Schedule of Activities for Q3W Dosing in Phase 1 Part 3 and Phase 2 Cohort B

A Cycle Is Defined as a 21-Day Period for Q3W Schedule										
	Screening	Treatment							Safety Follow-Up	
		Cycle 1			Other Cycles		Every 9 Weeks			
Visit Day (Range)	Days –28 to –1	Day 1	Day 8 (± 2 d)	Day 15 (± 2 d)	Day 1 (± 3 d)	Day 15 (± 2 d)	(± 7 d)	EOT	EOT + 30, 60, & 90 d (± 7 d)	Notes
Administrative procedures										
Informed consent	X									
Contact IRT	X	X			X			X	X	
Inclusion/exclusion criteria	X									
General and disease medical history	X									
Prior/concomitant medications	X	X	X	X	X			X	X	
Administer INCMGA00012		X*			X**					*For Phase 2 Cohort B, administer INCMGA00012 starting Cycle 1. **For Phase 1 Part 3, introduce INCMGA00012 starting Cycle 3.
Administer INCAGN02385		X			X					Depending on assigned treatment. Some participants in Phase 1 Part 3 will not receive INCAGN02385.
Administer INCAGN02390		X			X					Depending on assigned treatment. Some participants in Phase 1 Part 3 will not receive INCAGN02390.
Safety assessments										
AE assessments	X	X	X	X	X			X	X	Body systems with symptoms should be physically examined.
Physical examination	X	X	X	X	X			X	X	See Section 8.3.2
Vital signs/body weight/height	X	X	X	X	X			X	X	Height at screening only.
12-lead ECG	X	X*			X*			X		*ECG should be completed on Cycle 1 Day 1 (ONLY if not done at screening) and on Day 1 of Cycles 2, 3, and 4 only and then as indicated thereafter by the investigator and at EOT. ECG collection should occur within 10 minutes after the end of infusion on Cycle 1 Day 1 and Cycle 4 Day 1. All ECGs should be checked prior to dose administration (predose defined as within 3 calendar days prior to dose administration).

Table 6: Schedule of Activities for Q3W Dosing in Phase 1 Part 3 and Phase 2 Cohort B (Continued)

A Cycle Is Defined as a 21-Day Period for Q3W Schedule										
	Screening	Treatment							Safety Follow-Up	
		Cycle 1			Other Cycles		Every 9 Weeks			
Visit Day (Range)	Days –28 to –1	Day 1	Day 8 (± 2 d)	Day 15 (± 2 d)	Day 1 (± 3 d)	Day 15 (± 2 d)	(± 7 d)	EOT	EOT + 30, 60, & 90 d (± 7 d)	Notes
Safety assessments (continued)										
ECOG status	X	X	X	X	X			X	X	
Efficacy assessments										
Radiologic tumor assessments (CT of the chest and CT or MRI of the abdomen [pelvis is optional])	X						X*†	X**	X***	*For Phase 1 Part 3: Imaging will be performed every 9 weeks (± 7 days) for the first 12 months, then every 12 weeks (± 7 days) thereafter. †For Phase 2 Cohort B ONLY(first line melanoma): **First on-treatment imaging should be done at 12 weeks** with subsequent imaging performed every 9 weeks (± 7 days) for the first 12 months, then every 12 weeks (± 7 days) thereafter until disease progression or treatment discontinuation. NOTE: Imaging should not be adjusted for treatment delays. Participants with CR or PR require confirmatory assessment at least 4 weeks after the criteria for response are first met. **If scan is obtained within 4 weeks of discontinuation, then an EOT scan is not mandatory. ***For participants who discontinue for reasons other than PD, imaging should continue imaging every 9 weeks (± 7 days) for the first 12 months and then every 12 weeks (± 7 days) thereafter until 1) start of new therapy, 2) documented PD, 3) death, 4) withdrawal of consent, or 5) the end of the study, whichever occurs first.

Table 6: Schedule of Activities for Q3W Dosing in Phase 1 Part 3 and Phase 2 Cohort B (Continued)

A Cycle Is Defined as a 21-Day Period for Q3W Schedule										
	Screening	Treatment							Safety Follow-Up	
		Cycle 1			Other Cycles		Every 9 Weeks			
Visit Day (Range)	Days –28 to –1	Day 1	Day 8 (± 2 d)	Day 15 (± 2 d)	Day 1 (± 3 d)	Day 15 (± 2 d)	(± 7 d)	EOT	EOT + 30, 60, & 90 d (± 7 d)	Notes
Efficacy assessments (continued)										
Brain CT or MRI	X*									*Screening brain imaging should be performed on all participants who have previous history of CNS metastasis or as clinically indicated (eg, based on clinical symptoms). Repeated brain imaging will be performed only if the screening brain imaging was positive or as clinically indicated. If indicated, brain imaging should occur at approximately the same time (± 2 weeks) as disease assessment scans. Whenever feasible, contrast-enhanced brain MRI is preferred to CT. Brain imaging is required for patients in Cohort B at screening. Scans that were done prior to screening may be used if acquired within 8 weeks of Cycle 1 Day 1.
[redacted]										

Table 7: Schedule of Laboratory Assessments for Q3W Dosing in Phase 1 Part 3 and Phase 2 Cohort B

A Cycle Is Defined as a 21-Day Period for Q3W Schedule								
	Screening	**Treatment**					**Safety Follow-Up**	
		Cycle 1		**Other Cycles**				
Procedure	**Days –28 to -1**	**Day 1**	**Day 15 (± 3 d)**	**Day 1 (± 3 d)**	**Day 15 (± 3 d)**	**EOT**	**EOT + 30, 60, & 90 d (± 7 d)**	**Notes**
Clinical laboratory assessments								Assessments will be performed by **local** laboratory.
Comprehensive serum chemistries	X	X*	X	X		X	X**	*Only required at Cycle 1 Day 1 if screening assessment was not performed within 7 days. **30-day visit only. Note: If liver chemistry tests are abnormal (eg, change in grade from baseline), monitoring should increase to once per week until resolved to baseline. Persistent low grade abnormalities do not need to be monitored indefinitely. Appropriate monitoring intervals should be discussed with the medical monitor.
Hematology with differential	X	X*	X	X		X	X**	*Only required at Cycle 1 Day 1 if screening assessment was not performed within 7 days. **30-day visit only.
Fasting lipid panel	X	X*		X**				*Only required at Cycle 1 Day 1 if screening assessment was not performed within 7 days. **Perform Q6W (Day 1 of every other cycle; Cycle 2, Cycle 4, etc).
Urinalysis	X	X*		X**				*Only required at Cycle 1 Day 1 if screening assessment was not performed within 7 days. **Perform Q6W (Day 1 of every other cycle; Cycle 2, Cycle 4, etc). Note: If blood is suspected in urine (see Table 17).
Coagulation panel	X	X*		X**				*Only required at Cycle 1 Day 1 if screening assessment was not performed within 7 days. **Perform Q6W (Day 1 of every other cycle; Cycle 2, Cycle 4, etc). Note: Participants may be administered study treatment in subsequent cycles after Cycle 1 Day 1 while thyroid test results are pending.

Table 7: Schedule of Laboratory Assessments for Q3W Dosing in Phase 1 Part 3 and Phase 2 Cohort B (Continued)

A Cycle Is Defined as a 21-Day Period for Q3W Schedule								
	Screening	Treatment					Safety Follow-Up	
		Cycle 1		Other Cycles				
Procedure	Days –28 to -1	Day 1	Day 15 (± 3 d)	Day 1 (± 3 d)	Day 15 (± 3 d)	EOT	EOT + 30, 60, & 90 d (± 7 d)	Notes
Endocrine panel (thyroid panel, ACTH, cortisol)	X	X*		X**		X		*Only required at Cycle 1 Day 1 if screening assessment was not performed within 7 days. **Perform Q6W (Day 1 of every other cycle; C2, C4, etc). Note: Nycthemeral cortisol levels variation should be considered, sample collection at fixed time such as early morning is advised.
Troponin I or T monitoring	X	X*	X	X**	X**	X		* Only required predose on Cycle 1 Day 1 if screening assessment was not performed. **To be performed predose on C2D1, C2D15, C3D1, C3D15, and C4D1 and EOT. Predose defined as within 3 calendar days prior to dose administration. All labs should be checked prior to dose administration. In case of high troponin, perform cardiac imaging via echocardiography or cardiac MRI.
Hepatitis screening	X							Results obtained within the last 3 months before Cycle 1 Day 1 are acceptable.
Pregnancy testing	X*	X**		X***		X*	X****	*Serum pregnancy test; only required for women of childbearing potential during screening and must be within 72 hours before the first dose of study treatment and at EOT (optional if participant is going to hospice). **Urine pregnancy test before first dose. ***Urine pregnancy testing on Day 1 of each cycle. ****Serum or urine pregnancy test will be performed monthly for 6 months after the last dose of study treatment.

Table 8: Schedule of Pharmacokinetic and Pharmacodynamic Assessments for Q3W Dosing in Phase 1 Part 3 and Phase 2 Cohort B

A Cycle Is Defined as a 21-Day Period for Q3W Schedule											
	Screening	Treatment								Safety Follow-Up	
		Cycle 1			Cycle 2 and 3	Cycle 4	Cycle 6			EOT + 30, 60, & 90 d (± 7 d)	
Procedure	Days –28 to –1	Day 1	Day 8 (± 1 d)	Day 15 (± 1 d)	Day 1 (± 1 d)	Day 1 (± 1 d)	Day 1	Day 8	Day 15		Notes
[redacted]											
Plasma correlative		X*	X		X**	X**	X**				*Preinfusion, EOI, and 4 h after EOI for Phase 1 Part 3, preinfusion only for Phase 2 Cohort B **Preinfusion and EOI for Phase 1 Part 3, preinfusion only for Phase 2 Cohort B
Plasma cfDNA	X					X*					*One time collection, preferentially during disease status assessment visit.
Whole blood correlative for flow cytometry		X*	X		X**	X**	X**				*Preinfusion, EOI and 4 h after EOI for Phase 1 Part 3, preinfusion only for Phase 2 Cohort B. **Preinfusion and EOI for Phase 1 Part 3, preinfusion only for Phase 2 Cohort B.

Table 8: Schedule of Pharmacokinetic and Pharmacodynamic Assessments for Q3W Dosing in Phase 1 Part 3 and Phase 2 Cohort B (Continued)

A Cycle Is Defined as a 21-Day Period for Q3W Schedule											
	Screening	**Treatment**								**Safety Follow-Up**	
		Cycle 1			**Cycle 2 and 3**	**Cycle 4**	**Cycle 6**			**EOT + 30, 60, & 90 d (± 7 d)**	
Procedure	**Days –28 to –1**	**Day 1**	**Day 8 (± 1 d)**	**Day 15 (± 1 d)**	**Day 1 (± 1 d)**	**Day 1 (± 1 d)**	**Day 1**	**Day 8**	**Day 15**		**Notes**
Whole blood for PBMC	X		X		X*	X*	X*				*Preinfusion only.
Pretreatment tumor tissue collection	X*†										*Phase 1 Part 3: Provide fresh or archival except with medical monitor approval (see Section 8.5.2). †Phase 2 Cohort B: Mandatory pretreatment biopsy required A baseline biopsy obtained for other purposes (ie, not a Protocol-defined procedure) before signing consent may be used ONLY if the participant has not had any intervening systemic therapy from the time of the biopsy to the start of treatment (ie, Cycle 1 Day 1) and if sufficient tissue can be submitted.
Suitable archival tumor tissue collection	X										Applicable for Phase 1 Part 3 cohorts only. Whenever possible, provide archival tumor tissue collected before last anti–PD(L)-1 therapy.
Suitable on-treatment tissue collection						X*					*Optional biopsy once the participant meets the requirements for SD, response, or progression by radiographic disease assessment.

2. INTRODUCTION

2.1. Background

This is a Phase 1-2 study to determine safe combination doses and preliminary safety and efficacy for the combination of INCAGN02385 + INCAGN02390 + INCMGA00012. INCMGA00012 is a monoclonal antibody targeting PD-1. INCAGN02385 is a monoclonal antibody targeting LAG-3. INCAGN02390 is a monoclonal antibody targeting TIM-3. Phase 1 will consist of safety cohorts to determine preliminary safety of INCAGN02385 + INCAGN02390 followed by INCAGN02385 + INCAGN02390 + INCMGA00012. After a safe combination of the three study drugs has been established, additional doses and schedules for monotherapy, doublets, and triplets will be tested. Phase 2 will evaluate safety and preliminary efficacy of the triple combination of INCAGN02385 + INCAGN02390 + INCMGA00012 with the recommended doses from Phase 1 in participants with melanoma who have progressed or relapsed on or after anti–PD-(L)1 therapy (Cohort A) and participants with advanced melanoma who are naïve to systemic therapy (first line; Cohort B).

2.2. Study Rationale

While antibodies directed towards the PD-1/PD-L1 axis have revolutionized the treatment of cancer, the majority of patients either fail to respond or lose response to these drugs. Patients who relapse or are resistant to therapy with PD-1 inhibitors represent a high unmet need in oncology. The mechanisms for failure of anti–PD-1 therapy are poorly understood, but in some cases are likely due to existence of additional checkpoint pathways that either abrogate a response when present or cause loss of response when induced. This study aims to block key checkpoint pathways LAG-3 and TIM-3 implicated in the lack of/loss of response to PD-1 inhibitors.

The approval of PD-1 inhibitors for the treatment of patients with melanoma in the adjuvant setting has led to a significant challenge in treating those patients that relapse. In a study presented at the American Society of Clinical Oncology, the German Melanoma Treatment Registry was studied to determine re-treatment outcomes for patients with melanoma treated with ICI (Weichenthal et al 2019). Objective remission rates for subsequent therapies were 4.2% for ipilimumab, 19.5% with ipilimumab + nivolumab, 22.2% for BRAF/MEK inhibitors (in BRAF mutation positive patients), and 12.1% for other therapies (eg, chemotherapy). Median PFS in the ICI retreatment groups was 2.6 and 3.4 months for ipilimumab and ipilimumab/nivolumab, respectively. Another study at the same meeting evaluated subsequent therapies in patients who had relapsed while on anti–PD-1, specifically in the adjuvant setting. In this group, 0% responded to nivolumab alone, and only 24% responded to the combination of nivolumab + ipilimumab (Owens et al 2019). While these studies evaluated few patients, they illuminate a clear unmet need emerging as more patients with various tumor types that relapse after treatment with anti–PD-1.

Patients with advanced melanoma naïve to systemic treatment have more options for effective treatment. Both checkpoint inhibition and inhibition of RAF/MEK kinases have resulted in significant improvements in response rates and survival.

In patients with advanced melanoma harboring B-Raf mutations, targeted therapy towards BRAF and MEK also demonstrate significant antitumor activity and survival benefits. However, long-term outcome data with these drugs suggests that these benefits are likely confined to patients in the adjuvant setting and those with lower disease burden (Schadendorf et al 2017). Further, a retrospective analysis of long-term outcomes from the Checkmate 067 trial (Wolchock et al 2017), which compared nivolumab plus ipilimumab versus either nivolumab alone or ipilimumab alone, showed that the addition of ipilimumab to nivolumab contributes to efficacy only in the subset of patients with B-Raf mutations (Wolchock et al 2022). Based on these data, the DREAMseq trial aimed to compare outcomes of different sequencing of checkpoint inhibitors and BRAF targeted therapies in advanced melanoma (Atkins et at 2021). Results from this trial highlighted that using checkpoint inhibitor therapy first resulted in the highest benefit. Taken together, these data suggest that combinations of checkpoint inhibitors should have the highest possible benefit when used prior to BRAF inhibition in patients with advanced melanoma that have high disease burden and harbor B-Raf mutations.

Approvals for PD-1 inhibitors, either alone or in combination with other agents, have led to additional improvements in outcomes in patients with untreated advanced melanoma (Keytruda® 2020, Opdivo® 2019). Efficacy of checkpoint inhibition is substantially better in patients naïve to systemic therapy when compared to later lines of therapy. Programmed cell death protein 1 inhibitor therapy alone results in response rates of 30% to 45% as well as long-term survival benefits (Postow et al 2015, Robert et al 2015). Combinations of checkpoint inhibitors such as ipilimumab and nivolumab, have even better outcomes than anti–PD-1 monotherapy with survival benefits and response rates of 58% but increased toxicity in Phase 3 trials (Postow et al 2015).

Previously reported data evaluating a combination of nivolumab (anti–PD-1) and relatlimab (anti–LAG-3) in participants with melanoma who had failed previous anti–PD-(L)1 therapy demonstrated minimal efficacy in all patients tested but showed promising results in patients who were LAG-3 positive (≥ 1%; Ascierto et al 2017). These results led to further study in a Phase 2/3 study, RELATIVITY-047, which evaluated nivolumab plus relatlimab versus nivolumab alone in patients with first-line unselected melanoma (Tawbi et al 2022). This study demonstrated a clear PFS benefit of adding LAG-3 inhibition to nivolumab versus nivolumab alone (10.1 months vs 4.6 months and a response rate of 43% vs 32%, respectively). These data established the dual LAG-3 and PD-1 blockade as a promising treatment option in first-line metastatic melanoma setting. Nonetheless, an important subset of patients still did not respond, which highlighted the critical need for further improvement to treatment options.

This study will test the hypothesis that adding an inhibitor to an additional checkpoint, TIM-3, to the combination of anti–PD-1 and anti–LAG-3, will result in synergistic effect and further improvements in efficacy over existing regimens.

2.3. Scientific Rationale for Study Design

Significant focus has been placed on understanding the activity of the immune system within the tumor microenvironment and identification of mechanisms of tumor resistance to immune surveillance. Loss of CD8+ T cell effector function has been one such proposed mechanism. This loss of function, or T cell exhaustion, has been described as a loss of function due in part to the accumulation and increased diversity of inhibitory receptors, or checkpoints, on the cell

surface of CD8+ T cells (Wherry 2011). Recently, an HMG-box transcription factor, TOX, has been described as critical for development of the exhausted T cell phenotype. TOX expression results in induction of multiple checkpoint receptors as well as inhibitory transcription factors. In addition, TOX drives an epigenetic commitment towards T cell exhaustion. TOX expression potentially represents a more global control mechanism of T cell exhaustion instead of individually acquired resistance mechanisms described in previous models of T cell exhaustion. Thus single, or even double, inhibition of key checkpoints may not be sufficient to overcome an exhausted T cell phenotype (Khan et al 2019).

Recovery of function has been accomplished in an in vivo viral model of T cell exhaustion by simultaneous blockade of PD-1 and LAG-3 (Blackburn et al 2009). Furthermore, in an in vivo murine model of chronic infection, T cell exhaustion characterized by coexpression of TIM-3 and PD-1, combined blockade of these 2 inhibitory receptors markedly improved CD8+ T cell responses (Jin et al 2010, INCAGN02385 IB, INCAGN02390 IB). To date, blockade of PD-1 in combination with blockade of either LAG-3 or TIM-3 has resulted in only marginal responses in patients who have failed anti–PD-1 therapy alone (Ascierto et al 2017, Davar et al 2018). Thus, it remains challenging to intervene and disrupt the process of T cell exhaustion using dual blockade of checkpoints along the hierarchy of exhaustion. Potentially, multiple checkpoint inhibitors are required in order to restore anti-tumor T cell effector function in situ. Evidence for this approach was recently presented by Kaufmann et al (2018) at SITC 2018. In this study, the triple combination of antibodies directed against PD-1, TIM-3, and LAG-3 demonstrated enhanced tumor growth inhibition relative to inhibition of either PD-1 + LAG-3 or PD-1 + TIM-3 in a murine model. In addition, the combination of all 3 antibodies resulted in greater restoration of function to TILS isolated from human ovarian cancer patients. These results provide experimental support for the combination of all 3 antibodies in human cancer.

The basis of this study is to evaluate inhibition of 2 additional checkpoints, LAG-3 and TIM-3, on the background of PD-1 inhibition. The therapeutic hypothesis of combining anti–PD-1 blockade with anti–LAG-3 and anti–TIM-3 is to reinvigorate exhausted T cells in the tumor micro-environment and restore efficacious immune response against the tumor tissue. LAG-3 expression is mainly restricted to T cells, thus LAG-3 expression can indicate the presence of infiltrating T cells within the tumor microenvironment. As approximately 58% of patients with melanoma express LAG-3 (based on data from NCI), the primary endpoint will be tested in an all comers population. The current study will test LAG-3 status in order to determine retrospectively whether LAG-3 (or potentially its ligands) are markers of activity. Previously reported data evaluating a combination of nivolumab (anti–PD-1) and relatlimab (anti–LAG-3) in participants with melanoma who had failed previous anti–PD-(L)1 therapy demonstrated minimal efficacy in all patients tested but showed promising results in patients who were LAG-3 positive (≥ 1%; Ascierto et al 2017). These results led to further study in a Phase 2/3 study mentioned above, RELATIVITY-047, which evaluated nivolumab plus relatlimab versus nivolumab alone in patients with first line unselected melanoma (Tawbi et al 2022). This study demonstrated a clear benefit of adding LAG-3 inhibition to nivolumab versus nivolumab alone.

Efficacy of checkpoint inhibition is substantially better in patients naïve to systemic therapy when compared to later lines of therapy. Programmed cell death protein 1 inhibitor therapy alone results in response rates of 30% to 45% as well as long-term survival benefits (Postow et al 2015, Robert et al 2015). Combinations of checkpoint inhibitors have even better outcomes with survival benefits and response rates ranging from 43% to 58% in Phase 3 trials (Postow et al

2015, Tawbi et al 2022). This study will test the hypothesis that adding an inhibitor to an additional checkpoint, TIM-3, will result in further improvements in efficacy over existing regimens.

Safe doses for both INCAGN02385 and INCAGN02390 when given in combination as well as the triple combination including INCMGA00012 will be established in Phase 1. The triple combination will then be evaluated in a Phase 2 portion of the study in order to further evaluate safety and determine preliminary efficacy in participants with melanoma who progressed or relapsed on or after anti–PD(L)-1 therapy (Cohort A) as well as in participants with advanced melanoma naïve to systemic therapy (Cohort B). This allows for proof of concept for the combination.

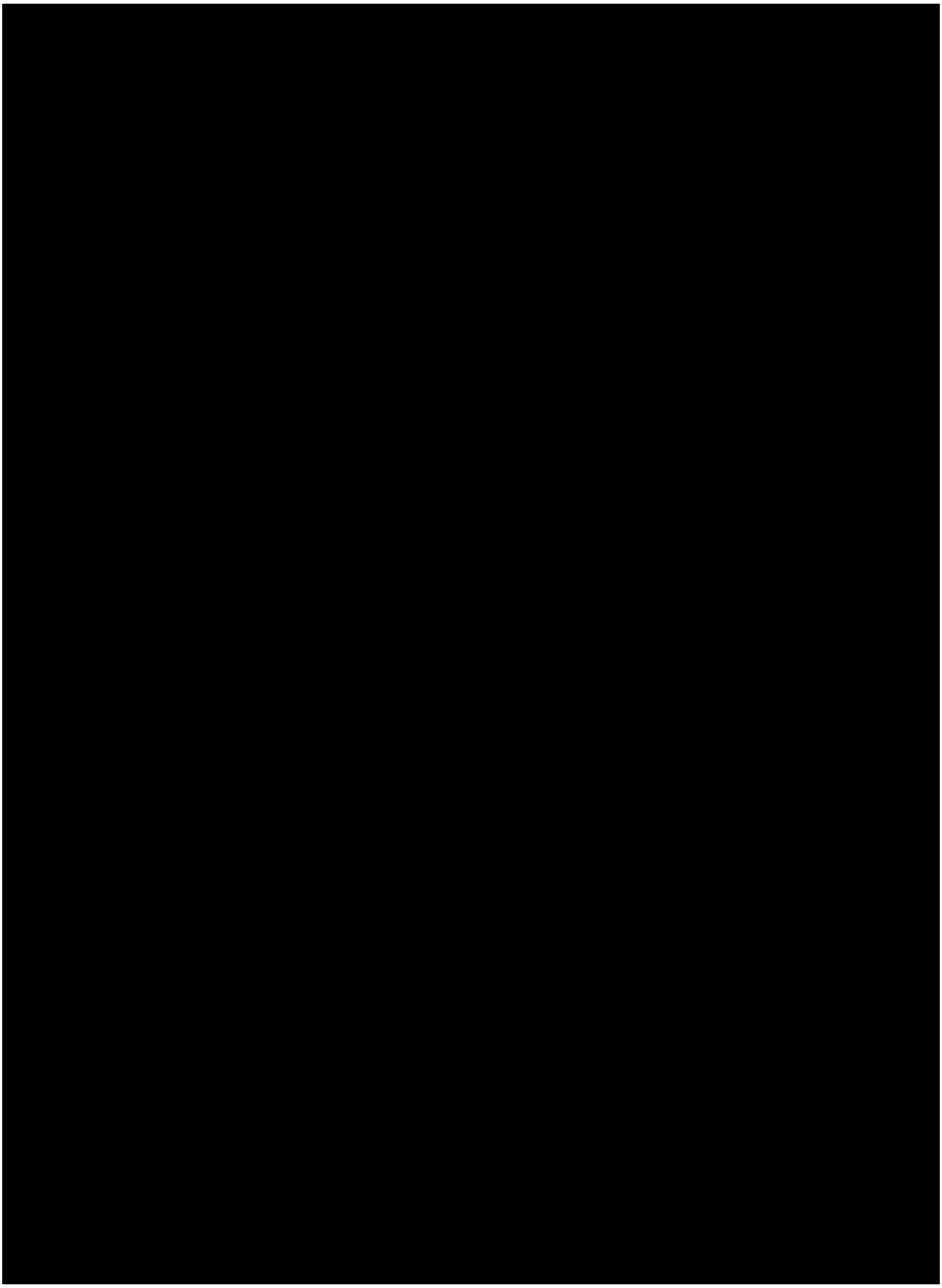
2.3.1. Justification for Dose

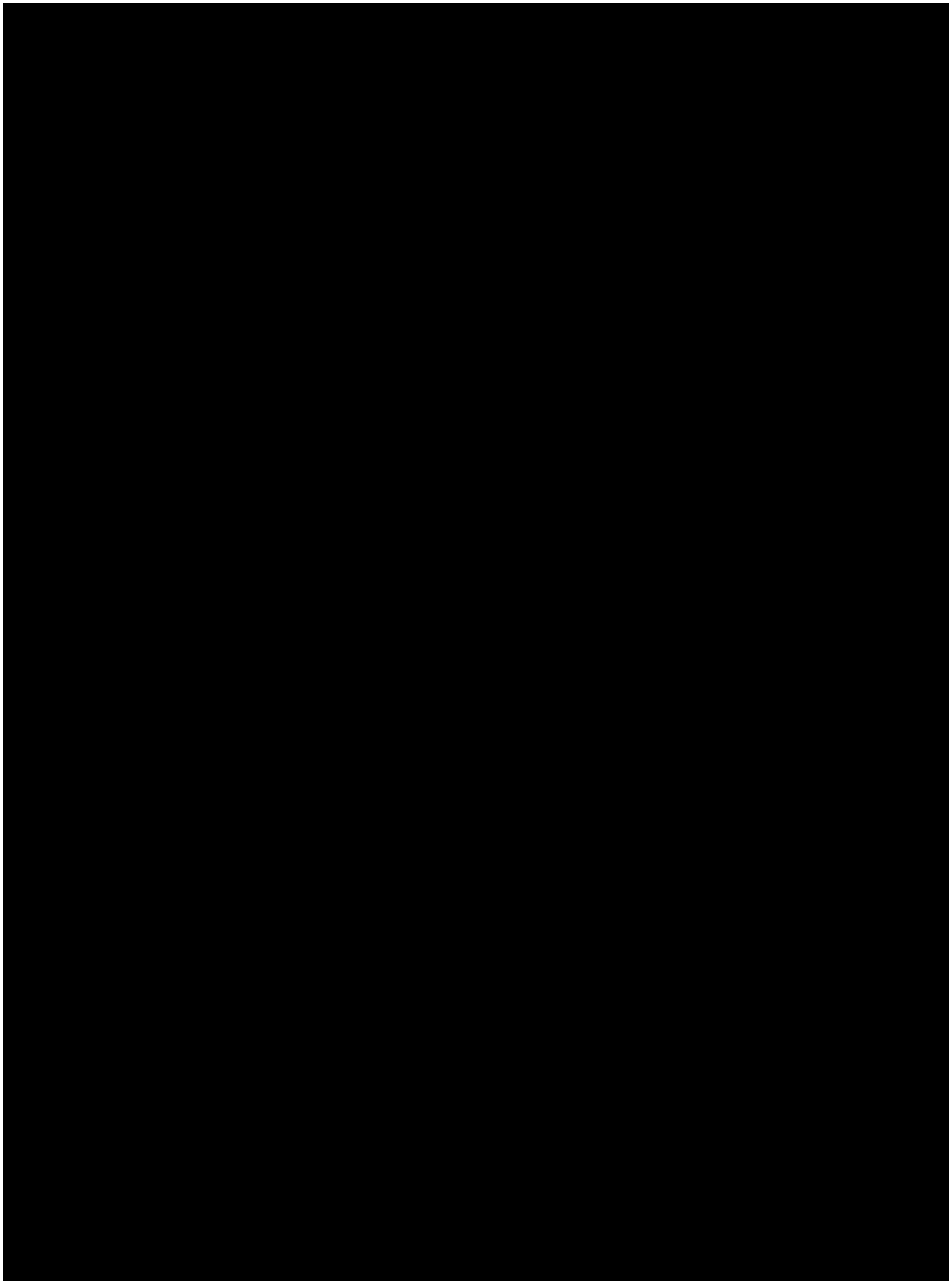
2.3.1.1. INCAGN02385 and INCAGN02390 Q2W Dose Selection (Phase 1 Parts 1 and 2 and Phase 2 Cohort A)

Doses for INCAGN02385 and INCAGN02390 were chosen based on safety, receptor occupancy, and pharmacodynamic data obtained from study results from studies evaluating monotherapy, INCAGN 2385-101 and INCAGN 2390-101, respectively (Incyte, data on file). In both cases, doses chosen were below the highest dose tested.

As of 06 JAN 2020, 22 participants have been treated in study INCAGN 2385-101 at doses ranging from 25 mg Q2W to 750 mg Q2W. All doses were well-tolerated, no DLTs were observed, and there were no treatment-related deaths. The dose of 350 mg Q2W was chosen for INCAGN02385 [redacted] At a dose of 350 mg Q2W (n = 3), the steady-state AUC was 30,200 µg/mL·h.

As of 27 JAN 2020, 38 participants have been treated in study INCAGN 2390-101 at doses ranging from 10 mg Q2W to 1600 mg Q2W. All doses were well-tolerated, no DLTs were observed, and there were no treatment-related deaths. [redacted] At a dose of 400 mg Q2W, the mean steady-state AUC determined in 4 participants was 43,400 µg/mL·h.





2.3.2. Justification for INCMGA00012 Dose

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

The flat dose regimen of INCMGA00012 500 mg Q4W was based on modeling of clinical PK data from the ongoing first-in-human monotherapy study, INCMGA 0012-101. The dose-escalation portion of this study evaluated 37 participants at doses of 1 mg/kg Q2W, 3 mg/kg Q2W, 3 mg/kg Q4W, 10 mg/kg Q2W, and 10 mg/kg Q4W. While supra–dose proportionality was observed for AUC and C_{max} for the first dose escalation from 1 mg/kg to 3 mg/kg, linear PK was shown from 3 mg/kg to 10 mg/kg.

The population PK analysis showed that the plasma concentrations of INCMGA00012 can be adequately described by a 2-compartment model with first-order elimination. Higher clearance of INCMGA00012 was estimated for the 1 mg/kg dose than for the other dose groups. Body-weight dependence of clearance was characterized by a power relationship with an exponent of 0.911.

A simulation was conducted to investigate the use of weight-based and fixed doses for INCMGA00012 with the aim of targeting a steady-state trough concentration of approximately 21 µg/mL, which is the median trough concentration for pembrolizumab 200 mg Q3W (Freshwater et al 2017). The median INCMGA00012 exposure and distribution around the median at 500 mg Q4W were similar to those at 7 mg/kg Q4W in the simulated population, which justified clinical exploration in an expansion cohort of Study INCMGA 0012-101. The median steady-state concentration at 500 mg Q4W was 24.8 µg/mL, and 58% of participants had trough concentrations greater than the target concentration.

Pharmacokinetic data were obtained from 15 participants who received INCMGA00012 500 mg Q4W in Study INCMGA 0012-101. The observed $AUC_{0-\infty}$ for 500 mg Q4W was close to the steady-state AUC_{0-t} based on the population PK analysis of weight-based doses, as is the estimated clearance. The estimated $t_{½}$ (333 hours) is slightly shorter than the previous estimate of 409 hours. The mean trough plasma concentration at Cycle 2 was 17.1 µg/mL, and the mean projected plasma $C_{min,ss}$ is 23.1 µg/mL with a mean accumulation index of 1.50. Overall, the 500 mg Q4W dose had very similar PK properties to 3 mg/kg doses. In addition, the 500 mg Q4W dose has approximately a 77% probability to obtain a steady-state trough plasma concentration ≥ 10 µg/mL, which is associated with maximum target engagement and greatest probability of efficacy.

A Q3W flat dose regimen is also being developed for combinations where additional flexibility in scheduling is desirable (eg, with chemotherapy). Pharmacokinetic data were obtained from 14 participants 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 $t_{½}$ (276 hours) and CL (14.8 mL/min) values comparable to those of the 500 mg Q4W and 750 mg Q4W doses. Furthermore, simulated C_{min} at steady-state 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 P2RD for further development for the INCMGA00012 program including the ongoing Phase 3 study of INCMGA00012 at 375 mg Q3W in combination with chemotherapy in first line advanced NSCLC (PODIUM-304).

In summary, clinical experience based on Study INCMGA 0012-101 (INCMGA00012 IB, Mehnert et al 2018, Incyte, data on file) showed good tolerability with favorable PK properties of INCMGA00012 at flat doses of either 500 mg Q4W or 375 mg Q3W, supporting further clinical development. INCMGA00012 administered as a Q3W regimen at a starting dose of 375 mg has been selected in this study, which accommodates combination with INCAGN02385 and INCAGN02385 when dosed every 3 weeks. INCMGA00012 administered as a Q4W regimen at a starting dose of 500 mg is been selected to accommodate combination with INCAGN02385 and INCAGN02385 when dosed every 4 weeks.

2.4. Benefit/Risk Assessment

2.4.1. INCMGA00012

Treatment directed at the PD-1/PD-L1 axis is a promising approach to the diseases under study. Monoclonal antibodies against PD-1 have shown benefit for these and other indications and safety of these agents has been well-characterized.

Antibodies targeting the PD-1 pathway have demonstrated activity in a wide variety of cancer types (ie, Bavencio® 2018, Imfinzi® 2018, Keytruda 2020, Libtayo® 2019, Opdivo 2019, Tecentriq® 2019), and the available preclinical and clinical data from study participants suggest that the pharmacologic and clinical profile of INCMGA00012 should be consistent with experience with other drugs in this class (Lakhani et al 2017, Mehnert et al 2018, Chen et al 2019, Condamine et al 2019). Based on these observations, the benefit/risk for INCMGA00012 should also be favorable, provided efficacy objectives in the proposed study are met, since the intended populations have a very limited prognosis with available therapy.

As of 23 SEP 2020, 289 participants have been exposed to INCMGA00012 monotherapy in study INCMGA 0012-101 (POD1UM-101, NCT03059823). Results of the dose-escalation and dose-expansion portions of this study demonstrated acceptable tolerability. In the dose escalation portion, no DLTs have been observed at any dose level up to 10 mg/kg Q2W. An MTD was not reached. In addition, encouraging early efficacy have been demonstrated in multiple tumor types with durable RECIST v1.1 response (non-small cell lung cancer [Mehnert et al 2018], cervical cancer [Mehnert et al 2018], biomarker-unselected endometrial cancer [Mehnert et al 2018], sarcoma [Mehnert et al 2018], Merkel cell carcinoma [Grignani et al 2020], and microsatellite stability high or deficient mismatch repair endometrial cancer [Berton-Rigaud et al 2020]). In Phase 2 (35 participants) in PD1-naive unresectable/metastatic melanoma setting, INCMGA00012 monotherapy achieved consistent objective response rate (37%) to that reported with other checkpoint inhibitors in this indication (Maio et al 2021).

A total of 578 participants have been treated with INCMGA00012 monotherapy across 5 clinical studies, and the adverse drug reactions are consistent with those observed with other anti–PD-1 antibodies (INCMGA00012 IB).

Combination of PD-1 inhibitors with inhibitors of other checkpoints is supported by substantial preclinical and clinical data. Also, dose-ranging for all individual components in the combination regimen under study has been completed as well as combination treatment with the selected doses; thus, the selected dose levels are not anticipated to produce unexpected or unmanageable toxicity. Based on results from studies combining PD-1 inhibitors with antibodies directed at either LAG-3 (Ascierto et al 2017) or TIM-3 (Davar et al 2018) toxicity of these combinations is expected to be similar to single-agent PD-1. Additionally, based on available preclinical and clinical data, combination of PD-1 inhibitors with other CPI may potentially provide responses in populations either unresponsive or who have lost response to PD-1 inhibitors.

2.4.2. INCAGN02385

As of the January 6, 2020, 22 participants with advanced malignancies have received INCAGN02385 at Q2W doses of 25 mg (n = 4), 75 mg (n = 4), 250 mg (n = 4), 350 mg (n = 3) and 750 mg (n = 7) in Part 1 (dose escalation) of Study INCAGN 2385-101. All participants had at least 1 TEAE. Treatment-emergent AEs related to INCAGN02385 occurring in more than 1 participant were fatigue (n = 7), creatinine increase (n = 2), lymphopenia (n = 2), myalgia (n = 2), pruritus (n = 2), and tumor pain(n = 2).

Nine participants had serious TEAEs; none of the serious TEAEs were considered by the investigator to be related to INCAGN02385.

Two participants had a TEAE with a fatal outcome: one participant on 25 mg of INCAGN02385 had disease progression, and one participant on 250 mg of INCAGN02385 experienced failure to thrive. Two participants experienced a TEAE leading to discontinuation of study drug: one for aspartate aminotransferase increase at a dose of 750 mg, and one for transient ischemic attack at a dose of 350 mg. A MTD was not reached for INCAGN02385, and there have been no DLTs. Enrollment in Part 1 of Study INCAGN 2385-101 is complete.

2.4.3. INCAGN02390

As of the 2020 JAN 27, 38 participants with advanced malignancies have received INCAGN02390 at Q2W doses of 10 mg (n = 6) 30 mg (n = 6), 100 mg (n = 4), 200 mg (n = 5), 400 mg (n = 6) 800 mg (n = 6) and 1600 mg (n = 5) in Part 1 (dose escalation) of Study INCAGN 2385-101. Thirty six participants (94.7%) had at least 1 TEAE. The most frequent TEAEs related to INCAGN02390 were fatigue (n = 9), anemia (n = 8), back pain (n = 8), hyponatremia (n = 6), nausea (n = 6), abdominal pain (n = 5), aspartate aminotransferase increased (n = 5), chills (n = 5), and dehydration (n = 5).

Serious TEAEs were observed in 16 participants (42.1%); one serious TEAE, tumor pain flare, was considered by the investigator to be related to INCAGN02390.

No participants had a TEAE with a fatal outcome. Three participants (7.9%) experienced a TEAE leading to discontinuation of study drug, though none of these were considered related to INCAGN02390 by the investigator. Participants had drug withdrawn for supraventricular tachycardia (n = 1, 10 mg Q2W), impaired wound healing and sepsis (n = 1, 10 mg Q2W), and retrovaginal fistula (n = 1, 200 mg Q2W). An MTD has not been reached for INCAGN02390, and there have been no DLTs. Enrollment in Part 1 of Study INCAGN 2390-101 is ongoing for the final cohort.

There will be a 48-hour observation period between the first and second participants of the Phase 1 cohorts in order to monitor participants for delayed reactions. Additionally, all participants will remain in the clinic for 4 hours following combination infusions on Cycle 1 Day 1 for safety observations. Close oversight of study conduct will be provided by an internal DMC (see Section 5.6) as well as through safety team meetings and contact with participating investigators. Additionally, irAEs will be monitored throughout the study and during the 90-day safety follow-up with appropriate guidance provided to investigators for their assessment and management (see Section 6.6.5).

More detailed information about the known and expected benefits and risks and reasonably expected AEs for the study drugs INCMGA00012, INCAGN02385 and INCAGN02390 may be found in the respective Investigator's Brochures (refer to INCMGA00012 IB, INCAGN02385 IB, INCAGN02390 IB).

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

Participants to be enrolled into this study have recurrent advanced or metastatic endometrial cancer and may be at higher risk for complications if they contract COVID-19. In this Phase 2 study population, standard-of-care therapy options for the advanced or metastatic endometrial cancer that progressed on or following the platinum-based chemotherapy are limited. An ESMO multidisciplinary panel highlighted the importance of clinical cancer research to find better therapeutic options for participants even during the pandemic, including potential investigational therapies similar to immunotherapy with a known survival benefit (Curigliano et al 2020). Preliminary data released based on real-world data indicate that the use of immunotherapy either alone or in combination with chemotherapy does not appear to increase the risk of hospitalization upon COVID-19 infection (Horn et al 2020) or cause an increased risk of mortality (Lee et al 2020). Effects of immune checkpoint inhibitors on SARC-CoV2 infection is yet unknown. However, it has been reported that at early stages of SARS-CoV2 infection, CD8+ T-cell exhaustion and PD-1 upregulation have been observed in patients (Riva et al 2020, Zheng et al 2020). Those findings may suggest the hypothesis that immune checkpoint inhibitors may ameliorate the early phase of COVID-19 disease through the reactivation of T cells expressing PD-1 (Maio et al 2020). Conversely, potential risks of cytokine release syndrome, pneumonitis or myocarditis related to immune checkpoint inhibitors therapy, may represent a clinical issue and impact a course of COVID-19 disease (Maio et al 2020, Sullivan et al 2020). Considering the critical medical need for alternative therapies in the setting of recurrent advanced/metastatic endometrial cancer and the importance of continuing clinical cancer research even during the pandemic, and taking into account the lack of conclusive clinical data on the impact of immune checkpoint inhibitors therapy on COVID disease course, the sponsor will implement additional guidance in this clinical study for participation in the study in the context of the COVID-19 pandemic and study-treatment management in the event of SARS-CoV2 infection (see Appendix C).

During the COVID-19 pandemic, additional risks to participants exist either related to going to a health care facility or as a result of study-related activities. The investigators would need to carefully assess both the benefit/risk and available participant's available medical data (eg, performance status, past medical history, comorbidities) at screening in order to determine whether it is in the best interests of the potential participant to enroll and participate into the

study. In addition, country-specific requirements will be followed with regard of COVID-19 testing as specified in Appendix C.

Investigators will be warranted to follow-up with repeated tests during the study as per medical judgment and/or local practices and also for enrolled participants who may be newly suspected of being exposed to SARS-CoV2 or have symptoms or to demonstrate recovery.

Participants will be monitored with safety procedures as described in Section 8.3 and with additional safety assessments as per standard of care. Additional information regarding the flexibility of assessments/visits scheduling, where possible and warranted, and strategy for participant management during the dynamic pandemic as applicable are described in Appendix C.

3. OBJECTIVES AND ENDPOINTS

Table 9 presents the objectives and endpoints.

Table 9: Objectives and Endpoints

Objectives	Endpoints
Primary	
Phase 1	
To determine RP2Ds for all study drugs to be used in the following regimens: Part 1 (Q2W): INCAGN02385 + INCAGN02390 Part 2 (Q2W): INCAGN02385 + INCAGN02390 + INCMGA00012 Part 3 (Q3W): INCAGN02385, INCAGN02390, INCAGN02385 + INCMGA00012 and INCAGN02390 + INCMGA00012 Part 4 (Q4W): INCAGN02385 + INCAGN02390 + INCMGA00012	• Safety and tolerability as assessed by monitoring the frequency and severity of AEs.
Phase 2	
To determine the preliminary efficacy of INCAGN02385 + INCAGN02390 + INCMGA00012 in Cohorts A and B. Cohort A: Participants with advanced melanoma who have progressed or relapsed on or after anti–PD-(L)1 therapy Cohort B: Participants with advanced melanoma naïve to systemic therapy (first line)	• ORR, defined as the percentage of participants having a CR or PR, will be determined by investigator assessment of radiographic disease assessments per RECIST v1.1. • DOR, defined as the time from earliest date of disease response (CR or PR) until earliest date of disease progression, will be determined by investigator assessment of radiographic disease per RECIST v1.1, or death from any cause, if occurring sooner than progression. • DCR, defined as percentage of participants having CR, PR, or SD as best on-study response. • PFS, defined as the time from date of first dose of study treatment until the earliest date of disease progression, as determined by investigator assessment of objective radiographic disease per RECIST v1.1, or death due to any cause.
To determine the safety of INCAGN02385 + INCAGN02390 + INCMGA00012.	• Safety and tolerability as assessed by monitoring the frequency and severity of AEs.

Table 9: Objectives and Endpoints (Continued)

Objectives	Endpoints
Secondary	
Phase 1	
To determine the preliminary efficacy of the combinations of INCAGN02385 + INCAGN02390 and of INCAGN02385 + INCAGN02390 + INCMGA00012 for both Q2W and Q4W schedules in participants with solid tumors who have failed anti–PD-1 therapy.	• ORR, defined as the percentage of participants having a CR or PR, will be determined by investigator assessment of radiographic disease assessments per RECIST v1.1. • DCR, defined as percentage of participants having CR, PR, or SD as best on-study response. • PFS, defined as the time from date of first dose of study treatment until the earliest date of disease progression, as determined by investigator assessment of objective radiographic disease per RECIST v1.1, or death due to any cause.
[redacted]	

Table 9: Objectives and Endpoints (Continued)

Objectives	Endpoints
[redacted]	

4. STUDY DESIGN

4.1. Overall Design

See Figure 1 for key study elements for INCAGN 2385-201.

4.1.1. Treatment Groups and Duration

This is an open-label, nonrandomized, Phase 1-2 study to determine the safety, tolerability, and preliminary efficacy of INCAGN02385 and INCAGN02390 given both as monotherapy as well as in combination with INCMGA00012 (ie, doublets and triplets) at multiple doses on Q2W, Q3W, and Q4W schedules.

- **Phase 1** is to determine safe combination doses given on various schedules. Combination doses for further study will be chosen based on safety.

  [redacted]

  - **Part 1:** Part 1 will use a BOIN design and will determine whether the doses selected for further study from the respective monotherapy studies (Q2W INCAGN02385 dose is 350 mg and INCAGN02390 dose is 400 mg) are safe when used in the combination of INCAGN02385 and INCAGN02390 ($n \leq 9$). If the safety of doses tested cannot be established, then the dose level will be reduced 1 level from doses tested in monotherapy studies (ie, 250 mg Q2W for INCAGN02385 and 200 mg Q2W for INCAGN02390).
  - **Part 2:** Following confirmation of the safety of the doublet, the safety of the triple combination of INCAGN02385 (350 mg Q2W) + INCAGN02390 (400 mg Q2W) + INCMGA00012 (500 mg Q4W) will be tested ($n \leq 9$). If safety of doses tested in the triplet cannot be established, the dose levels for INCAGN02385 and INCAGN02390 will be dropped 1 level from doses tested in monotherapy studies (ie, 250 mg Q2W for INCAGN02385 and 200 mg Q2W for INCAGN02390).
  - **Part 3:** Once safety for the Q2W schedule has been established for the PD-1-free doublet (INCAGN02385 + INCAGN02390) and the triplet (INCAGN02385 + INCAGN02390 + INCMGA00012), a Q3W schedule will be evaluated in a stepwise manner.
    - Q3W schedule validation will better accommodate the combination of INCAGN02385 and INCAGN02390 with INCMGA00012 (at the established RP2D of 375 mg Q3W) and limit the number of visits for participants.

- [redacted]
  - Two doses of INCAGN02385, 450 mg Q3W and 750 mg Q3W, will be administered to participants (n = 6 each) as monotherapy for 2 21-day cycles. Following 2 monotherapy cycles, these same participants will then remain on their current dose of INCAGN02385 and be given INCMGA00012 (375 mg Q3W) in combination. Concurrently, 2 doses of INCAGN02390, 500 mg Q3W and 1000 mg Q3W, will be administered to participants (n = 6 each) as monotherapy for 2 21-day cycles. Following 2 monotherapy cycles, these same participants will then remain on their current dose of INCAGN02390 and be given INCMGA00012 (375 mg Q3W) in combination.
  - Participants in Part 3 will be evaluated for safety and occurrence of DLTs from first dose until Day 21. After 21 days, the DMC will review safety data and if the DMC determines the doses to be tolerable, will make a recommendation to the study team that Phase 2 Cohort B should be opened to evaluate the Q3W schedule of INCMGA0012 + INCAGN02385 + INCAGN02390 utilizing doses tested in Phase 1 Part 3.
  - Part 3 cohorts [redacted] will inform doses that will be selected to carry into Phase 2 expansion cohort(s) in order to evaluate safety, preliminary efficacy and optimal dose administration of the triplet combination INCAGN02385 + INCAGN02390 + INCMGA00012 on Q3W schedule.
  - Additional doses and schedules may be evaluated based on data from Phase 1 Part 3.

– **Part 4:** Q4W schedule will be evaluated as alternative schedule to accommodate future combinations with other agents of interest and in a stepwise manner. [redacted]

- **Phase 2** will further assess safety and determine preliminary efficacy for the combination of INCAGN02385 + INCAGN02390 + INCMGA00012.
  - **Cohort A:** A population of participants with unresectable/metastatic or adjuvant-treated melanoma (n = 15) who progressed or relapsed on or after prior anti–PD-(L)1 therapy will receive INCAGN02385 + INCAGN02390 + INCMGA00012 Q2W at doses selected in Part 2. If a sufficient number of responses are seen (≥ 1/15 responses), the population will be expanded to include additional participants (+ n = 15) in a Simon 2-stage expansion to further evaluate safety and efficacy.
  - **Cohort B:** Following DMC review of Phase 1 Part 3, a population of participants with advanced melanoma naïve to systemic therapy (1L) will receive INCAGN02385 + INCAGN02390 + INCMGA00012 Q3W at the doses selected in Phase 1 Part 3 (n = 32 for each dose level). Initially, 14 participants will be enrolled in Cohort B. If a sufficient efficacy signal is seen (eg, ≥ 6/14 responses in a nonbinding analysis) in Stage 1, additional participants (+ n = 18) will be enrolled. See Section 10.1.2 for further description of the nonbinding analysis. Cohort B is designed with 1-sided $\alpha = 0.09$ with an approximate 98% power to observe at least 17 responses in the total population enrolled (N = 32) using a Bayesian predicted probability.

See Figure 1 for the study design schema and Table 3 and Table 6 for the SoA.

4.2. Overall Study Duration

The study begins when the first participant signs the ICF. The end of the study is defined as the date of the last visit of the last participant in the study.

A participant is considered to have completed the study if he/she has completed all parts of the study including the last visit.

Study treatment will be provided for a maximum of 2 years.

The end of the study may be designated as the timepoint when all participants have discontinued the study or are a minimum of 6 months after initial study medication administration. If by the end of the study there remains at least 1 participant still on study treatment for at least 6 months, the participant(s) may enter additional treatment cycles. At this point, a database lock of the study may occur to allow the analysis of the study data. Any remaining participants may continue to receive study medication and be seen by the investigator per protocol. In addition, the investigator will be expected to monitor for and report any SAEs and pregnancies, as detailed in Section 9.2 (Serious Adverse Events). The participant is considered on study until such time that he/she meets any of the discontinuation criteria and written notification is given to the sponsor.

4.3. Study Termination

The investigator retains the right to terminate study participation at any time, according to the terms specified in the study contract. The investigator is to notify the IRB/IEC in writing of the

study's completion or early termination, send a copy of the notification to the sponsor or sponsor's designee, and retain 1 copy for the site study regulatory file.

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

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. Men and women, aged 18 or older.
2. Willingness to provide written informed consent for the study.
3. **Phase 1 (Parts 1-4):** Participants with locally advanced or metastatic solid tumors (locally advanced disease must not be amenable to resection with curative intent) that have failed available therapies, including anti-PD-(L)1 therapy if applicable, that are known to confer clinical benefit, or who are intolerant to, or ineligible for standard treatment. Prior anti-PD-(L)1 therapy should not have been discontinued because of intolerance.

   Removed during Protocol Amendment 3.

   a. Removed during Protocol Amendment 3.
   b. Removed during Protocol Amendment 3.
   c. Removed during Protocol Amendment 3.
   d. Removed during Protocol Amendment 3.
4. **Phase 2 Cohort A:**

   a. Participant with histologically confirmed unresectable/metastatic melanoma, whose disease failed prior anti–PD-(L)1 therapy (alone or as part of a combination) and meeting one of the following criteria:

      – Participant who failed prior adjuvant anti–PD-(L)1 therapy for resectable melanoma must have received prior anti–PD-(L)1 for ≥ 6 weeks and experienced disease progression while still on active adjuvant therapy containing anti–PD-(L)1, or participant who had early relapse occurring < 24 weeks after end of adjuvant anti–PD-(L)1 therapy. Progressive disease must be ascertained by confirmatory biopsy collected at baseline.

- Participant whose unresectable/metastatic disease progressed while on or within 24 weeks of completion of anti–PD-(L)1 for unresectable/metastatic melanoma. Progressive disease must have been confirmed by imaging ≥ 4 weeks after evidence of initial disease progression.

b. Participant must have received no more than 2 prior lines of therapy for melanoma and at least one prior regimen must have contained anti–PD-(L)1 therapy (alone or as part of a combination) either in the adjuvant and/or advanced/metastatic setting.
Note: Participants who have tumors that are BRAF mutant may have received up to 2 prior lines of therapy for melanoma in addition to prior BRAF directed therapies).
Note: Participant may have received anti–PD-(L)1 therapy both in adjuvant and advanced/metastatic setting.
c. Participants must have had known BRAF V600 mutation status per local institutional testing standards.
d. Participants must have fresh biopsy available after completing prior PD-(L)1 therapy or be willing and able to safely undergo pretreatment tumor biopsies (core or excisional). Determination of whether participants can safely undergo biopsy should be made by the treating physician in consultation with the individual performing the biopsy.
Note: A baseline biopsy obtained for other purposes (ie, not a Protocol-defined procedure) before signing consent may be used ONLY if the participant has not had any intervening systemic therapy from the time of the biopsy to the start of treatment (ie, Cycle 1 Day 1) and if sufficient tissue can be submitted.
e. Participant must have at least 1 measurable tumor lesion per RECIST v1.1.
Note: Lesions to be used as measurable disease for the purpose of response assessment must not be lesion used for biopsy and must either a) not reside in a field that has been subjected to prior radiotherapy, or b) have demonstrated clear evidence of radiographic progression since the completion of prior radiotherapy or biopsy and prior to study enrollment.

5. **Phase 2 Cohort B:**

a. Participant with previously untreated, histologically confirmed Stage III (unresectable) or IV melanoma per the American Joint Committee on Cancer v8 staging system.

b. Participants must not have had prior systemic anticancer therapy for unresectable or metastatic melanoma.

Note: That the following prior adjuvant or neoadjuvant melanoma therapies are allowed if all related adverse events had either returned to baseline or stabilized:

- Participant who had received previous adjuvant or neoadjuvant therapies containing a PD-1, CTLA-4, BRAF, or MEK inhibitor (or a combination of BRAF and MEK inhibitors) must have the therapy completed at least 6 months before the date of recurrence.

- Participant who received previous treatment with interferon must have the last dose received at least 6 weeks before randomization.

c. Participants must have had known BRAF V600 mutation status per local institutional testing standards.

d. Participants must have fresh biopsy available or be willing and able to safely undergo pretreatment tumor biopsies (core or excisional). Determination of whether participants can safely undergo biopsy should be made by the treating physician in consultation with the individual performing the biopsy.

   Note: A baseline biopsy obtained for other purposes (ie, not a Protocol-defined procedure) before signing consent may be used ONLY if the participant has not had any intervening systemic therapy from the time of the biopsy to the start of treatment (ie, Cycle 1 Day 1) and if sufficient tissue can be submitted.

6. **Phase 2 (Cohorts A and B):** Participant must have at least 1 measurable tumor lesion per RECIST v1.1.

   Note: Lesions to be used as measurable disease for the purpose of response assessment must not be lesion used for biopsy and must either a) not reside in a field that has been subjected to prior radiotherapy, or b) have demonstrated clear evidence of radiographic progression since the completion of prior radiotherapy or biopsy and prior to study enrollment.

7. ECOG performance status 0 or 1.

8. Willingness to avoid pregnancy or fathering children based on the criteria below:

   a. Men must agree to take appropriate precautions to avoid fathering children (with at least 99% certainty) from screening through 90 days (corresponding to time needed to eliminate study treatment therapy for both genotoxic and teratogenic study drugs plus an additional 90 days [a spermatogenesis cycle] for study treatments with genotoxic potential) after the last dose of study treatment and must refrain from donating sperm during this period. Permitted methods that are at least 99% effective in preventing pregnancy should be communicated to the participants and their understanding confirmed (Appendix A).
   b. Women of childbearing potential must have a negative serum pregnancy test at screening and before the first dose on Day 1 and must agree to take appropriate precautions to avoid pregnancy (with at least 99% certainty) from screening through 6 months after the last dose of study treatment and must refrain from donating oocytes during this period.
   c. Permitted methods that are at least 99% effective in preventing pregnancy should be communicated to the participants and their understanding confirmed (Appendix A).

5.2. Exclusion Criteria

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

1. Laboratory and medical history parameters defined in Table 10.

Table 10: Exclusion Laboratory Values

Laboratory Parameter		Exclusion Criterion
Hematology		
a.	Platelets	≤ 100×10^9/L.
b.	Hemoglobin	≤ 9 g/L.
c.	ANC	≤ 1.5×10^9/L.
Hepatic		
d.	ALT	Phase 1: ≥ 1.5 × ULN. Phase 2: ≥ 2.5 × ULN OR > 5 × ULN for participants with liver metastases.
e.	AST	Phase 1: ≥ 1.5 × ULN. Phase 2: ≥ 2.5 × ULN OR > 5 × ULN for participants with liver metastases.
f.	Total bilirubin	≥ 1.5 × ULN, unless conjugated bilirubin ≤ ULN (conjugated bilirubin only needs to be tested if total bilirubin exceeds ULN). If there is no institutional ULN, then direct bilirubin must be < 40% of total bilirubin. Note: In no case can the total bilirubin exceed 3 × ULN.
g.	Lactate dehydrogenase	> 3 × ULN in the absence of hemolysis (not applicable to Phase 2 Cohort B).
Renal		
h.	Calculated creatinine clearance	< 50 mL/min. CrCl calculated by Cockcroft-Gault equation.
Coagulation		
i.	International normalized ratio or prothrombin time	> 1.5 × ULN.
j.	Activated partial thromboplastin time	> 1.5 × ULN.
Cardiac		
k.	TnT or TnI	> 2 × Institutional ULN. Participants with TnT or TnI levels between > 1 to 2 × ULN will be permitted if repeat levels within 24 hours are ≤ 1 × ULN. See Note below.

Note: If the screening laboratory tests were conducted > 7 days before treatment initiation, they will need to be repeated on Day 1 before initiation of treatment. Participants with 1) bone metastases and 2) no hepatic parenchymal metastases on screening radiographic examinations may enroll if the alkaline phosphatase ≤ 5 × ULN.

Note: If TnT or TnI levels are > 1 to 2 × ULN within 24 hours, the participant may undergo a cardiac evaluation and be considered for treatment, following a discussion with the sponsor medical monitor or designee. When repeat levels within 24 hours are not available, a repeat test should be conducted as soon as possible. If TnT or TnI repeat levels beyond 24 hours are < 2 × ULN, the participant may undergo a cardiac evaluation and be considered for treatment, following a discussion with the sponsor medical monitor or designee.

2. Known hypersensitivity or severe reaction to any component of the study drugs or formulation components for INCMGA00012 or INCAGN02385 or INCAGN02390.
3. Participant who had prior treatment with a LAG-3 or TIM-3 targeted agent.
4. **Phase 1 (Parts 1-4):**

   Receipt of anticancer medications or investigational drugs within the following intervals before the first administration of study treatment:

   a. Removed during Protocol Amendment 3.
   b. Removed during Protocol Amendment 3.
   c. Removed during Protocol Amendment 3.
   d. Removed during Protocol Amendment 3.
   e. Removed during Protocol Amendment 3.
   f. ≤ 28 days or 5 half-lives (whichever is longer) before the first dose for all other investigational agents or devices. For investigational agents with long half-lives (eg, > 5 days), enrollment before the fifth half-life requires medical monitor approval.
   g. Administration of colony-stimulating factors (including granulocyte colony–stimulating factor, granulocyte macrophage colony–stimulating factor, or recombinant erythropoietin) within 14 days before study Day 1.
   h. Removed during Protocol Amendment 3.
5. **Phase 2:**

   a. Cohort A: Participant who has discontinued anti–PD-(L)1 therapy due to toxicity or other reasons unrelated to toxicity, then subsequently experienced disease progression.
   b. Cohort A: Participant who had experienced objective response (PR/CR) and had stopped anti–PD-(L)1 therapy due to maximal benefit.
   c. Cohort A: Participant with multiple metastases that achieved mixed tumor response to prior anti–PD-(L)1 therapy (such as isolated progressive lesion in a context of PR/CR or SD for other lesions) or achieved overall disease progression based only on a single new lesion.
   d. Removed during Protocol Amendment 3.
   e. Cohort B: Participant who has or has had uveal melanoma.
6. Receipt of anticancer therapy (immunotherapy, chemotherapy, targeted therapy or hormonal therapy) within 21 days of the first administration of study treatment, with the exception of localized radiotherapy.
7. Palliative radiation therapy administered within 1 week of first dose of study treatment or radiation therapy in the thoracic region that is > 30 Gy within 6 months of the first dose of study treatment.

   Note: Participants must have recovered from all radiation-related toxicities, not require corticosteroids for this purpose, and not have had radiation pneumonitis.
8. If participant received major surgery, then they must have recovered adequately from toxicities and/or complications from the intervention before starting study treatment.

9. Treatment-related toxicity related to prior therapy that has not recovered to ≤ Grade 1 (with the exception of alopecia and anemia not requiring transfusional support), unless approved by the medical monitor.
10. History of immune-related toxicity during prior checkpoint inhibitor therapy for which permanent discontinuation of therapy is recommended (per product label or consensus guidelines), OR any immune-related toxicity requiring intensive or prolonged immunosuppression to manage (with the exception of endocrinopathy that is well-controlled on stable dose of replacement hormones such as hypothyroidism or adrenal insufficiency, or Grade 3 rashes that resolved with topical therapy or asymptomatic lipase elevations that do not require treatment interruption or uveitis that resolved with steroid drops).

    Note: Participants who did not tolerate anti–CTLA-4 plus anti–PD-(L)1 combination therapy and discontinued anti–CTLA-4 therapy due to toxicity but tolerated continuation on PD(L)-1 therapy may be eligible upon discussion with the medical monitor.
11. Has an active autoimmune disease requiring systemic immunosuppression with corticosteroids (> 10 mg/day of prednisone or equivalent) or immunosuppressive drugs within 14 days before the first dose of study treatment.
12. Receiving chronic systemic corticosteroids (> 10 mg/day of prednisone or equivalent).

    Notes:

    - Physiologic corticosteroid replacement therapy at doses > 10 mg daily of prednisone or equivalent for adrenal or pituitary insufficiency and in the absence of active autoimmune disease is permitted.
    - Participants with a condition that requires intermittent use bronchodilators, inhaled steroids, or local steroid injections may be admitted (eg, asthma or chronic obstructive pulmonary disease exacerbation).
    - Participants using topical, ocular, intra-articular, or intranasal steroids (with minimal systemic absorption) may be admitted.
    - Brief course of corticosteroids for prophylaxis (eg, contrast dye allergy) or study treatment-related standard premedication is permitted.
13. Active infections requiring systemic antibiotics, or antifungal or antiviral treatment within 7 days before first dose of study treatment.

    Note: A participant should be excluded if they have a positive screening test result for SARS-CoV2 infection until test normalization and clinical recovery.
14. History of organ transplant, including allogeneic stem cell transplantation.
15. Evidence of interstitial lung disease or active, noninfectious pneumonitis.
16. Known active HBV or HCV infection or risk of reactivation of HBV or HCV.

    - Active hepatitis B infection is defined by positive HBsAg and positive total anti-HBc results.

Note: When HBsAg is negative AND HBcAb and/or HBsAb is positive, HBV-DNA should be measured. When HBV-DNA is negative, this participant could be enrolled with close monitoring of HBV activities.

- Active hepatitis C is defined by a positive hepatitis C antibody result and quantitative HCV-RNA results greater than the lower limits of detection of the assay.

  Note: Participants positive for HCV antibody will be eligible if they are negative for HCV-RNA. Participants who have had definitive treatment for HCV are permitted if HCV RNA is undetectable.

17. Participants who are known to be HIV-positive.
18. Known active brain or CNS metastases including carcinomatous meningitis.

    Note: Participants who have previously treated and clinically stable brain or CNS metastases (without evidence of progression by imaging for at least 4 weeks before the first dose of study drug and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases or CNS edema and have not required steroids for at least 7 days before the study treatment period are eligible.
19. Known additional malignancy that is progressing or requires active treatment, or history of other malignancy within 2 years of study entry with the exception of cured basal cell or squamous cell carcinoma of the skin, superficial bladder cancer, carcinoma in situ of the cervix, or other noninvasive or indolent malignancy after treatment with curative intent.
20. Participants with impaired cardiac function or clinically significant cardiac disease, including but not limited to:
    - New York Heart Association Class III or IV cardiac disease, including preexisting clinically significant ventricular arrhythmia, congestive heart failure, or cardiomyopathy.
    - Unstable angina pectoris.
    - Acute myocardial infarction ≤ 6 months before study participation.
    - Other clinically significant heart disease (eg, ≥ Grade 3 hypertension).
21. History or presence of an abnormal ECG that, in the investigator's opinion, is clinically meaningful. Average QTc interval > 460 milliseconds is excluded (corrected by Fridericia or Bazett formula).
22. Women who are pregnant or breastfeeding.
23. Receipt of a live vaccine within 30 days of planned start of study treatment.

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

24. Any condition that would, in the investigator's judgment, interfere with full participation in the study, including administration of study treatment and attending required study visits; pose a significant risk to the participant; or interfere with interpretation of study data.

5.3. Lifestyle Considerations

No restrictions are required.

5.4. Screen Failures

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

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 assessments that are repeated, the most recent available result before treatment assignment will be used to determine eligibility. Additionally, a participant who fails screening may repeat the screening process 1 time if the investigator believes that there has been a change in eligibility status. Participants who rescreen must reconsent and be assigned a new participant number.

5.5. Replacement of Participants

Participants may be replaced for any of the following reasons:

- In Phase 1 (Parts 1 and 2), any participant who withdraws from treatment before the completion of the DLT observation period for any reason other than a DLT (eg, not evaluable for DLT), may be replaced to ensure a minimum number of evaluable participants.
- In Phase 2, a participant who has not met the biopsy requirements for the study (ie, pretreatment biopsy samples), may be replaced to allow for a minimum number of evaluable biopsied participants.
- Participants who do not meet the eligibility requirements of the study may be replaced.

5.6. Data Monitoring Committee

This study will use a study team independent, internal DMC to monitor safety and efficacy at the planned analyses. In Phase 1 Parts 1 and 2, the DMC will assess the initial safety of INCAGN02385 + INCAGN02390 and of INCAGN02385 + INCAGN02390 + INCMGA00012. In Phase 1 Part 3, the DMC will review safety data and occurrence of DLTs prior to opening Phase 2 Cohort B. In Phase 2 Cohort A, there will be 1 planned interim analysis after 15 participants have been enrolled. In Phase 2 Cohort B, there will be 1 planned interim analysis after 17 participants have been enrolled. Regular DMC reviews will then begin as described in the DMC charter. The voting members of the committee will be external to the study team. The members of the DMC 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.

6. STUDY TREATMENT

6.1. Study Treatments Administered

Table 11 presents the study treatment information. A 48-hour observation period between the first and second participants of the Phase 1 cohorts is required in order to monitor participants for delayed reactions. Additionally, all participants will remain in the clinic for 4 hours on Cycle 1 Day 1 following combination infusions for safety observations.

Table 11: Study Treatment Information

	Study Treatment 1	Study Treatment 2	Study Treatment 3 Administered Only in Part 2 of Phase 1 and in Phase 2
Study treatment name:	INCAGN02385	INCAGN02390	INCMGA00012
Dosage formulation:	Solution for infusion	Solution for infusion	Solution for infusion
Unit dose strength(s)/dosage level(s):	50 mg/mL; 150 mg/vial in 3 mL extractable volume Dose level Q2W: 350 mg Dose level Q3W: 450 mg or 750 mg Dose level Q4W: to be determined based on Phase 1 Part 3 monotherapy data	50 mg/mL; 150 mg/vial in 3 mL extractable volume Dose level Q2W: 400 mg Dose level Q3W: 500 mg or 1000 mg Dose level Q4W: to be determined based on Phase 1 Part 3 monotherapy data	25 mg/mL in a glass vial for single use Dose level Q3W: 375 mg Dose level Q4W: 500 mg
Route of administration	IV (30-minute infusion with filter)	IV (30-minute infusion with filter)	IV (30-minute infusion with filter)
Packaging and labeling	Study drug will be provided in a vial. Each vial will be labeled as required per country requirement.	Study drug will be provided in a vial. Each vial will be labeled as required per country requirement.	Study drug will be provided in a vial. Each vial will be labeled as required per country requirement.
Status of treatment in participating countries:	Investigational	Investigational	Investigational

Order of administration of study drugs should be INCAGN02385, followed by INCAGN02390, followed by INCMGA00012.

INCAGN02385 will be administered for up to 2 years. INCAGN02385 is a liquid form in sodium acetate, trehalose, polysorbate 80, pH 5.5 with a target protein concentration of 50 mg/mL to be used for IV infusion. The infusion site should not be used for blood sampling. Study drug should be prepared for infusion as outlined in the Pharmacy Manual.

INCAGN02390 will be administered for up to 2 years. INCAGN02390 is a liquid form in sodium citrate, sucrose, arginine, polysorbate 80, pH 6.0 with a target protein concentration of 50 mg/mL to be used for IV infusion. The infusion site should not be used for blood sampling. Study drug should be prepared for infusion as outlined in the Pharmacy Manual.

INCMGA00012 will be administered for up to 2 years.

Before administration of study treatments, 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 according to institutional policy.

6.2. Preparation, Handling, and Accountability

For detailed information concerning the reconstitution, preparation, and infusion of the study drugs, please refer to the Pharmacy Manual.

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

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

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

- Delivery of study drugs to the study site.
- Inventory of study drugs at the site.
- Participant use of the study drugs including vial counts from each supply dispensed.
- Lot numbers and/or vial numbers (as applicable) of study drugs used to prepare the infusion solution.

The investigational product must be used only in accordance with the Protocol. The investigator will also maintain records adequately documenting that the participants were provided the specified study treatment. 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 the study drugs 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 drugs back to the sponsor or its designee for destruction according to institutional SOPs. If local procedures mandate on-site destruction of investigational supply, the site should (where local procedures allow) maintain the investigational supply until the study monitor inspects the accountability records in order to evaluate compliance and accuracy of accountability by the investigative site. At sites where the study drugs are destroyed before monitor inspection, the monitors rely on documentation of destruction per the site SOP.

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

6.3. Measures to Minimize Bias: Randomization and Blinding

This is an open-label study. Measurements of safety and efficacy are objective measurements, and only comparisons to pretreatment conditions will be made. When there is more than one dose level within a part or cohort of the study, the participant will be randomly assigned into each dose level.

6.4. Study Treatment Compliance

Compliance with study treatment administration will be calculated by the sponsor based on study treatment accountability and infusion records documented by the site staff and monitored by the sponsor/designee.

6.5. Dose-Limiting Toxicity and Determination of Maximum Tolerated Dose and/or Pharmacologically Active Dose for Phase 1

6.5.1. Definition of a Dose-Limiting Toxicity

Dose-limiting toxicity will be defined as the occurrence of any of the toxicities in Table 12 occurring any time after Cycle 1 Day 1 and up to and including Day 28 for study parts or cohorts dosed on 28-day cycle (Q2W and Q4W) and Day 21 for study parts or cohorts dosed on 21-day cycle (Q3W), except those with a clear alternative explanation. Additionally, delayed immune-mediated toxicities ≥ Grade 3 occurring from first dose up to 90 days following the EOT should be considered DLTs and included in the definition of the MTD. All DLTs will be assessed for severity by the investigator using CTCAE v5.0 criteria. Participants who receive at least one dose of study treatment at the level assigned or have a DLT will be considered evaluable for determining tolerability of the dose.

Continuous evaluation of toxicity events will be performed throughout Phase 1 to assess for any late-onset immune-related toxicities that occur beyond the 28-day or 21-day DLT observation period (as applicable) up to a minimum of 90 days after the last dose of study drug. In Phase 2, participants will be continually evaluated for safety, including AEs ≥ Grade 3 that are attributable to the investigational agent. If warranted, enrollment of participants may be suspended until the sponsor, investigators, and DMC have determined the appropriate course of action.

Individual participant dose reductions are not allowed.

Table 12: Definition of Dose-Limiting Toxicity

Toxicity	Definition
Nonhematologic	• Any liver function abnormalities that meet the definition of Hy's law.[a] • Any grade encephalopathy. • Any ≥ Grade 3 nonhematologic toxicity EXCEPT: – Transient (≤ 72 hours) abnormal laboratory values without associated clinically significant signs or symptoms. – Nausea, vomiting, and diarrhea adequately controlled with medical therapy within 48 hours. – Changes in cholesterol and triglycerides. – An event clearly associated with the underlying disease, disease progression, a concomitant medication, or comorbidity. – Asymptomatic changes in lipid profiles. • Singular or nonfasting elevations in blood glucose (ie, blood glucose excursions will be considered toxicities if fasting blood glucose is elevated on 2 separate occasions).
Hematologic	• Grade 3 thrombocytopenia with bleeding. • Grade 4 thrombocytopenia. • Febrile neutropenia (ANC < 1.0×10^9/L and fever > 101°F/38.5°C). • Grade 4 neutropenia that does not recover to ≤ Grade 2 in ≤ 3 days after interrupting study treatment. • Grade 4 anemia.
Immune-related toxicity	• Grade 3 irAEs that do not improve to ≤ Grade 2 within < 5 days and to ≤ Grade 1 within 14 days with appropriate care or corticosteroid therapy. • ≥ Grade 2 ocular irAEs. • ≥ Grade 2 pneumonitis. • ≥ Grade 3 myocarditis. • Grade 4 irAEs.
General	• Although the rules for adjudicating DLTs in the context of dose escalation are specified in this table, an AE not listed in this table may be considered a DLT after a consultation with the sponsor and investigators based on the emerging safety profile.
MTD	
• See Section 10.1.1 for rules defining MTD using BOIN model.	

[a] Hy's law is defined as 1) ALT or AST elevation > 3 × ULN, 2) total bilirubin > 2 × ULN without initial findings of cholestasis (elevated serum alkaline phosphatase), AND 3) no other apparent possible causes of aminotransferase elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

6.5.2. Procedures for Cohort Review

Telephone conferences with study investigators will be scheduled by the sponsor in order to review cohort-specific data and overall safety data, to adjudicate individual high-grade AEs as potentially dose-limiting, and to guide other major study decisions.

6.6. Dose Modifications

Dose interruptions may occur for individual study participants. The identification of DLTs will define the doses used in planned cohorts. Further, the occurrence of DLTs and other toxicities (related or unrelated to study treatment) will guide decisions for treatment interruptions and discontinuation for individual participants. **Intraparticipant dose escalations or reductions are not permitted.**

The decision to proceed to the next Study Treatment combination will be made by the DMC as well as the study team and the investigators based on safety, tolerability, and preliminary pharmacodynamic data obtained in at least 3 participants at the prior Study Treatment combination.

6.6.1. Management of Dose-Limiting Toxicities or Other Urgent Situations

Investigators may employ any measures or concomitant medications necessary to optimally treat the participant after discussion with the sponsor (whenever possible).

6.6.2. Follow-Up of Dose-Limiting Toxicities in Phase 1

Any DLT should be monitored until it resolves to baseline or appears to have stabilized for a minimum of 4 weeks. During follow-up, participants should be seen as often as medically indicated to assure safety.

6.6.3. Criteria and Procedures for Dose Interruptions and Adjustments of Study Treatment

Instructions for dose interruptions for study drugs (INCAGN02385, INCAGN02390, and retifanlimab) are outlined in Table 13. Adverse events that have a clear alternative explanation, or transient (≤ 72 hours) abnormal laboratory values without associated clinically significant signs or symptoms, may be exempt from dose-reduction rules.

Safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.

Dose modification of study drugs (INCAGN02385, INCAGN02390, retifanlimab) is not permitted. If a dose interruption is necessary for management of drug-related TEAEs, study drugs will be reinitiated at starting dose.

Treatment with study drugs may be interrupted for up to 12 weeks to allow for resolution of toxicity. All study drugs should be interrupted at the same time for the same duration. Participants may resume treatment if no medical condition or other circumstance exists that, in the opinion of the investigator, would make the participant unsuitable for further participation in the study. The treating investigator should contact the sponsor to discuss the case of any participant whose treatment has been delayed for more than 12 weeks before restarting treatment with the study treatment.

For participants given INCAGN02385 plus INCAGN02390 on the Q2W infusion schedule, if Day 15 infusions are skipped because of toxicity, the next dose of INCAGN02385 plus INCAGN02390 can be resumed once the toxicity resolves as per protocol guidance:

- If treatment is restarted ≤ 4 weeks from the last treatment dose, resume INCAGN02385 plus INCAGN02390 only (that would be considered Day 15), then the subsequent treatment visit should occur 2 weeks later with the triplet (including INCMGA00012) and continue per protocol schedule.
- If treatment is restarted ≥ 4 weeks from last treatment dose, proceed with the triplet combination (ie, omit the Day 15 dose of INCAGN02385 plus INCAGN02390) and continue per study schedule.

Decisions regarding dose interruptions and restarting study drugs will be made according to Table 14 for suspected infusion reactions, and Table 13 for irAEs. For reasons other than infusion reactions and irAEs, the investigator and medical monitor will make decisions jointly regarding dose interruptions and restarting study drugs on a case-by-case basis.

Dose interruptions are permitted in the case of medical or surgical events (eg, elective surgery, unrelated medical events). In such a case, study treatment should resume within 4 weeks of the scheduled interruption, unless otherwise discussed with the sponsor. Delayed study treatment administration in the case of logistical reasons not related to study therapy (eg, participant vacation, holidays) is permitted. In such a case, study treatment should resume within 3 to a maximum of 7 days of the scheduled interruption, unless otherwise discussed with the sponsor.

For participants who have active confirmed (positive results from an approved COVID-19 test) or presumed (test pending/clinical suspicion) SARS-CoV2 infection, guidelines in Appendix C should be followed.

If any of the combination agents are permanently discontinued for toxicity, all immunotherapy agents should be discontinued.

Table 13: Guidelines for Interruption and Restarting of Study Treatment

CTCAE Grade/Severity	Hold Treatment (Y/N)	Timing for Restarting Treatment	Dose Level for Restarting Immune Therapies	Treatment Discontinuation
1-2 (Mild-Moderate)	No	Continue treatment at the discretion of the investigator.	N/A	N/A
3 (Severe)	Yes	Toxicity resolves to Grade 0-1.	Restart same dose.	Toxicity does not resolve within 4 weeks (28 days) of last dose, except by approval of the medical monitor. OR Second occurrence of previously resolved Grade 3 AE.
4 (Life-Threatening)	Yes	Permanent discontinuation, except by approval of the medical monitor. If continuing, toxicity must resolve to Grade 0-1.	Permanent discontinuation, except by approval of the medical monitor. If continuing, restart same dose.	Permanent discontinuation for any severe or life-threatening event, except by approval of the medical monitor.

6.6.4. Management of Suspected Infusion Reactions

Immunotherapies have been associated with the occurrence of infusion reactions. The incidence of infusion reactions to INCMGA00012 in company-sponsored studies is low (2.2%). No infusion reactions have been observed with INCAGN02385 nor INCAGN02390. Infusion or hypersensitivity reactions may be observed with administration of any foreign protein. Premedication with an antipyretic (eg, acetaminophen/paracetamol) and a histamine blocker (eg, diphenhydramine) should be considered for participants who have had previous systemic reactions to protein product infusions or when recommended by institutional policy. Routine prophylaxis is not required.

Guidelines for management of suspected infusion reactions are provided in Table 14.

Table 14: Guidelines for Management of Suspected Infusion Reactions

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

6.6.5. Procedures for Participants Exhibiting Immune-Related Adverse Events

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

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

Recommendations for the management of specific irAEs known to be associated with other PD-1 inhibitors (eg, pembrolizumab, nivolumab) are detailed in Table 15. For additional management guidance for irAEs not detailed in the Protocol, or for details on diagnostic algorithms for an irAE if needed, refer to the ASCO, ESMO, or NCCN Clinical Practice Guidelines (Haanen et al 2017, NCCN 2021, Schneider et al 2021).

Continuous evaluation of toxicity events will be performed throughout Phase 1 to assess for any late-onset immune-related toxicities that occur beyond the 28-day DLT observation period up to

a minimum of 90 days after the last dose of study drug. In Part 2, participants will be continually evaluated for safety, including AEs ≥ Grade 3 that are attributable to the investigational agent. If warranted, enrollment of participants may be suspended until the sponsor, investigators, and DMC have determined the appropriate course of action.

Table 15: Toxicity Management Guidelines for Immune-Related Adverse Events

Immune-Related Adverse Event	Toxicity Grade or Conditions (CTCAE v5.0)	Action Taken With Immunotherapy Combinations	Adverse Event Management With Corticosteroid and/or Other Supportive Care Therapies[a]
Pneumonitis	Grade 1	No action.	None.
	Grade 2	Withhold until ≤ Grade 1.	• Evaluate participants with suspected pneumonitis with radiographic imaging and administer systemic corticosteroids per local practice followed by taper. • Add prophylactic antibiotics for opportunistic infections.
	Grades 3 or 4 or recurrent Grade 2	Permanently discontinue.	
Diarrhea/colitis	Grade 1	No action.	None.
	Grades 2 or 3	Withhold until ≤ Grade 1.	• Consider prompt initiation of standard antidiarrheal agents and other necessary supportive care as needed (eg, oral and/or IV fluids). • Administer systemic corticosteroids per local practice followed by taper. • Consider prophylactic antibiotics per local practice. • Consider gastrointestinal consultation and performing endoscopy to rule out colitis. • 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 > 1.5 × and up to 3 × 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).
	Grades 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 > 2 × ULN or In participants with liver metastases and elevated total bilirubin at baseline Grade ≥ 3	Permanently discontinue.	

Table 15: Toxicity Management Guidelines for Immune-Related Adverse Events (Continued)

Immune-Related Adverse Event	Toxicity Grade or Conditions (CTCAE v5.0)	Action Taken With Immunotherapy Combinations	Adverse Event Management With Corticosteroid and/or Other Supportive Care Therapies[a]
Endocrinopathies • Hypothyroidism • Hyperthyroidism • Type 1 diabetes mellitus • Hyperglycemia • Adrenal insufficiency • Hypophysitis	Grades 1 or 2	No action.	None.
	Grades 3 or 4 hypothyroidism	Withhold until ≤ Grade 1 or is otherwise clinically stable.	Initiate thyroid replacement hormones (eg, levothyroxine, liothyronine) per SoC.
	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.
	Grade 1 adrenal insufficiency	No action.	None.
	Grade 2 adrenal insufficiency	Withhold until ≤ Grade 1 or otherwise clinically stable.	Initiate treatment with hormone replacement therapy 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.	Administer prednisone or equivalent at initial dose of 1-2 mg/kg/day followed by a taper and initiate treatment with hormone replacement therapy as clinically indicated.
	Grade 1 hypophysitis	No action.	None.
	Grade 2 hypophysitis (asymptomatic)	• Withhold until ≤ Grade 1. • May restart study drug after controlled by hormone replacement therapy.	Initiate treatment with hormone replacement therapy.
	Grade 2 hypophysitis (symptomatic; eg, headaches, visual disturbances)	• Withhold until ≤ Grade 1. • May restart study drug after controlled by hormone replacement therapy, if indicated, and corticosteroid taper is complete.	• Administer corticosteroids at initial dose of 1-2 mg/kg/day prednisone or equivalent followed by a taper and initiate treatment with hormone replacement therapy as clinically indicated. • Consult with endocrinologist as needed.
	Grades 3 or 4 hypophysitis (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/day prednisone or equivalent 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.	

Table 15: Toxicity Management Guidelines for Immune-Related Adverse Events (Continued)

Immune-Related Adverse Event	Toxicity Grade or Conditions (CTCAE v5.0)	Action Taken With Immunotherapy Combinations	Adverse Event Management With Corticosteroid and/or Other Supportive Care Therapies[a]
Nephritis with renal dysfunction	Grade 1	No action.	None.
	Grades 2 increased blood creatinine	Withhold until ≤ Grade 1.	Administer corticosteroids per local practice followed by taper.
	Grades 3 or 4 increased blood creatinine	Permanently discontinue[b].	
Skin reactions	Grade 1	No action.	None.
	Grade 2	No action.	Manage with topical corticosteroids with or without drug interruption.
	Grade 3[c], persistent Grade 2 (≥ 2 weeks) or Grade 3 SJS or Suspected SJS or suspected TEN	Withhold until ≤ Grade 1 after corticosteroid taper to ≤ 10 mg/day prednisone or equivalent.	• Administer corticosteroids per local practice followed by taper. Additionally, oral histamine blockers such as diphenhydramine or famotidine (per institutional preference) may be utilized as needed. • Refer to dermatology consult if no resolution with these measures. • Refer to dermatology consult if SJS or TEN is suspected.
	Grade 4 or Grade 4 SJS or TEN	Permanently discontinue.	• Administer prednisone or equivalent at initial dose of 1-2 mg/kg/day followed by a taper. • Refer to dermatology consult.
Myocarditis	Grade 2	• Depending on severity of symptoms, withhold until symptoms fully resolve and management with corticosteroids is complete. • Permanent discontinuation of 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 to cardiology consult. • Manage cardiac symptoms according to SOC 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-Barré syndrome, autoimmune encephalitis, myasthenia gravis, autonomic neuropathy, transverse myelitis)	Grade 2	Withhold until ≤ Grade 1.	• Refer to neurology consult. • Initiate treatment with systemic corticosteroids (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 SOC and with guidance from neurology.
	Grades 3 or 4	Permanently discontinue.	

Table 15: Toxicity Management Guidelines for Immune-Related Adverse Events (Continued)

Immune-Related Adverse Event	Toxicity Grade or Conditions (CTCAE v5.0)	Action Taken With Immunotherapy Combinations	Adverse Event Management With Corticosteroid and/or Other Supportive Care Therapies[a]
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 Grade 2 or Grade 3	Permanently discontinue.	
	Grade 4[d] (excluding endocrinopathies)	Permanently discontinue.	

[a] As general instructions, the following should be followed: if treatment-related toxicity does not resolve to Grade 0-1 within 12 weeks after the last dose of study drug, or if the corticosteroid dose cannot be reduced to ≤ 10 mg prednisone or equivalent per day within 12 weeks, study drug should be permanently discontinued. Severe and life-threatening irAEs should be treated with IV corticosteroids followed by oral corticosteroids. Other immunosuppressive treatment should begin if irAEs are not controlled by corticosteroids.
[b] If INCMGA00012 ± INCAGN02385 ± INCAGN02390 is directly implicated in the renal toxicity.
[c] Participants with Grade 3 rash in the absence of desquamation, with no mucosal involvement, not requiring systemic corticosteroids, and resolving or improving to ≤ Grade 1 within 14 days do not have to interrupt study treatment. Permanent discontinuation of study treatment may be necessary if there is recurrence of Grade 3 rash after resuming study treatment.
[d] If Grade 4 lipase/amylase elevation is asymptomatic and abdominal imaging suggests no pathology, then study treatment administration may continue with medical monitor approval.

6.6.6. Criteria for Permanent Discontinuation of Study Treatment

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

- Occurrence of an AE that is related to study treatment that, in the judgment of the investigator or the sponsor's medical monitor, compromises the participant's ability to continue study-specific procedures or is considered to not be in the participant's best interest.
- Persistent AE requiring a delay of therapy for more than 12 weeks unless a greater delay has been approved by the sponsor.

See Section 7 for discontinuation procedures.

6.6.7. Criteria and Procedures for Dose Increases of Study Treatment

Intraparticipant dose escalation is not permitted.

6.6.8. Treatment After Initial Evidence of Radiologic Disease Progression

Combinations of immunotherapeutic agents such as the combination of INCMGA00012, INCAGN02385 and INCAGN02390 may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such as 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 even the appearance of new lesions.

If radiologic imaging shows PD, tumor assessment should be repeated ≥ 4 weeks later to confirm PD, with the option of continuing treatment per below while awaiting radiologic confirmation of progression. If repeat imaging shows a reduction in the tumor burden compared to the initial scan demonstrating PD, treatment may be continued as per treatment calendar. If repeat imaging confirms PD, participants will be discontinued from study therapy. In determining whether the tumor burden has increased or decreased, investigators should consider all target lesions as well as nontarget lesions.

When feasible, participants should not be discontinued until progression is confirmed; however, the decision to continue study treatment after the first evidence of disease progression is at the investigator's discretion based on the clinical status of the participant as described in Table 16. Treatment should not continue beyond 2 years.

Participants may receive study treatment while waiting for confirmation of PD if they are clinically stable as defined by the following criteria:

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

Table 16: Imaging and Treatment After First Radiologic Evidence of Progressive Disease

	Clinically Stable		Clinically Unstable	
	Imaging	**Treatment**	**Imaging**	**Treatment**
First radiologic evidence of PD	Repeat imaging at ≥ 4 weeks to confirm PD	May continue study treatment at the investigator's discretion while awaiting confirmatory scan	Repeat imaging at ≥ 4 weeks to confirm PD if possible	Discontinue treatment
Repeat scan confirms PD	No additional imaging required	Discontinue treatment	No additional imaging required	N/A
Repeat scan shows SD, PR, or CR	Continue regularly scheduled imaging assessments	Continue study treatment at the investigator's discretion	Continue regularly scheduled imaging assessments	May restart study treatment if condition has improved and/or clinically stable per investigator's discretion

6.7. Concomitant Medications and Procedures

All concomitant medications and treatments (including over-the-counter or prescription medicines, vitamins, vaccines, and/or herbal supplements) must be recorded in the eCRF. Any

prior medication received up to 28 days before the first dose of study treatment and 90 days after the last dose of study treatment regardless of whether the participant begins a new anticancer therapy, whichever occurs first, will be recorded in the eCRF. Any addition, deletion, or change in the dose of these medications will also be recorded. Concomitant medications administered after 90 days after the last dose of study treatment should be recorded for SAEs as defined in Section 8.3.1. Concomitant treatments/procedures that are required to manage a participant's medical condition during the study will also be recorded in the eCRF. The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.7.1. Permitted Medications and Procedures

All treatments that the investigator considers necessary for a participant's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medications will be recorded on the eCRF, including all prescription and over-the-counter medications, herbal supplements, and IV medications and fluids. If changes occur during the study period, then documentation of drug regimen, frequency, route, and date must also be included on the eCRF.

Note: The use of bisphosphonates and denosumab are permitted in this study.

6.7.2. Restricted Medications and Procedures

Use of systemic glucocorticoids is restricted to prophylaxis for contrast allergies for radiographic procedures or to modulate symptoms or treat an AE of suspected immunologic etiology. The use of physiologic corticosteroid replacement therapy should be used as per the guidelines in Section 6.6.5.

Note: Inhaled and topical steroids are allowed. A short course of steroids (prednisone or equivalent) ≤ 10 mg/day may be permitted with medical monitor approval.

6.7.3. Prohibited Medications and Procedures

Medications or vaccinations specifically prohibited in the exclusion criteria (see Section 5.2) are not allowed during the ongoing study. If there is a clinical indication for one of these medications or vaccinations specifically prohibited during the study, discontinuation from study treatment or vaccination may be required. The investigator should discuss any questions regarding this with the medical monitor. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study treatment or vaccination schedule requires the mutual agreement of the investigator, the medical monitor, and the participant.

6.8. Treatment After the End of the Study

Once a participant has discontinued study treatment, no further treatment will be provided in this study. Participants who discontinue study drug will enter the follow-up period to be evaluated for safety and survival for up to 2 years. Any participants entering the follow-up period for any reason other than PD will continue to be evaluated for disease status according to the scheduled assessments found in Table 3 and Table 6.

7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Treatment

7.1.1. Reasons for Discontinuation

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

- The participant becomes pregnant.
- Consent is withdrawn.
  Note: Consent withdrawn means that the participant has explicitly indicated that they do not want to be followed any longer; in this case no further data, except data in public domain, may be solicited from or collected on the participant. Participants may choose to discontinue study treatment and remain in the study to be followed for progression and survival.
- Further participation would be injurious to the participant's health or well-being, in the investigator's medical judgment.
- Unacceptable toxicity as noted in Section 6.6.
- The study is terminated by the sponsor.
- The study is terminated by the local health authority, IRB, or IEC.

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

- Confirmed or unequivocal radiographic progression of disease per RECIST v1.1. See Section 8.2.

  Note: A participant may be granted an exception to continue on treatment with confirmed progression if clinically stable or clinically improved.
- 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 treatment administration in the investigator's opinion, the sponsor should be consulted for instruction on handling the participant.

7.1.2. Discontinuation Procedures

In the event that the decision is made to permanently discontinue the study treatment, the EOT visit should be conducted. Reasonable efforts should be made to have the participant return for a follow-up visit. These visits are described in Table 3 and Table 6. The last date of the last dose of study treatment and the reason for discontinuation of study treatment will be recorded in the eCRF.

If a participant is discontinued from study treatment:

- The study monitor or sponsor must be notified.
- The reason(s) for 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 date of the EOT visit should be recorded in the IRT.
- Participants must be followed for safety until the time of the follow-up visit or until study treatment–related toxicities resolve, return to baseline, or are deemed irreversible, whichever is longest.

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

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 and Table 6 for data to be collected at the time of study withdrawal and follow-up and for any further evaluations that need to be completed.

7.3. Lost to Follow-Up

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

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.

- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Administrative and General Procedures

8.1.1. Informed Consent Process

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

- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must provide consent to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

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

8.1.2. Screening Procedures

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

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

Results from the screening visit evaluations will be reviewed to confirm eligibility before enrollment or the administration of study treatment. Tests with results that fail eligibility requirements may be repeated once during screening if the investigator believes the results to be in error. For screening assessments that are repeated, the most recent available result before treatment assignment will be used to determine eligibility. Additionally, a participant who fails screening may repeat the screening process 1 time if the investigator believes that there has been a change in eligibility status. Participants who rescreen must reconsent and be assigned a new participant number. Treatment should start as soon as possible, but within 7 days after the date of enrollment.

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

8.1.3. Interactive Response Technology Procedure

Each participant will be identified in the study by a participant ID number, which is a combination of the site ID and participant number. Site staff should contact the IRT to obtain the participant ID number during screening. Upon determining that the participant is eligible for study entry, the IRT will be contacted to obtain the treatment assignment. 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. Demography and Medical History

8.1.4.1. 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 year of birth/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.

8.1.4.2. 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, as well as best response to prior systemic therapy, date of disease progression and reason for prior systemic therapy discontinuation will be recorded.

8.2. Efficacy Assessments

8.2.1. Tumor Imaging

The same imaging technique should be used for a participant throughout the study. The baseline scan must be a contrast CT or MRI, except in circumstances where there is a contrast allergy or with medical monitor approval. When the CT component of a positron emission tomography/CT uses higher energy and thinner slices, it may be acceptable with medical monitor approval if it is of diagnostic quality. Images of the chest and abdomen are required for all participants.

8.2.1.1. Tumor Imaging During Screening

Initial tumor imaging must be performed within 28 days before the first dose of study treatment. For the Phase 2 cohorts, the site study team must review prestudy images to confirm that the participant has measurable disease per RECIST v1.1. Tumor lesions that are located in a previously irradiated area or in an area subjected to other locoregional therapy should not be selected as target lesions. If a participant only has lesions in an area previously irradiated or subjected to locoregional therapy, then the participant will be allowed to enroll. Additionally, it is recommended that tumor lesions selected for biopsy **not** be selected as target lesions.

Computed tomography or MRI scan of the brain will be performed at screening if there are signs or symptoms suggesting that the participant has disease involvement in the CNS. An MRI of the brain will also be required at screening for all participants with melanoma.

Scans performed as part of routine clinical management are acceptable for use as the screening scan if they are of diagnostic quality and performed within 28 days before the first dose of study treatment.

8.2.1.2. Tumor Imaging During the Study

For participants on Q2W or Q4W schedule, the first imaging assessment should be performed 8 weeks after the first dose of study treatment and then every 8 weeks (56 ± 7 days) for

12 months and then every 12 weeks thereafter until disease progression is determined. For participants on Q3W schedule, the first imaging assessment should be performed 9 weeks after the first dose of study treatment and then every 9 weeks (63 ± 7 days) for 12 months and then every 12 weeks thereafter until disease progression is determined.

For Phase 2 Cohort B only (first-line melanoma), first on-treatment imaging should be done at 12 weeks with subsequent imaging performed every 9 weeks (± 7 days) for the first 12 months and then every 12 weeks (± 7 days) thereafter until disease progression or treatment discontinuation.

Imaging assessments may be done more frequently if clinically indicated. **Imaging should not be delayed for delays in cycle starts.**

Repeated brain imaging during the treatment phase will be performed only if the screening brain imaging was positive or as clinically indicated. If indicated, brain imaging should occur at same time (± 2 weeks) as disease assessment scans. Whenever feasible, contrast-enhanced brain MRI is preferred to CT.

Per RECIST v1.1, response should be confirmed by a repeat radiographic assessment not less than 4 weeks from the date that the response was first documented. The scan 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.

Imaging should continue to be performed until documented disease progression, the start of new anticancer treatment, withdrawal of consent, death, or the end of the study, whichever occurs first. Disease progression should be confirmed at least 4 weeks, but no later than 8 weeks, after the first scan indicating progression in clinically stable participants. A central imaging vendor will not be used in this study.

8.3. Safety Assessments

See Section 6.6 for guidelines regarding the management of relevant laboratory or other safety assessment abnormalities.

8.3.1. Adverse Events

Adverse events will be monitored from the time the participant signs the ICF until at least 28 days after the last dose of study treatment regardless of the start of a new anticancer therapy. Immune-related AEs will be collected until 90 days after the last dose of study drug. Adverse events that begin or worsen after informed consent should be recorded on the Adverse Events Form in the eCRF regardless of the assumption of a causal relationship with the Study Treatment. 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 and irAEs (see Section 6.6.5) will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

8.3.2. Physical Examinations

Physical examinations must be performed by a medically qualified individual, such as a licensed physician, physician's assistant, or an advanced registered nurse practitioner, as local law permits. Abnormalities identified after 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. Investigators should pay special attention to clinical signs related to previous serious illnesses.

At the screening visit, a comprehensive physical examination should be conducted. The comprehensive physical examination will include height 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.

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

8.3.3. Vital Signs

Vital sign measurements (to be taken before blood collection for laboratory tests) include blood pressure, pulse, respiratory rate, pulse oximetry, and body temperature. If vital signs cannot be taken before blood collection for laboratory tests, there must be a minimum of 30 minutes from the completion of the blood collection procedures to the beginning of the vital signs collection. Blood pressure and pulse will be taken with the participant in the recumbent, semirecumbent, or sitting position after 5 minutes of rest. Weight will also be assessed at each study visit. 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.

8.3.4. Electrocardiograms

Triplicate 12-lead ECGs will be obtained as outlined in the SoA at screening or Cycle 1 Day 1 and on Day 1 of Cycles 2, 3, and 4 and then at EOT. ECGs may also be collected as clinically indicated at any time during the study. ECG collection should occur within 10 minutes after the end of infusion on Cycle 1 Day 1 and Cycle 4 Day 1 (see Table 3 and Table 6).

An ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals should be used. All 12-lead ECGs will be performed with the participant in a recumbent or semirecumbent position after 5 minutes of rest.

At each timepoint at which triplicate ECGs are required, 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart. The full set of triplicates should be completed in less than 4 minutes.

The 12-lead ECGs will be interpreted by the investigator at the site to be used for immediate participant management. Additional 12-lead ECGs may be performed as clinically indicated to manage participant safety. The decision to include or exclude a participant or withdraw a participant from the study treatment based on an ECG flagged as "Abnormal, Clinically Significant" is the responsibility of the investigator, in consultation with the sponsor's medical monitor, as appropriate. Clinically notable abnormalities that are considered clinically significant in the judgment of the investigator are to be reported as AEs. In the event that a single QTc is > 460 milliseconds at screening, the participant may enroll if the average QTc for the 3 ECGs is ≤ 460 milliseconds or with approval from the medical monitor. For participants with an intraventricular conduction delay (QRS interval > 120 milliseconds) at screening, the JTc interval may be used in place of the QTc with medical monitor approval. In addition, the JTc interval should be used for all subsequent assessments.

8.3.5. Laboratory Assessments

See Table 17 for the list of clinical laboratory tests to be performed and the SoA (Table 4 and Table 7) for the timing and frequency. 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 testing may be required by the sponsor based on emerging safety data. Additional tests may also be performed if clinically indicated.

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 30 days after the last dose of study treatment should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

Screening laboratory assessments must be performed within 7 days of Cycle 1 Day 1. If performed more than 7 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.

Table 17: Required Laboratory Analytes

Blood Chemistries	Hematology	Urinalysis With Microscopic Examination (Only if Blood is Suspected in Urine)	Serology	Coagulation
Albumin Alkaline phosphatase ALT AST Amylase Bicarbonate or CO_2 Blood urea nitrogen or urea Calcium Chloride Creatinine Glucose Lactate dehydrogenase Lipase Magnesium Phosphate Potassium Sodium Total bilirubin Direct bilirubin (if total bilirubin is elevated above ULN) Total protein Troponin (per local standard) Uric acid Urea	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	Color and appearance pH and specific gravity Bilirubin Glucose Ketones Leukocytes Nitrite Occult blood Protein	Hepatitis B surface antigen Hepatitis B surface antigen antibody Hepatitis B core antibody HBV-DNA HCV antibody HCV-RNA HIV	PT PTT or aPTT INR
		Lipid Panel	**Endocrine Function**	**Pregnancy Testing**
		Total cholesterol Triglycerides LDL HDL	TSH T4 T3/FT3 ACTH Cortisol[a]	Female participants of childbearing potential only require a serum test at screening and EOT and a urine pregnancy test before the first dose on Cycle 1 Day 1. Pregnancy tests (serum or urine) should be repeated if required by local regulations.

Note: Additional laboratory analytes used for management of AEs/SAEs, ruling out a diagnosis, or participant management are permissible during the study.
Note: Additional tests may be required, as agreed upon by the investigator and sponsor, based on emerging safety data.
[a] Nycthemeral cortisol levels variation should be considered, sample collection at fixed time such as early morning is advised.

8.3.5.1. Pregnancy Testing

A serum pregnancy test will be required for all women of childbearing potential during screening and must be within 72 hours before the first dose of study treatment and at the EOT visit. EOT pregnancy testing is optional if the participant is going to hospice. Urine pregnancy tests will be performed locally as outlined in Table 4 and Table 7, as medically indicated (eg, in case of loss of menstrual cycle, when pregnancy is suspected), or per country-specific requirement (note that country-required urine pregnancy testing will be outlined and communicated to investigational sites under separate cover). If a urine pregnancy test is positive, the results should be confirmed with a serum pregnancy test.

If the serum pregnancy test is negative after a urine test was positive, the investigator will assess the potential benefit/risk to the participant and determine whether it is in the participant's best interest to resume study treatment and continue participation in the study.

If a pregnancy is confirmed by a serum pregnancy test, see Section 9.6 for reporting requirements.

8.3.5.2. Serology

Hepatitis screening assessments will be performed at the screening visit to rule out hepatitis infection; required analytes are shown in Table 17. Generally, hepatitis tests should be performed early in the screening process due to the length of time needed to obtain the results. Additional tests may be performed if clinically indicated.

8.5.2. Tissue Biopsy Collection Requirements

8.5.2.1. Phase 1

Tumor tissue (fresh or archival) should be provided at screening for Phase 1 if available. If no tumor tissue is available, the participant **may** still be enrolled after discussion with the medical monitor.

If an archival pre—anti–PD-(L)1 treatment biopsy is available, this tissue is suitable for analysis of [redacted] biomarkers.

An additional optional biopsy, referred to as the disease assessment biopsy, may be collected once the participant meets the requirements for SD, response, or progression by radiographic disease assessment.

8.5.2.2. Phase 2

Fresh tumor tissue is required for participation in Phase 2 of this study. Mandatory tumor biopsies will be collected at baseline (before Day 1 administration). Fine-needle aspirates are not acceptable. Fresh tumor biopsies should be taken from nontarget lesions when possible.

A baseline biopsy obtained for other purposes (ie, not a Protocol-defined procedure) before signing consent may be used ONLY if the participant has not had any intervening systemic therapy from the time of the biopsy to the start of treatment (ie, Cycle 1 Day 1) and if sufficient tissue can be submitted.

An additional optional biopsy, referred to as the disease assessment biopsy, may be collected once the participant meets the requirements for SD, response, or progression by radiographic disease assessment. The optional specimen may be used to correlate the degree and type of immune cell infiltration and other [redacted] biomarkers, including analysis of RNA-based transcriptional profiles or somatic mutations with response.

For Phase 2 Cohort A only, if pre—anti–PD-(L)1 treatment archival tissue is available, this tissue is suitable for analysis of [redacted] biomarkers.

8.5.3. Fresh/Archived Tissue Biopsy Assessment

Tissue biopsy samples collected during screening will be used to assess LAG-3 (and its ligands or other tissue markers) expression in participants enrolled in both Phase 1 and Phase 2 LAG-3 expression will be assessed by IHC using an investigative test at a central laboratory. The LAG-3 antibody clone L3-PL33 (Enzo) will be used (see Appendix B).

Tissue biopsy samples will also be used to investigate molecular signatures associated with response or resistance to treatment with the study drug. DNA and/or RNA may be extracted from these samples to perform somatic mutation analysis, epigenetic analysis, and gene expression analysis. Tissue may also be examined by histology and immunohistochemistry or by [redacted] methods to evaluate markers of immune cell populations, growth, signaling, apoptosis, etc that may be associated with safety, response, or resistance to treatment with the study drug.

8.5.4. Plasma Correlative Assessments

A number of tumor and immune response–derived proteins can be shed from tumors or activated normal cells and released into the blood. Correlation of presence and abundance of certain proteins with clinical response may identify new approaches for predictive biomarkers in blood, representing a major advance from today's reliance on assessing tumor biomarkers. Plasma analytes may include cytokines and other markers of inflammation and immune status, tumor markers, and markers of metabolism and nutritional status. Other assays relevant to the objectives of the study may be performed based on emerging data.

8.5.5. Plasma cfDNA Assessments

A sample of plasma will be collected for possible analysis of mutations identified in tumor biopsies using tumor circulating DNA.

8.5.6. Whole Blood Correlative Flow Cytometry Assessments

Whole blood correlative samples may be analyzed by flow cytometry to identify relevant changes in cell populations or in various markers expression by cell populations with treatment. Receptor occupancy for LAG-3, TIM-3 and PD-1 will be assessed by flow cytometry. Other assays relevant to the objectives of the study may be performed based upon emerging data.

8.5.7. Whole Blood for PBMC Assessments

Whole blood PBMC samples may be analyzed by DNA and/or RNA profiling or similar methods to identify cell populations and changes in cell populations or expression by cell populations with treatment. RNA analysis may include expression analysis by RNASeq or RNAscope® analysis for specific gene expression. Immune cell subsets function may also be assessed using ex vivo restimulation assays. Other assays relevant to the objectives of the study may be performed based upon emerging data.

8.5.8. Whole Blood Correlative DNA Assessments

DNA analysis may provide a control to define tumor somatic mutations or be used for T-cell and B-cell receptor profiling and/or epigenetic analysis. Other assays relevant to the objectives of the study may be performed based upon emerging data.

8.6. Unscheduled Visits

Not applicable.

8.7. End of Treatment and/or Early Termination

When the participant permanently discontinues study treatment whether the participant is terminating the study early or the participant has completed the study, the EOT visit should be conducted. 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. The participant should be encouraged to return for the follow-up visit.

8.8. Follow-Up

8.8.1. Safety Follow-Up

The safety follow-up period is the interval between the EOT visit and the scheduled follow-up visit, which should occur 30 to 90 days after the EOT visit (or after the last dose of study treatment if the EOT visit was not performed). Adverse events and SAEs must be reported up until 1) at least 28 days after the last dose of study treatment regardless of the start of a new anticancer therapy or 2) until toxicities resolve, return to baseline, or are deemed irreversible, whichever is longer. Immune-related AEs will be collected until 90 days after the last dose of study drug. 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 (eg, lives far away), the participant should be contacted by telephone for assessment of AEs and SAEs. Sites should be instructed to document this contact in the source.

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

8.8.2. Post-Treatment Disease Follow-Up

Participants who discontinue study treatment for a reason other than disease progression will move into the disease status follow-up period and should continue to be assessed by radiologic imaging to monitor disease status on the same schedule as outlined in Section 8.2.1.2 and the SoA. Every effort should be made to collect information regarding disease status until:

- The start of new anticancer therapy.
- Disease progression.
- Death.
- The end of the study.

8.8.3. Survival Follow-Up

Once a participant has received the last dose of study treatment, has confirmed disease progression, or starts a new anticancer therapy, the participant moves into the survival follow-up period and should be contacted by telephone, email, or visit at least every 6 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

For participants having entered the survival follow-up period of the study, the site will use continuing participant records to supply data on subsequent treatment regimens, tumor assessments (if discontinued treatment for a reason other than progression), and overall survival in the eCRF. For participants who do not intend to return to the study investigator for their ongoing care, follow-up should be maintained by phone contact, patient records, and public records/databases at intervals of no longer than 6 weeks.

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

9.1. Definition of Adverse Event

Adverse Event Definition

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

Events 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 treatment. Whenever possible, a diagnosis (eg, anemia, thrombocytopenia) should be recorded in the eCRF rather than the abnormal laboratory result (eg, low hemoglobin, platelet count decreased).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study treatment administration even though they may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT Meeting the Adverse Event Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition or considered to be treatment-related by the investigator.

- Efficacy endpoints as outlined in Section 3 will not be reported as AE/SAEs, specifically, any event that is related to disease progression of the cancer under study. Unblinded aggregated efficacy endpoint events and safety data will be monitored to ensure the safety of the participants in the study. Any suspected endpoint that upon review is not progression of the cancer under study will be forwarded to Incyte Pharmacovigilance as a SAE within 24 hours of determination that the event is not progression of the cancer under study.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE if it occurred after signing informed consent. If present before entering the study, the condition should be captured as medical history.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

9.2. Definition of Serious Adverse Event

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

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

a. Results in death

b. Is life-threatening

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

c. Requires inpatient hospitalization or prolongation of existing hospitalization

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

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

d. Results in persistent or significant disability/incapacity

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

e. Is a congenital anomaly/birth defect

f. Other situations (Important Medical Event)

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

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

Adverse Event and Serious Adverse Event Recording

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

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

- The severity grade (CTCAE v5.0 Grade 1 to 5). See below for further instructions on the assessment of intensity.
- Whether there is at least a reasonable possibility that the AE is related to the study treatment: suspected (yes) or not suspected (no). See below for further instructions on the assessment of causality.
- The start and end dates, unless unresolved at final follow-up.
- The action taken with regard to study treatment as a result of the AE/SAE(s)
- The event outcome (eg, not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown).
- The seriousness, as per the SAE definition provided in Section 9.2.
- The action taken with regard to the event. Note: If an AE is treated with a concomitant medication or nondrug therapy, this action should be recorded on Adverse Event Form and the treatment should be specified on the appropriate eCRF (eg, Prior/Concomitant Medications, Procedures and Non-Drug Therapy).

Assessment of Intensity

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

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

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

Assessment of Causality

- The investigator is obligated to assess the relationship between study 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 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. • 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 treatment, the interventions required to treat the event, and the outcome. • When the severity of an AE changes over time for a reporting period (eg, between visits), each change in severity will be reported as a separate AE until the event resolves.

9.4. Reporting of Serious Adverse Events

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

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

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and immune-related AEs 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 any of the study drugs (refer to INCMGA00012 IB, INCAGN02385 IB, or INCAGN02390 IB) for the study drug (new occurrence) and is thought to be related to the sponsor's study drug, the sponsor or its designee may urgently require further information from the investigator for reporting to health authorities. The sponsor or its designee may need to issue an Investigator Notification to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected unexpected serious adverse reactions will be collected and reported to the competent authorities and relevant ethics

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

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

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

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

9.5. Emergency Unblinding of Treatment Assignment

Not applicable.

9.6. Pregnancy

Pregnancy, in and of itself, is not regarded as an AE unless there is suspicion that study treatment 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 treatment, the following procedures should be followed in order to ensure safety:

- The study treatment must be interrupted immediately (female participants only).
- If the female participant is no longer pregnant and meets the treatment continuation criteria within 28 days of the scheduled start of a cycle, study treatment may be resumed after approval has been received from the sponsor medical monitor.
- The investigator must complete and submit the Incyte Clinical Trial Pregnancy Form to the sponsor or its designee within **24 hours** of learning of the pregnancy.

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

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

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

9.7. Warnings and Precautions

Special warnings or precautions for the study treatment, derived from safety information collected by the sponsor or its designee, are presented in INCMGA00012 IB, INCAGN02385 IB, INCAGN02390 IB.

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

9.8. Product Complaints

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

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

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

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

9.9. Treatment of Overdose

There has been no clinical experience with overdose of INCMGA00012, INCAGN02385, or INCAGN02390. Treatment of overdose should consist of general supportive measures.

10. STATISTICS

10.1. Sample Size Determination

10.1.1. Phase 1

10.1.1.1. Parts 1 and 2

For Parts 1 and 2, the BOIN design (described in Section 10.4) will be used to determine the RP2D of combination of INCAGN02385 and INCAGN02390 as well as the combination INCAGN02385 + INCAGN02390 + INCMGA00012 in participants with immunogenic tumor types. Dose escalation and de-escalation will follow the BOIN design algorithm (Liu and Yuan 2015). Given the target DLT rate of 28% for the combinations of INCAGN02385, INCAGN02390, or both with INCMGA00012, the dose escalation and de-escalation rules are shown in Table 20. The BOIN design also includes an elimination rule. When ≥ 3 participants have been treated at a certain dose level, if the probability that the estimated toxicity rate that is above the target DLT rate is > 95% at this dose level, then this dose level and higher dose levels are assumed to be too toxic and will be eliminated. If the lowest dose level is eliminated, then the whole dose escalation will be terminated. Table 20 (in the bottom row) provides the elimination rules.

The dose escalation will continue, based on the rules in Table 20, until at least 1 of the following occurs:

- Enrollment of additional participants in a dose level that already has 9 evaluable participants, or
- Dose escalation to a dose level that has already been eliminated.

At that point, the dose escalation will be stopped. Based on this algorithm, a maximum of 9 evaluable participants will be enrolled at each tested dose level.

Table 20: Planned Dose Escalation, De-Escalation, and Elimination Boundaries for Target DLT Rate of 28% in Phase 1 Parts 1 and 2

	Number of Evaluable Participants Treated at the Current Dose								
Action	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9[a]**
Escalate if # of DLTs ≤	0	0	0	0	1	1	1	1	1
De-escalate if # of DLTs ≥	1	1	2	2	2	3	3	3	4
Elimination if # of DLTs ≥	N/A	N/A	3	3	4	4	4	5	5

[a] If 9 evaluable participants are enrolled in a dose level and 2 or 3 of those participants experience a DLT, the medical monitor and the investigators will review the entirety of the data and decide whether to escalate the dose level, de-escalate the dose level, or stop at that dose level.

10.1.1.2. Part 3

Once safety for the Q2W schedule has been established for INCAGN02385 + INCAGN02390 and INCAGN02385 + INCAGN02390 + INCMGA00012, a Q3W schedule will be evaluated in a stepwise manner. For dose optimization purposes for each agent (INCAGN02385 and INCAGN02390), two Q3W doses were selected based on single agents PK simulation and RO data (from Q2W data) and will be evaluated in parallel. Two doses of INCAGN02385, 450 mg Q3W and 750 mg Q3W, will be administered to participants (n = 6 each) as monotherapy for 2 21-day cycles. Following 2 monotherapy cycles, these same participants will then remain on their current dose of INCAGN02385 and be given INCMGA00012 (375 mg Q3W) in combination. Concurrently, 2 doses of INCAGN02390, 500 mg Q3W and 1000 mg Q3W, will be administered to participants (n = 6 each) as monotherapy for 2 21-day cycles. Following 2 monotherapy cycles, these same participants will then remain on their current dose of INCAGN02390 and be given INCMGA00012 (375 mg Q3W) in combination.

Participants in Part 3 will be evaluated for safety and occurrence of DLTs from first dose until Day 21. Analysis of safety data from participants in Phase 1, Part 3 will be descriptive.

10.1.1.3. Part 4

In Part 4, a Q4W schedule of INCMGA0012 + INCAGN02385 + INCAGN02385 will be evaluated in a single cohort of participants (n = 10) as alternative schedule to accommodate future combinations with other agents of interest and in a stepwise manner. [redacted] data from the monotherapy Q3W evaluation in Phase 1 Part 3 are obtained, these data will inform Q4W dose estimations for the triplet combination (INCAGN02385 + INCAGN02390 + INCMGA00012 500 mg) to be evaluated on a Q4W schedule. Analysis of safety data from participants in Phase 1, Part 4 will be descriptive.

10.1.2. Phase 2

Phase 2 will evaluate preliminary efficacy of the triple combination of INCAGN02385 + INCAGN02390 + INCMGA00012 in Cohort A and Cohort B.

For Cohort A, a historical control for efficacy of immuno-oncology therapy in participants refractory to anti–PD-1/L1 therapy is estimated to be approximately ORR = 5%. In order for the triple combination to be considered effective, a 15% benefit is required (ie, ORR = 20%). The Simon 2-stage design (Simon 1989) with the minimax design option will be applied to this cohort. An interim analysis will be conducted after 15 participants are enrolled and assessed for response in Stage 1. If ≥ 1 responders are observed, an additional 15 participants will be enrolled for Stage 2. At the end of Stage 2, if ≤ 3 responses are observed among the total 30 participants, the treatment will be considered non-promising. The design is based on a Type I error of 10% with 86% power to detect a 20% response rate.

For Cohort B, a historical control for efficacy of immuno-oncology therapy in participant with untreated advanced melanoma is estimated to be approximately ORR = 40% (Postow et al 2015, Robert et al 2015, Tawbi et al 2022). In order for the triple combination to be considered effective, a 30% benefit is required (ie, ORR = 70%). To determine whether the target response rate (p_1) of 70% against the historical control response rate (p_0) of 40% is likely, an initial 14 participants (n_1) will be enrolled in each dose cohort for the interim analysis. A nonbinding analysis of efficacy will be conducted after Stage 1. If a sufficient efficacy signal (eg,

≥ 6 responses (r_1)) is observed, an additional 18 participants maybe enrolled into the each dose level. The decision by the sponsor to enroll Stage 2 will take into consideration the depth (defined as the decrease in tumor burden) and duration of responses in addition to the number of responses in Stage 1. A total of ≥ 17 responses (r) will claim treatment efficacy. A total sample size (N) of 32 participants provides a 1-sided Type I error (α) of 9% and an approximate power of 98%. Table 21 lists the detailed design rules, generated by an R-shiny tool using the Bayesian predictive probability (Chen et al 2019).

Table 21: Planned Bayesian Predictive Probability Design for Phase 2 Cohort B

p_0	p_1	n_1	N	r_1	r	α	Power
40%	70%	14	32	≥ 6	≥ 17	9%	98%

10.2. Populations for Analysis

See Table 22 for populations for analysis.

Table 22: Populations for Analysis

Population	Description
FAS	The FAS includes all participants enrolled in the study who received at least 1 dose of assigned study treatment. This population will be used in the analyses of demographic, baseline, safety, study treatment administration, and efficacy data.
PK evaluable	[redacted]
RECIST evaluable	Participants in the RECIST evaluable population includes all participants enrolled in the study who have received at least 1 dose of study treatment and completed a baseline scan and meet at least 1 of the following criteria: • The participant has had ≥ 1 postbaseline scan. • The participant has been on the study for a minimum of 56 days of follow-up. • The participant has discontinued from treatment.
DLT evaluable	The DLT evaluable population includes all participants from the Phase 1 who received at least 1 dose of assigned study treatment, and either: (1) experienced a DLT during the safety evaluation period or (2) received 2 doses of INCAGN02385 and 2 doses of INCAGN02390, plus 1 dose of INCMGA00012 (if applicable) during the first 28 days (Q2W and Q4W) or 21 days (Q3W) as applicable per cycle definition, and have sufficient monitoring for the investigator and sponsor to conclude that no DLT occurred.

10.3. Statistical Analyses

10.3.1. Safety Analysis

Safety analyses will be conducted for the safety population. Adverse events will be coded by the MedDRA dictionary, and TEAE (ie, AEs reported for the first time or worsening of a pre-existing event after first dose of study treatment) will be tabulated by preferred term and system organ class for all events, related events, and events of Grade 3 or higher. Quantitative safety variables and their changes from baseline (laboratory, vital signs, etc) will be summarized with descriptive statistics. Clinically notable abnormal values will be flagged and tabulated based on predefined criteria.

The clinical laboratory data will be analyzed using summary statistics; no formal treatment group comparisons are planned. In addition, distributions of key laboratory parameters may be plotted over time; these values will also be classified into CTCAE toxicity grades and tabulated. Descriptive statistics and mean change from baseline will be determined for vital signs at each assessment time. Vital sign results will be reviewed for clinically notable abnormalities.

Descriptive statistics and mean change from baseline will be determined for each ECG parameter at each assessment time. Electrocardiogram results will be reviewed for clinically notable abnormalities according to predefined criteria (see Table 23). Participants exhibiting clinically notable ECG abnormalities will be listed.

Table 23: Criteria for Clinically Notable Electrocardiogram Abnormalities

Parameter	High Threshold	Low Threshold
QTcF/QTcB	> 460 msec	< 295 msec
PR	> 220 msec	< 75 msec
QRS	> 120 msec	< 50 msec
QT	> 500 msec	< 300 msec
RR	> 1330 msec	< 600 msec

10.3.2. Efficacy Analysis

For the RECIST evaluable population, the ORR, defined as the percentage of participants with CR or PR according to RECIST v1.1 (Eisenhauer et al 2009) will be evaluated. ORR and its 95% confidence interval will be presented by treatment group. ORR and its 95% confidence interval will also be presented by LAG-3 status with no formal comparison between LAG-3 positive and LAG-3 negative participants. Furthermore, ORR and its 95% confidence interval will also be presented by primary versus secondary resistance; no formal comparison will be performed between these 2 groups. DOR, defined as the time from earliest date of disease response (CR or PR) until earliest date of disease progression per RECIST v1.1 or death from any cause, will be summarized for responders. PFS, defined as the time from date of first dose of study treatment until the earliest date of disease progression, as determined by investigator assessment of objective radiographic disease per RECIST v1.1, or death from any cause if occurring sooner than progression. Both DOR and PFS will be analyzed by the Kaplan-Meier method, treating participants with no observed death or disease progression as censored at the

date of last adequate assessment. Median DOR and PFS will be estimated and the 95% confidence intervals will be provided for each treatment group in the FAS population. DCR, defined as the proportion of participants with CR, PR, or SD as a best response, will be summarized using the RECIST evaluable population.

10.4. Interim Analysis

The BOIN design will be used to determine the RP2D of combination of INCAGN02385 and INCAGN02390 as well as the combination INCAGN02385 + INCAGN02390 + INCMGA00012 in participants with immunogenic tumor types.

For the design parameters, let ϕ denote the target DLT rate. Let $\phi 1$ (= 0.6ϕ) denote the highest toxicity probability below the MTD so that dose escalation is required, and $\phi 2$ (= 1.4ϕ) denote the lowest toxicity probability deemed overly toxic so that dose de-escalation is required. Per the BOIN method with non-informative priors, for ϕ=28%, if an observed DLT rate of a dose level $\leq$ $\log((1-\phi 1)/(1-\phi))/\log(\phi*(1-\phi 1)/(\phi 1*(1-\phi)) = 0.221$, then that dose level can be escalated; if an observed DLT rate of a dose level $\geq$ $\log((1-\phi)/(1-\phi 2))/\log(\phi 2*(1-\phi)/(\phi*(1-\phi 2)) = 0.334$, then that dose level will be de-escalated. The dose escalation, de-escalation boundaries based on ϕ, $\phi 1$ and $\phi 2$ are provided in Table 20.

A dose elimination rule is also applied to avoid assigning participants to an overly toxic dose. Let pj represents the DLT rate, nj the number of participants in the cohort treated at dose level j, and mj the number of participants with a DLT at dose level j. If $P(pj > \phi|mj, nj) > 0.95$ and $nj \geq 3$, then dose levels j and higher are eliminated from the dose escalation, and the dose escalation is terminated if the first dose level is eliminated.

Assuming a non-informative beta(1,1) prior for pj, then posterior (pj | mj, nj) will follow a beta(1+ mj, 1+ nj - mj) distribution. The elimination boundary in Table 20 (bottom row) will satisfy the requirement that $P(pj > \phi|\ mj, nj\ ) > 0.95$. For example, when the number of participants treated at the current dose nj = 4, we will eliminate that dose and higher doses if 3 or more participants experience toxicity.

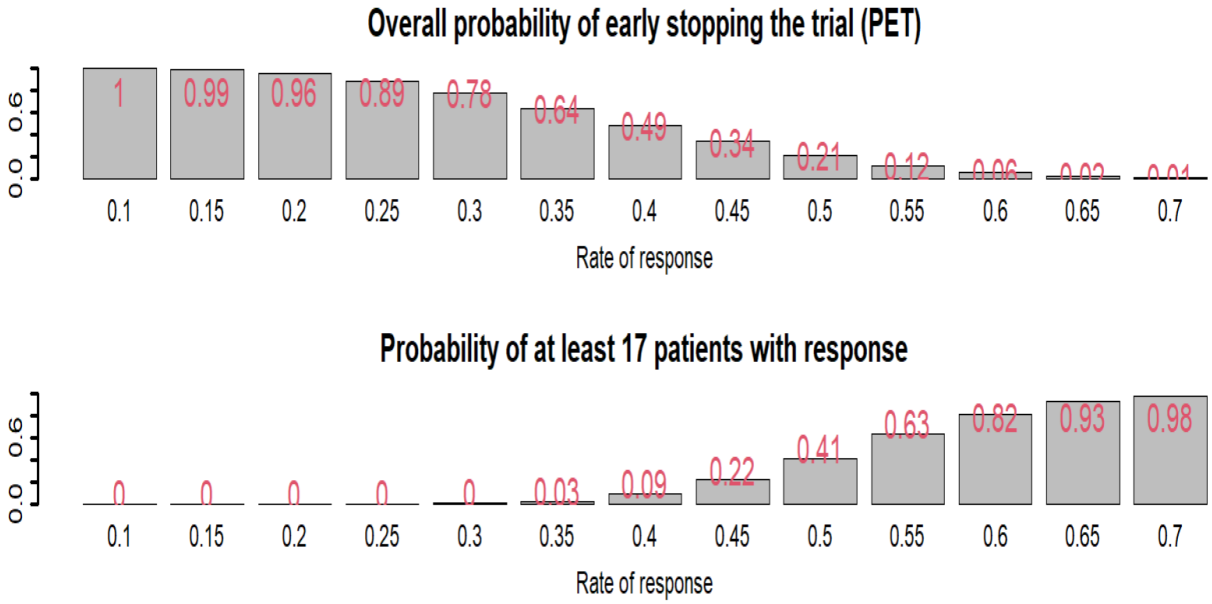
An interim analysis will be conducted in Phase 2 for each cohort.

For Cohort A, an interim analysis will be conducted after 15 participants are enrolled. If no responses are observed, the cohort will be terminated for futility. If 1 or more responses are observed, an additional 15 participants will be enrolled for Stage 2 evaluation. If the true ORR is 5%, the design will have a 46% probability of terminating at the end of Stage 1.

For each dose level of Cohort B, a nonbinding interim analysis using a Bayesian predictive probability will be performed when 14 evaluable participants have at least 2 tumor assessments. If a sufficient efficacy signal is not observed (eg, < 6 responses, but also taking into account the depth and duration of response), the sponsor may determine that the treatment will be discontinued given a 9% cutoff of the predictive probability (ie, chance to stop the study in the interim analysis). Otherwise, an additional 18 participants will be enrolled into the study, for a total of 32 participants. With a historical control response rate of 0.4 and posterior probability of 0.9 as the threshold, a total of ≥ 17 of the 32 participants must have response to claim treatment efficacy. A noninformative beta prior, beta(1,1), is used to calculate the posterior probability and predictive probability for the rate of response. Enrollment will be held during the interim analysis. However, if there is a sufficient efficacy signal observed before having 14 evaluable

participants with at least 2 tumor assessments, then there is no need to hold enrollment, and the study can directly continue with enrollment of the additional 18 participants. Performance of the design (see Figure 6) shows that if the true rate of response is 40%, the chance to reach a total of ≥ 17 participants with response at the end of the study is 9% (Type I error); however, the probability to stop the study early is 49%. If the true rate of response is indeed 70%, then the chance to reach ≥ 17 participants with response at the end of the study is 98% (power), and the corresponding probability to stop the treatment early is 1%.

Figure 6: Performance (Probability of Early Termination [PET], Type I Error, and Power) of Cohort B



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.

11.2. Data Management

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

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

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

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

The investigator will be responsible for the following:

- Recording, or ensuring the recording of, all relevant data relating to the study in the eCRF.
- Delivering, or ensuring the delivery of, all other results, documents, data, know-how, or formulas relating to the study to the sponsor or designee electronically and/or centrally (eg, laboratory data, imaging data, biomarker data, photographs, diary data) or as otherwise specified in the Protocol.
- Maintaining adequate and accurate source documents and 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, 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 data monitoring plan.

Quality tolerance limits will be predefined in the operational manual to identify systematic issues that can impact participants' 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 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.

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 their institution agree that the results of the study may be used by the sponsor, Incyte Biosciences International Sàrl (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. 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.

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APPENDIX A. INFORMATION REGARDING EFFECTIVENESS OF CONTRACEPTIVE METHODS

For male participants in the study:

Male participants should use a condom from screening through 90 days after the end of systemic exposure. If the male participant has a partner that is of child-bearing potential, the partner should also use contraception through 90 days after the end of relevant systemic exposure. In addition, male participants must refrain from donating sperm from screening through 90 days after the end of relevant systemic exposure. Males who have had a vasectomy qualify as having met the requirement for a highly effective birth control method.

For female participants in the study:

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

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

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

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

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

[d] In the context of this guidance, sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the participant.

Source: Clinical Trial Facilitation Group 2014.

APPENDIX C. COVID-19 PANDEMIC MITIGATION STRATEGIES AND INSTRUCTIONS

The COVID-19 global pandemic presents challenges to the ongoing conduct of clinical studies. In line with regulatory guidance regarding clinical study execution during the pandemic, the sponsor has issued the following Protocol considerations to ensure participant safety is maintained and adequate benefit/risk analyses are applied relative to the completion of study procedures and maintaining the investigational product supply chain.

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

Given the critical medical need for alternative treatments for patients in the setting of recurrent/ metastatic cancer and the importance of continuing cancer research, a positive COVID-19 screening test should not result in definitive exclusion. Participants with a positive COVID-19 test during screening may be reassessed for eligibility in the study only after normalization of their COVID-19 screening test and clinical recovery as per the investigator's evaluation.

SARS-CoV2 Infection and Participation in the Study

Benefit/risk assessment in the context of the COVID-19 pandemic is provided in Section 2.4.4. During the COVID-19 pandemic, additional risks to participants exist either related to going to a healthcare facility or as a result of study-related activities. It is at the investigator's discretion to balance the risk/benefit while considering the participant's safety, existing comorbidities, and current malignancy. In addition, country-specific requirements are to be followed with regard to COVID-19 testing.

A participant who fails screening due to COVID-19 infection may repeat the screening process upon recovery and COVID test normalization.

Study Site Visits

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

- In order to minimize participant risk, study visits may be conducted via telemedicine modalities (phone or video) or as per site institutional guidelines. At a minimum, a review of AEs and concomitant medications must be completed. On-site visits should be conducted whenever feasible and are required for administration of study treatment. The participant may also be asked to undergo additional safety laboratory assessments.

- In order to support investigator oversight of participant safety and disease management, the participant may be asked to undergo some laboratory tests or study procedures at a local laboratory or facility closer to the participant's residence rather than at the investigational site. In this case, the study physician will provide the participant with the list of parameters to be checked. These tests should be performed in certified laboratories.
- Some tests, such as ECG or CT scan assessments, may require longer windows of time to perform due to the COVID-19 pandemic and may be performed outside the regularly scheduled visit window or may be conducted at the next scheduled visit. It is the investigator's responsibility to check with the facility (if performed at a different facility) that the data will be obtained and available for evaluation. General procedures performed outside of protocol parameters will be captured as protocol deviations due to COVID-19.

Study Treatment Management in the Event of SARS-CoV2 Infection

If a participant develops a SARS-CoV2 infection, the event should be reported as SAE (if it meets the SAE definition requirements) and appropriate medical intervention provided.

Postbaseline COVID-19 testing should follow country-specific requirements depending on the extent of COVID19-pandemic, local institutional guidance, or investigator's clinical judgment.

For participants who are diagnosed with COVID-19 during the study (positive COVID-19 test) or presumed affected by SARS-CoV2 infection (test pending/clinical suspicion), study treatment should be delayed until COVID-19 test normalization and clinical recovery. Before restarting treatment, the study medical monitor should be notified with the participant's condition, that is, 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 infection should be implemented as per institutional guidance or clinical judgment (eg, coagulation factors). Concomitant medication administered for treatment of SARS-CoV2 infection should be carefully considered for potential drug-drug interactions and recorded in the clinical database (EDC).

COVID-19 Vaccination

Participants may receive the COVID-19 vaccine as long as it is not a live vaccine. A live COVID-19 vaccine requires prior consultation with the medical monitor (see Section 5.2 Exclusion Criterion 14). COVID-19 vaccination will be captured in the eCRF as a concomitant medication. Vaccination on the day of study treatment administration is not recommended. Administration of study treatment may be delayed to ensure vaccination is completed.

Clinical Study Monitoring

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

Reimbursement of Additional Expenses

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

APPENDIX D. PROTOCOL AMENDMENT SUMMARY OF CHANGES

Document	Date
Amendment 1:	07 APR 2020
Amendment 2:	02 JUN 2021
Amendment 3:	12 MAY 2022
Amendment 4:	02 MAR 2023

Amendment 4 (02 MAR 2023)

Overall Rationale for the Amendment: The primary aim of this amendment is to amend the primary endpoint. In addition, the interim analysis for Phase 2 Cohort B has been made a nonbinding analysis, allowing the sponsor to make the decision whether to proceed to Stage 2.

1. **Section 1, Protocol Summary (Table 1: Primary Objectives and Endpoints); Section 3, Objectives and Endpoints; Section 4.1.1, Treatment Groups and Duration**

   Description of change: Adjusted the endpoints to reflect [redacted]

   Rationale for change: Safety is the primary endpoint for Phase 2. [redacted]. However, dose selection for further study and as per FDA guidance will be based on all data available, including safety, RO, and PK.

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

   Description of change: Added coordinating investigator.

   Rationale for change: A coordinating investigator is required prior to study close.

3. **Section 1, Protocol Summary; Section 4.1.1, Treatment Groups and Duration; Section 10.1.2, Phase 2; Section 10.4, Interim Analysis**

   Description of change: Added further description of the interim analysis for Phase 2 Cohort B.

   Rationale for change: To clarify that the sponsor will make the final determination whether to proceed with Stage 2 of Cohort B based on a nonbinding interim analysis that includes all of the efficacy data available after Stage 1, including the number, duration, and depth of responses observed.

4. **Section 1, Protocol Summary (Table 3: Schedule of Activities for Q2W Dosing [Phase 1 Parts 1 and 2 and Phase 2 Cohort A] and Q4W Dosing [Phase 1 Part 4]; Table 6: Schedule of Activities for Q3W Dosing in Phase 1 Part 3 and Phase 2 Cohort B); Section 8.3.4, Electrocardiograms**

   Description of change: Clarified that ECG collection should occur within 10 minutes after the end of infusion on Cycle 1 Day 1 and Cycle 4 Day 1.

   Rationale for change: To align ECG collection to the approximate time of C_{max}.

5. **Section 1, Protocol Summary (Table 5: Schedule of Pharmacokinetic and Pharmacodynamic Assessments for Q2W Dosing [Phase 1 Parts 1 and 2 and Phase 2 Cohort A] and Q4W Dosing [Phase 1 Part 4]; Table 8: Schedule of Pharmacokinetic and Pharmacodynamic Assessments for Q3W Dosing in Phase 1 Part 3 and Phase 2 Cohort B)**

   Description of change: Removed Cycle 1 Day 15 and Cycle 6 Day 15 serum sample collection for ADA to align with Table 18.

   Rationale for change: ADA samples are not required for these timepoints. For Phase 1 Part 3 and Phase 2 Cohort B, it is not advisable to collect ADA samples on Cycle 1 Day 15 as the drug levels are still quite high and may interfere in the ability of the assay to detect ADA.

6. **Section 1, Protocol Summary (Table 5: Schedule of Pharmacokinetic and Pharmacodynamic Assessments for Q2W Dosing [Phase 1 Parts 1 and 2 and Phase 2 Cohort A] and Q4W Dosing [Phase 1 Part 4])**

   Description of change: Added details regarding timing for collection of translational samples (plasma correlative, whole blood correlative for flow cytometry, whole blood for PBMC, and whole blood DNA).

   Rationale for change: Added flexibility for plasma correlative, whole blood correlative for flow cytometry, and whole blood for PBMC samples for Phase 1 Part 4 and specified timing for regimens including Q2W administration. In addition, specified that whole blood DNA should be collected for regimens including Q2W administration.

7. **Section 1, Protocol Summary (Table 5: Schedule of Pharmacokinetic and Pharmacodynamic Assessments for Q2W Dosing [Phase 1 Parts 1 and 2 and Phase 2 Cohort A] and Q4W Dosing [Phase 1 Part 4]; Table 8: Schedule of Pharmacokinetic and Pharmacodynamic Assessments for Q3W Dosing in Phase 1 Part 3 and Phase 2 Cohort B); Section 8.5.2, Tissue Biopsy Collection Requirements**

   Description of change: Revised the tissue requirements relative to the phase of study and aligned with the description in the SoA.

   Rationale for change: Clarification and alignment with the SoA.

8. **Section 1, Protocol Summary (Table 6: Schedule of Activities for Q3W Dosing in Phase 1 Part 3 and Phase 2 Cohort B)**

   Description of change: Added requirement for baseline brain imaging for Cohort B.

   Rationale for change: Standard of care to ensure there are no brain metastases in participants with newly diagnosed melanoma.

9. **Section 5.2, Exclusion Criteria (Table 10: Exclusion Laboratory Values)**

   Description of change: Added clarifying note that the lactate dehydrogenase requirement is not applicable to Phase 2 Cohort B.

   Rationale for change: For first-line melanoma, lactate dehydrogenase is the tumor marker included in disease staging based on the new American Joint Committee on Cancer classification.

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

    Description of change: Added clarifying note that participants who tolerated anti–PD(L)-1 but not anti–CTLA-4 therapy could be considered for enrollment with medical monitor approval.

    Rationale for change: Many participants will continue on anti–PD-(L)1 therapy while stopping anti–CTLA-4 therapy due to toxicity. Due to lack of toxicity to anti–PD-(L)1 therapy, these participants are appropriate for this study.

11. **Section 6.6.5, Procedures for Participants Exhibiting Immune-Related Adverse Events (Table 15: Toxicity Management Guidelines for Immune-Related Adverse Events)**

    Description of change: Changed requirements for bilirubin increases.

    Rationale for change: Added flexibility for higher bilirubin levels in participants with liver metastases.

12. **Section 8.2.2, Patient-Reported Outcomes**

    Description of change: Added FACT-M for Phase 2 Cohort B.

    Rationale for change: To align with the SoA as Cohort B requires a different instrument than Cohort A.

13. **Section 8.4.1, Blood Sample Collection (Table 18: Timing of Pharmacokinetics and Antidrug Antibody Sample Collection for Phase 1 Parts 1 and 2 and Phase 2 Cohort A (Q2W) and Phase 1 Part 4 (Q4W) (Cycles Are Based on Q4W Cycles for INCMGA00012)**

    Description of change: [redacted]

    Rationale for change: To remain consistent with predose sampling times.

14. **Section 8.8.2, Post-Treatment Disease Follow-Up**

    Description of change: Aligned post-treatment disease follow-up with the SoA.

    Rationale for change: When Q3W regimens were added, there became additional possibilities for timing of post-treatment disease follow-up.

15. **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 3 (12 MAY 2022)

Overall Rationale for the Amendment: The primary aim of this Protocol amendment is to provide additional information for dose optimization for both INCAGN02385 and INCAGN02390 agents as monotherapy and in combination, and evaluate alternative dose administration schedules (ie, Q3W and Q4W) to accommodate combination regimens. Additional changes are summarized below.

1. **Section 1, Protocol Summary (Table 1: Primary Objectives and Endpoints; Table 2: Key Study Design Elements; Figure 1: Study Design Schema; Table 3: Schedule of Activities for Q2W Dosing [Phase 1 Parts 1 and 2 and Phase 2 Cohort A] and Q4W Dosing [Phase 1 Part 4]; Table 6: Schedule of Activities for Q3W Dosing in Phase 1 Part 3 and Phase 2 Cohort B); Section 3, Objectives and Endpoints (Table 9: Objectives and Endpoints); Section 4.1.1, Treatment Groups and Duration; Section 5.6, Data Monitoring Committee; Section 6.1, Study Treatments Administered (Table 11: Study Treatment Information); Section 8.4.1, Blood Sample Collection (Table 19: Timing of Pharmacokinetics and Antidrug Antibody Sample Collection for Phase 1 Part 3 (Q3W) and Phase 2 Cohort B (Q3W) (Cycles are Based on Q3W Cycles for INCMGA00012); Section 10.1.1.2, Part 3; Section 10.1.1.3, Part 4**

   Description of change: Inclusion of Parts 3 (Q3W) and 4 (Q4W) for Phase 1. Evaluation of Q3W dose administration for INCAGN02385 and INCAGN02390 as monotherapies for the first cycles then as doublet combination with INCMGA00012 each, and evaluation of Q4W dose administration for the combination of INCAGN02385, INCAGN02390, and INCMGA00012.

   Rationale for change: Testing and validation of Q3W dose administration will accommodate future combination studies by aligning schedules for INCAGN2385 and INCAGN2390 with that of INCMGA00012 (at the established RP2D of 375 mg Q3W) and limit the number of visits for participants. The Q4W schedule will be evaluated as alternative schedule to accommodate other future combinations with other agents of interest.

2. **Section 1, Protocol Summary (Table 1: Primary Objectives and Endpoints; Table 2: Key Study Design Elements; Figure 1: Study Design Schema; Table 3: Schedule of Activities for Q2W Dosing [Phase 1 Parts 1 and 2 and Phase 2 Cohort A] and Q4W Dosing [Phase 1 Part 4]; Table 6: Schedule of Activities for Q3W Dosing in Phase 1 Part 3 and Phase 2 Cohort B); Section 2.1, Background; Section 3, Objectives and Endpoints (Table 9: Objectives and Endpoints); Section 4.1.1, Treatment Groups and Duration; Section 5.1, Inclusion Criteria (Inclusion Criterion 5); Section 5.6, Data Monitoring Committee; Section 6.1, Study Treatments Administered (Table 11: Study Treatment Information); Section 8.4.1, Blood Sample Collection (Table 19: Timing of Pharmacokinetics and Antidrug Antibody Sample Collection for Phase 1 Part 3 (Q3W) and Phase 2 Cohort B (Q3W) (Cycles are Based on Q3W Cycles for INCMGA00012); Section 10.1.2, Phase 2; Section 10.4, Interim Analysis**

   Description of change: Phase 2 included an additional expansion cohort. Cohort A is the initial cohort for participants with advanced melanoma who have progressed or relapsed on or after anti–PD(L)1 therapy, and Cohort B is the new cohort for participants with advanced melanoma naïve to systemic therapy (first line). At least two doses for INCAGN02385 and INCAGN02390 will be tested in Cohort B and will be informed by Phase 1 Part 3 data.

   Rationale for change: The initial Cohort A tests Q2W dose administration of the triplet combination. The new Cohort B will test at least 2 doses for the triplet combination on Q3W schedule in patient population (first line systemic treatment naïve melanoma) where dual LAG-3 plus PD-1 blockade is established as standard of care option and with the hypothesis that the addition of TIM-3 blockade may improve efficacy further. This homogeneous cohort (Cohort B, first line setting) will allow collating additional exposure safety and exposure response data to inform the optimal doses for the triplet combination.

3. **Section 1, Protocol Summary (Table 1: Objectives and Endpoints); Section 3, Objectives and Endpoints (Table 9: Objectives and Endpoints)**

   Description of change: Evaluation of PFS was added to primary efficacy endpoints being captured in Phase 2.

   Rationale for change: Inadvertently omitted in prior version.

4. **Section 1, Protocol Summary (Table 3: Schedule of Activities for Q2W Dosing [Phase 1 Parts 1 and 2 and Phase 2 Cohort A] and Q4W Dosing [Phase 1 Part 4])**

   Description of change: Included additional ECG.

   Rationale for change: Based on emerging safety data from competitor studies of LAG-3 class, ECGs were included for additional visits in order to more closely monitor cardiac function.

5. **Section 1, Protocol Summary (Table 3: Schedule of Activities for Q2W Dosing [Phase 1 Parts 1 and 2 and Phase 2 Cohort A] and Q4W Dosing [Phase 1 Part 4]; Table 6: Schedule of Activities for Q3W Dosing in Phase 1 Part 3 and Phase 2 Cohort B); Section 3, Objectives and Endpoints (Table 9: Objectives and Endpoints); Section 8.2.2 Patient Reported Outcomes; Section 8.2.2.2, EORTC QLQ-C30 Questionnaire; Section 8.2.2.3 FACT-M Questionnaire**

   Description of change: Clarification that EORTC QLQ-C30 is designated to capture PRO for Phase 2 Cohort A and addition of the FACT-M Questionnaire to capture PRO for Phase 2 Cohort B.

   Rationale for change: Standard PRO measure integrated for the new Phase 2 Cohort B.

6. **Section 1, Protocol Summary (Table 3: Schedule of Activities for Q2W Dosing [Phase 1 Parts 1 and 2 and Phase 2 Cohort A] and Q4W Dosing [Phase 1 Part 4]); Section 3, Objectives and Endpoints (Table 9: Objectives and Endpoints); Section 8.2.2, iRECIST Assessment of Disease**

   Description of change: iRECIST evaluation was removed.

   Rationale for change: iRECIST is used for participants management and guide treatment continuation based on imaging and clinical status. However, efficacy assessment and endpoints are based on standard RECIST v.1.1. Therefore, it is determined that collection of iRECIST data is of high and unnecessary burden for sites.

7. **Section 1, Protocol Summary (Table 3: Schedule of Activities for Q2W Dosing [Phase 1 Parts 1 and 2 and Phase 2 Cohort A] and Q4W Dosing [Phase 1 Part 4], Table 4: Schedule of Laboratory Assessments for Q2W Dosing [Phase 1 Parts 1 and 2 and Phase 2 Cohort A] and Q4W Dosing [Phase 1 Part 4]; Table 5: Schedule of Pharmacokinetic and Pharmacodynamic Assessments for Q2W Dosing [Phase 1 Parts 1 and 2 and Phase 2 Cohort A] and Q4W Dosing [Phase 1 Part 4], Table 6: Schedule of Activities for Q3W Dosing in Phase 1 Part 3 and Phase 2 Cohort B, Table 7: Schedule of Laboratory Assessments for Q3W Dosing in Phase 1 Part 3 and Phase 2 Cohort B, Table 8: Schedule of Pharmacokinetics and Pharmacodynamics Assessments for Q3W Dosing in Phase 1 Part 3 and Phase 2 Cohort B); Section 6.5.1, Definition of a Dose-Limiting Toxicity; Section 8.2.1.2, Tumor Imaging During the Study; Section 10.2, Populations for Analysis (Table 22: Populations for Analysis)**

   Description of change: Language added to clarify 21-day cycles for Q3W dose administration versus 28-day cycles for Q2W and Q4W regimens.

   Rationale for change: Cycle intervals vary between cohorts and parts of study and cycle length needs to reflect that.

8. **Section 1, Protocol Summary (Table 4: Schedule of Laboratory Assessments for Q2W Dosing [Phase 1 Parts 1 and 2 and Phase 2 Cohort A] and Q4W Dosing [Phase 1 Part 4]; Table 7: Schedule of Laboratory Assessments Q3W Dosing in Phase 1 Part 3 and Phase 2 Cohort B); Section 8.3.5, Laboratory Assessments (Table 17: Required Laboratory Analytes)**

   Description of change: Added ACTH and cortisol testing to endocrine panel.

   Rationale for change: Standard endocrine monitoring for both ACTH and cortisol level added to align with standard guidelines and practice for participants treated with immune checkpoint inhibitors.

9. **Section 1, Protocol Summary (Table 4: Schedule of Laboratory Assessments for Q2W Dosing [Phase 1 Parts 1 and 2 and Phase 2 Cohort A] and Q4W Dosing [Phase 1 Part 4]; Table 7: Schedule of Laboratory Assessments for Q3W Dosing in Phase 1 Part 3 and Phase 2 Cohort B); Section 5.2, Exclusion Criteria (Table 10: Exclusion Laboratory Values); Section 8.3.5, Laboratory Assessments (Table 17: Required Laboratory Analytes)**

   Description of change: Information for the monitoring of troponin levels and exclusion of participants with high troponin levels at baseline was included.

   Rationale for change: Based on emerging data from competitor studies of LAG-3 class, troponin monitoring is added for all participants receiving combinations including anti–LAG-3.

10. **Section 2.2, Study Rationale; Section 2.3, Scientific Rationale for Study Design**

    Description of change: Included new data and additional background information to support the justification of both Phase 2 cohorts (A and B).

    Rationale for change: To provide additional justification for populations to be treated.

11. **Section 2.3.1.1, INCAGN023585 and INCAGN02390 Q2W Dose Selection (Phase 1 Parts 1 and 2 and Phase 2 Cohort A); Section 2.3.1.2, INCAGN02385 and INCAGN02390 Q3W Dose Selection (Phase 1 Part 3 and Phase 2 Cohort B); Section 2.3.1.3, INCAGN023585 and INCAGN02390 Q4W Dose Selection (Phase 1 Part 4)**

    Description of change: Section 2.3.1 was divided into three subsections, Sections 2.3.1.1, 2.3.1.2, and 2.3.1.3 to discuss each of the 3 dose administration schedules, Q2W (initial dose administration schedule), Q3W, and Q4W, respectively.

    [redacted]

    Rationale for change: To provide justification for dose range to be tested for Q3W and Q4W schedules.

12. **Section 2.3.2, Justification for INCMGA00012 Dose**

    Description of change: Added expanded justification for dose of INCMGA00012.

    Rationale for change: Alignment to INCMGA00012 program data updates.

13. **Section 3, Objectives and Endpoints (Table 9: Objectives and Endpoints)**

    Description of change: [redacted]

    Rationale for change: To support addressing FDA requirement for assessment of drug exposure relationship to response/safety.

14. **Section 3, Objectives and Endpoints (Table 9: Objectives and Endpoints)**

    Description of change: Evaluation of DCR was added to analysis of efficacy in secondary endpoints.

    Rationale for change: Inadvertently omitted in prior version.

15. **Section 5.1, Inclusion Criteria (Inclusion Criterion 3); Section 5.2, Exclusion Criteria**

    Description of change: Updated inclusion/exclusion criteria for Phase 1 population, removed redundant exclusion criteria, and corrected the criteria regarding PD-1 refractory patients which pertains more to Phase 2 Cohort A.

    Rationale for change: PD-1 refractory participants are included in Phase 2 Cohort A, the criteria was erroneously stated for Phase 1, which has been corrected in this amendment. Also, redundant criteria have been removed to simplify and improve the protocol readability for sites.

16. **Section 5.1, Inclusion Criteria, Inclusion Criterion 4c**

    Description of change: Requirement for prior BRAF targeted therapy in participants with BRAF mutation removed (see Section 2.2 for supporting data). Requirement changed to have known BRAF mutation status.

    Rationale for change: Emerging clinical data (DREAMseq) demonstrated limited benefit of BRAF targeted therapy in this population relative to immuno-oncology therapy. Treatment with BRAF inhibitor has potential to change tumor microenvironment and decrease efficacy of subsequent immuno-oncology therapy. Therefore, treatment sequence (BRAF therapy versus immunotherapy) is per clinical investigator judgment before study entry.

17. **Section 5.2, Exclusion Criteria (Exclusion Criterion 5d)**

    Description of change: Removed criteria for Phase 2 population, which stated, "Has disease eligible for potentially curative treatment such as surgical resection. Note: Single resection of metastatic lesion in the context of disease progression on prior therapy is not considered curative."

    Rationale for change: This criteria is determined to be unnecessary and increased challenge to enroll participants.

18. **Section 6.5.1, Definition of a Dose-Limiting Toxicity (Table 12: Definition of Dose-Limiting Toxicity)**

    Description of change: Additional criteria added for definition of DLT.

    Rationale for change: Based on emerging information about the study drugs and to align with standard DLT determination for immunotherapies, the inclusion of irAEs and general guidance on DLT monitoring was added.

19. **Section 6.6.3, Criteria and Procedures for Dose Interruptions and Adjustments of Study Treatment**

    Description of change: Window for drug interruption for toxicity management increased and specific guidance for restarting study drug is given.

    Rationale for change: Based on emerging information about the study drugs, the window for interruption of study drugs was increased and to align with standard practice with checkpoint inhibitors. Further guidance was given to clarify which study drugs should be restarted at a given timepoint.

20. **Section 6.6.5, Procedures for Participants Exhibiting Immune-Related Adverse Events (Table 15: Toxicity Management Guidelines for Immune-Related Adverse Events)**

    Description of change: Additional updates for management of irAEs was added.

    Rationale for change: INCMGA0012 irAE management was recently updated in INCMGA0012 program to align with ASCO guidelines (Schneider et al 2021); changes here reflect those updates in addition to guidance for management of troponin rise.

21. **Section 6.6.6., Criteria for Permanent Discontinuation of Study Treatment**

    Description of change: Updated requirement for discontinuation due to persistent AE requiring a delay of therapy from more than 4 weeks to more than 12 weeks.

    Rationale for change: To align to standard practice for checkpoint inhibitors, including INCMGA0012.

22. **Appendix A, Information Regarding Effectiveness of Contraceptive Methods**

    Description of change: Updated contraceptive methods to remove some "acceptable methods."

    Rationale for change: While characterized as "acceptable" in the Clinical Trial Facilitation Group guidance these methods are not acceptable to some regions. As the study may be expanded, these methods were removed proactively.

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

Amendment 2 (02 JUN 2021)

Overall Rationale for the Amendment: The Protocol was amended to accommodate a broader melanoma cohort in Phase 2 to enroll participants with melanoma previously treated with anti–PD-(L)1, regardless of LAG-3 status.

1. **Section 1, Protocol Summary (Table 1: Primary Objectives and Endpoints; Table 2: Key Study Design Elements; Treatment Groups and Duration; Figure 1: Study Design Schema); Section 2.1, Background; Section 2.2, Study Rationale; Section 3, Objectives and Endpoints (Table 6: Objectives and Endpoints); Section 4.1.1, Treatment Groups and Duration**

   Description of change: Study population updated to include participants with metastatic unresectable melanoma who relapsed on or after treatment with a PD-(L)1 inhibitor regardless of LAG-3 status.

   Rationale for change: Change in program strategy based on emerging data.

2. **Section 1, Protocol Summary (Table 2: Key Study Design Elements; Figure 1: Study Design Schema); Section 5.6, Data Monitoring Committee; Section 10.1.2, Phase 2; Section 10.4, Interim Analysis**

   Description of change: Population size updated to reflect change in assumptions.

   Rationale for change: Assumptions changed based on emerging data.

3. **Section 1, Protocol Summary (Table 3: Schedule of Activities [Cycles Are Based on Q4W Cycles for INCMGA00012])**

   Description of change: Detail added to describe radiologic assessments**.**

   Rationale for change: Clarification.

4. **Section 1, Protocol Summary (Table 3: Schedule of Activities[Cycles Are Based on Q4W Cycles for INCMGA00012]); Section 8.2.1.2, Tumor Imaging During Study**

   Description of change: Screening and monitoring brain CT or MRI added.

   Rational for change: Participants with active CNS metastasis are excluded.

5. **Section 1, Protocol Summary (Table 4: Schedule of Laboratory Assessments [Cycles Are Based on Q4W Cycles for INCMGA00012])**

   Description of change: Note added that comprehensive serum chemistries and hematology with differential will only be collected at the 30-day safety follow-up visit.

   Rationale for change: Decrease patient burden.

6. **Section 1, Protocol Summary (Table 4: Schedule of Laboratory Assessments [Cycles Are Based on Q4W Cycles for INCMGA00012])**

   Description of change: Note added that urinalysis would only be performed at screening and then Q8W (every other cycle; C2, C4, etc).

   Rationale for change: Decrease patient burden.

7. **Section 1, Protocol Summary (Table 4; Schedule of Laboratory Assessments [Cycles Are Based on Q4W Cycles for INCMGA00012])**

   Description of change: Added additional coagulation, thyroid, and lipid panel testing (every other cycle).

   Rationale for change: Additional safety measures added to align to INCMGA00012 program.

8. **Section 1, Protocol Summary (Table 4; Schedule of Laboratory Assessments [Cycles Are Based on Q4W Cycles for INCMGA00012])**

   Description of change: Added note that hepatitis screening results obtained within the last 3 months before C1D1 are acceptable.

   Rationale for change: Reduce patient burden for those who have already had testing.

9. **Section 1, Protocol Summary (Table 4; Schedule of Laboratory Assessments [Cycles Are Based on Q4W Cycles for INCMGA00012])**

   Description of change: Added note that serum or urine pregnancy testing will be performed monthly for 6 months after the last dose of study treatment.

   Rationale for change: Align to INCMGA00012 program following regulatory feedback.

10. **Section 1, Protocol Summary (Table 5: Schedule of Pharmacokinetic and Pharmacodynamic Assessments [Cycles Are Based on Q4W Cycles for INCMGA00012])**

    Description of change: Clarification added to state that pretreatment biopsy required at or following progression on/after prior PD-1 therapy as last line of therapy for melanoma cohort.

    Rationale for change: Clarification for timing of biopsy.

11. **Section 1, Protocol Summary (Table 5: Schedule of Pharmacokinetic and Pharmacodynamic Assessments [Cycles Are Based on Q4W Cycles for INCMGA00012]); Section 8.5.2, Tumor Biopsies Collection Requirements**

    Description of change: Added request for archival tumor tissue and an optional, on-treatment biopsy.

    Rationale for change: Additional planned translational science analyses would benefit from additional timepoint biopsies.

12. **Section 1, Protocol Summary (Table 5: Schedule of Pharmacokinetic and Pharmacodynamic Assessments [Cycles Are Based on Q4W Cycles for INCMGA00012])**

    Description of change: [redacted]

    Rationale for change: Alignment with Table 15.

13. **Section 1, Protocol Summary (Table 5: Schedule of Pharmacokinetic and Pharmacodynamic Assessments [Cycles Are Based on Q4W Cycles for INCMGA00012])**

    Description of change: [redacted]

    Rationale for change: Alignment with Table 15.

14. **Section 2.3, Scientific Rationale for Study Design**

    Description of change: Added additional rationale for updated patient population.

    Rationale for change: Strategy change due to emerging data.

15. **Section 2.3.1, Justification for Dose, Section 2.3.2, Justification for INCMGA00012 Dose**

    Description of change: Added expanded justification for dose of INCMGA00012.

    Rationale for change: Alignment to INCMGA00012 program.

16. **Section 2.4.1, INCMGA00012**

    Description of change: Added expanded benefit risk assessment of INCMGA00012.

    Rationale for change: Alignment to INCMGA00012 program.

17. **Section 2.4.4, Benefit/Risk Assessment During the COVID-19 Pandemic; Appendix C, COVID-19 Pandemic Mitigation Strategies and Instructions**

    Description of change: Additional guidance has also added to help sites manage participants during the COVID-19 pandemic.

    Rationale for change: Adding guidance for study management during the COVID-19 pandemic.

18. **Section 3, Objectives and Endpoints (Table 6, Objectives and Endpoints); Section 10, Statistics (10.3.2, Efficacy Analysis)**

    Description of change: [redacted]

    Rationale for change: Subgroup analysis added based on emerging data.

19. **Section 3, Objectives and Endpoints (Table 6, Objectives and Endpoints); Section 10.3.2, Efficacy Analysis**

    Description of change: [redacted]

    Rationale for change: Subgroup analysis added based on emerging data.

20. **Section 5, Study Population (Section 5.1, Inclusion Criteria; Section 5.2, Exclusion Criteria)**

    Description of change: Updated patient population to add detailed description of Phase 2 population.

    Rationale for change: Change in program strategy based on emerging data.

21. **Section 5, Study Population (Section 5.1, Inclusion Criteria; Section 5.2, Exclusion Criteria)**

    Description of change: Updated inclusion/exclusion criteria to incorporate attributes that could potentially confuse analysis or put participants at risk.

    Rationale for change: Additional changes to align to INCMGA00012 program.

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

    Description of change: Removed WBC requirement.

    Rationale for change: Redundant with ANC.

23. **Section 2.4.3, INCAGN02390; Section 6.1, Study Treatments Administered**

    Description of change: Note added that participants need to be observed for 4 hours postinfusion only on C1D1.

    Rationale for change: Clarification.

24. **Section 2.4.3, INCAGN02390; Section 6.6.5, Procedures for Participants Exhibiting Immune-Related Adverse Events**

    Description of change: Information moved from Section 9.5 to within Section 6, Study Treatment.

    Rationale for change: Improved alignment of information.

25. **Section 8.2.2.7, Management Following Confirmatory Imaging; Section 6.6.8 Treatment After Initial Evidence of Radiologic Disease Progression**

    Description of change: Added sentence highlighting 2-year maximum treatment duration for participants receiving treatment after progression who maintain clinical benefit.

    Rationale for change: Clarification and consistency.

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

    Description of change: Added note allowing additional laboratory analytes as clinically needed.

    Rationale for change: Program alignment and to improve patient management.

27. **Section 8.4.1, Blood Sample Collection (Table 15: Timing of Pharmacokinetics and Antidrug Antibody Sample Collection [Cycles Are Based on Q4W Cycles for INCMGA00012])**

    Description of change: EOT added to last row in Table 14 to indicate that sample draw for PK would occur at EOT and safety follow-up visit 1 (30-day).

    Rationale for change: Alignment with Table 5.

28. **Section 8.5.3, Fresh/Archival Tissue Biopsy Assessment; Appendix B, Test for LAG-3 Expression**

    Description of change: Updated information on LAG-3 antibody.

    Rationale for change: New antibody to be used for this study.

29. **Section 10, Statistics (Table 17: Populations for Analysis)**

    Description of change: Added DLT evaluable population for Phase 1.

    Rationale for change: Not originally described.

30. **Section 12, References**

    Description of change: References added for TCGA data, support for INCMGA00012 risk section, and support for COVID-19 benefit risk section.

    Rationale for change: Support inclusion of additional data in Section 2.2, Study Rationale and Section 2.4, Benefit/Risk Assessment.

31. **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 (07 APR 2020)

Overall Rationale for the Amendment: Changes were made to address comments from FDA review of the Protocol.

1. **Section 1, Protocol Summary (Table 3: Schedule of Activities [Cycles Are Based on Q4W Cycles for INCMGA00012]; Table 4: Schedule of Laboratory Assessments [Cycles Are Based on Q4W Cycles for INCMGA00012]; Table 5: Schedule of Pharmacokinetic and Pharmacodynamic Assessments [Cycles Are Based on Q4W Cycles for INCMGA00012]); Section 6.7, Concomitant Medications and Procedures; Section 8.8.1, Safety Follow-Up**

   Description of change: A 90-day safety follow-up visit was added.

   Rationale for change: FDA request.

2. **Section 2.4.3, Risks Associated With INCAGN02390; Section 6.5.1, Definition of a Dose-Limiting Toxicity; Section 8.3.1, Adverse Events; Section 8.8.1, Safety Follow-Up; Section 9.4, Reporting of Serious Adverse Events; Section 9.5, Procedures for Participants Exhibiting Immune-Related Adverse Events**

   Description of change: Monitoring of irAEs was changed to continue through the 90-day safety follow-up visit.

   Rationale for change: FDA request.

3. **Section 5.1, Inclusion Criteria**

   Description of change: Eligibility Criteria 3 and 4 were changed to more clearly define relapse during or following anti–PD-1 therapy depending on the population.

   Rationale for change: FDA request.

4. **Section 10.1.1, Phase 1; Section 10.4, Interim Analysis**

   Description of change: Target DLT rate decreased to 28%, and both the escalation boundary and the de-escalation boundary specified based on the new target DLT rate.

   Rationale for change: FDA request.

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

   Description of change: Renal function exclusion criterion revised to specify creatinine clearance (CrCl) is used rather than serum creatinine.

   Rationale for change: FDA request.

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

   Description of change: ALT and AST exclusion criteria expanded in the Phase 2 portion of study to ALT and AST $\geq 2.5 \times$ ULN.

   Rationale for change: FDA request.

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Approval Task	[redacted] [redacted] Clinical Research Scientist 02-Mar-2023 13:57:10 GMT+0000
Approval Task	[redacted] [redacted] Hematology Oncology Clinical Development 02-Mar-2023 14:12:34 GMT+0000
Approval Task	[redacted] [redacted] Clinical Development 02-Mar-2023 15:59:35 GMT+0000
Approval Task	[redacted] Approver [redacted] Hematology Oncology Clinical Development 03-Mar-2023 11:49:46 GMT+0000
Approval Task	[redacted] Approver [redacted] Clinical Operations 03-Mar-2023 13:26:12 GMT+0000
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