Official Title: An Open-Label, Randomized, Phase 2, Umbrella Study of Various Neoadjuvant Therapies for Participants With Muscle-Invasive Urothelial Carcinoma of the Bladder Who Are Cisplatin-Ineligible or Refuse Cisplatin Therapy and Undergoing Radical Cystectomy (Optimus)

NCT Number: NCT04586244

Document Date: Clinical Study Protocol (Amendment 4): 01 MAR 2022

Clinical Study Protocol

INCB 24360-901

An Open-Label, Randomized, Phase 2, Umbrella Study of Various Neoadjuvant Therapies for Participants With Muscle-Invasive Urothelial Carcinoma of the Bladder Who Are Cisplatin-Ineligible or Refuse Cisplatin Therapy and Undergoing Radical Cystectomy (Optimus)

Product:	**Epacadostat (INCB024360), retifanlimab (INCMGA00012), INCAGN02385, INCAGN02390**
IND Number:	**146,743**
EudraCT Number:	**2020-002244-23**
Phase of Study:	**2**
Sponsor:	**Incyte Corporation 1801 Augustine Cut-Off Wilmington, DE 19803**
Original Protocol:	**12 MAY 2020**
Protocol Amendment 1:	**04 SEP 2020**
Protocol Amendment 2:	**02 FEB 2021**
Protocol Amendment 3:	**10 MAY 2021**
Protocol Amendment 2-IT	**14 JUL 2021**
Protocol Amendment 4:	**01 MAR 2022**

INVESTIGATOR'S AGREEMENT

I have read the INCB 24360-901 Protocol Amendment 4 (dated 01 MAR 2022) and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this Protocol.

(Printed Name of Investigator)

(Signature of Investigator) (Date)

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LIST OF ABBREVIATIONS

Abbreviations and Special Terms	Definition
AE	adverse event
AESI	adverse event of special interest
AJCC	American Joint Committee on Cancer
ALT	alanine aminotransferase
ANC	absolute neutrophil count
anti-HBc	anti–hepatitis B core antibody
anti-HBs	anti–hepatitis B surface antibody
aPTT	activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the curve
$AUC_{0-\infty}$	area under the single-dose plasma or serum concentration-time curve extrapolated to infinity
AUC_{0-t}	area under the plasma or serum concentration-time curve from time = 0 to the last measurable concentration at time = t
BCG	Bacillus Calmette-Guérin
BID	twice daily
BSA	body surface area
[redacted]	[redacted]
CI	confidence interval
C_{max}	maximum observed plasma or serum concentration
C_{min}	minimum observed plasma or serum concentration over the dose interval
CO_2	carbon dioxide
COVID-19	coronavirus disease 2019
CPS	combined positive score
CR	complete response
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTFG	Clinical Trials Facilitation and Coordination Group
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
CYP	cytochrome P450
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DSMB	Data Safety Monitoring Board

Abbreviations and Special Terms	Definition
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EDTA	ethylenediaminetetraacetic acid
ELISA	enzyme-linked immunosorbent assay
EORTC	European Organisation for Research and Treatment of Cancer
EOI	end of infusion
EOT	end of treatment
ESMO	European Society for Medical Oncology
Fc	fragment crystallizable
FDA	Food and Drug Administration
FGFR	fibroblast growth factor receptor
GCP	Good Clinical Practice
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act of 1996
HIV	human immunodeficiency virus
IB	Investigator's Brochure
IC_{50}	concentration that results in 50% inhibition
IC_{90}	concentration that results in 90% inhibition
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICF	informed consent form
IDO1	indoleamine 2,3-dioxygenase
IEC	independent ethics committee
IFN-γ	interferon gamma
Ig	immunoglobulin
IHC	immunohistochemistry
IL	interleukin
INR	international normalized ratio
irAE	immune-related adverse event
IRB	institutional review board
IRT	interactive response technology
IV	intravenous

Abbreviations and Special Terms	Definition
LAG-3	lymphocyte activation gene 3
LFT	liver function test
MAOI	monoamine oxidase inhibitor
MedDRA	Medical Dictionary for Regulatory Activities
miUBC	muscle-invasive urothelial bladder cancer
MRC	Medical Research Council
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
N/A	not applicable
NCI	National Cancer Institute
NE	no estimate
NSAID	nonsteroidal anti-inflammatory drug
NSCLC	non–small cell lung cancer
NYHA	New York Heart Association
ORR	overall response rate
OS	overall survival
pCR	pathological complete response
PD	progressive disease
PD-1	programmed cell death protein 1
PD-L1	programmed cell death-ligand 1
PD-L2	programmed cell death-ligand 2
PFS	progression-free survival
PK	pharmacokinetic
PO	oral
PP	per Protocol
PR	partial response
PS	performance status
PT	prothrombin time
PTT	partial thromboplastin time
Q2W	every 2 weeks
Q3W	every 3 weeks
Q4W	every 4 weeks
[redacted]	[redacted]
QD	once daily
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid

Abbreviations and Special Terms	Definition
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SD	stable disease
SJS	Stevens-Johnson syndrome
SNRI	selective serotonin/norepinephrine reuptake inhibitors
SoA	schedule of activities
SOP	standard operating procedure
SSRI	selective serotonin reuptake inhibitors
T3/FT3	triiodothyronine
T4	thyroxine
TEN	toxic epidermal necrolysis
TIM-3	T cell immunoglobulin and mucin domain-containing protein 3
TEAE	treatment-emergent adverse event
TEAOSI	treatment-emergent adverse event of special interest
TIL	tumor-infiltrating lymphocyte
TSH	thyroid-stimulating hormone
TURBT	transurethral resection of bladder tumor
ULN	upper limit of normal
WBC	white blood cell

1. PROTOCOL SUMMARY

This is an umbrella study to investigate the biological rationale and outcomes for selected monotherapy and combination therapies in order to inform of potential neoadjuvant treatment combinations to be further tested in miUBC in cisplatin-ineligible participants or participants who refuse cisplatin-based therapy and are awaiting radical cystectomy.

Protocol Title:

An Open-Label, Randomized, Phase 2, Umbrella Study of Various Neoadjuvant Therapies for Participants With Muscle-Invasive Urothelial Carcinoma of the Bladder Who Are Cisplatin-Ineligible or Refuse Cisplatin Therapy and Undergoing Radical Cystectomy (Optimus)

Protocol Number: INCB 24360-901

Objectives and Endpoints:

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

Table 1: Primary and Secondary Objectives and Endpoints

Objectives	Endpoints
Primary	
To determine biologic response in participants with muscle-invasive cisplatin-ineligible or those refusing cisplatin therapy, urothelial carcinoma of the bladder.	For each treatment group, the primary endpoint is the change from baseline in CD8+ lymphocytes within resected tumor.
Secondary	
To evaluate the safety and tolerability of each of the treatment groups.	• Safety and tolerability assessed by monitoring the frequency and severity of AEs, including delay in cystectomy due to AEs.
To evaluate the preliminary efficacy of each of the treatment groups.	• pCR rate, defined as percentage of participants with ypT0N0 in each treatment group. • Major pathological response, defined as residual ypT0/1/a/isN0M0.

Overall Design:

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

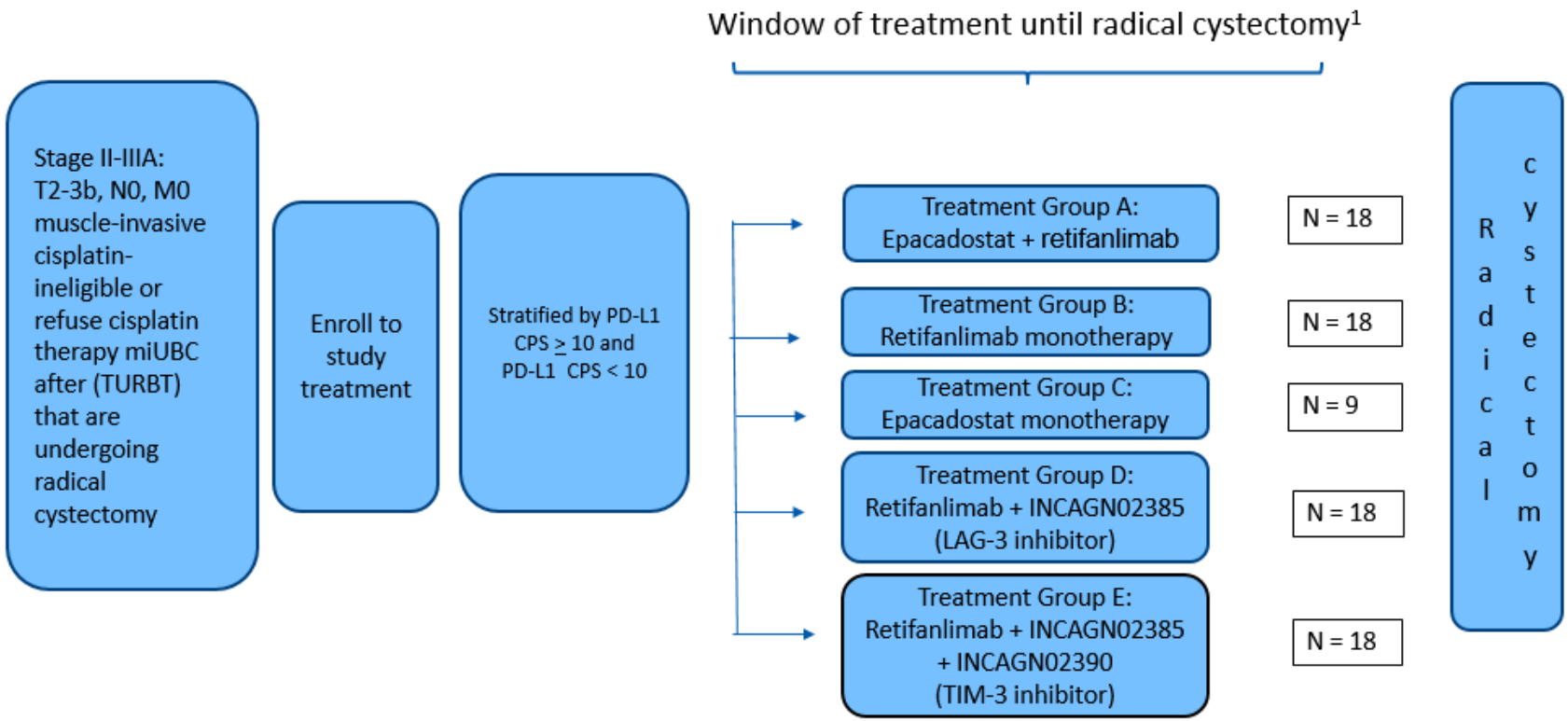
Table 2: Key Study Design Elements

Study Phase	Phase 2
Clinical Indication	Patients with muscle-invasive urothelial carcinoma of the bladder who are undergoing radical cystectomy and are either cisplatin-ineligible or refuse cisplatin therapy.
Population	Male and female participants at least 18 years of age who have miUBC and are undergoing radical cystectomy and refuse cisplatin therapy or are not eligible for cisplatin-based neoadjuvant chemotherapy, based on Galsky criteria.
Number of Participants	This is a platform design, and new treatment arms may be added or others removed. Currently, approximately 81 evaluable participants will be assigned to 1 of 5 treatment groups (18 participants in Treatment Groups A, B, D, and E, respectively, and 9 participants in Treatment Group C).
Study Design	This is a multicenter, open-label, randomized, Phase 2, multitreatment group, window-of-opportunity, umbrella study for participants with miUBC undergoing radical cystectomy who refuse or are not eligible for cisplatin-based neoadjuvant chemotherapy. Participants will be assigned based on tumor tissue PD-L1 CPS ≥ 10 or PD-L1 CPS < 10 to 1 of the following treatment groups: Treatment Group A (epacadostat plus retifanlimab) Treatment Group B (retifanlimab monotherapy) Treatment Group C (epacadostat monotherapy) Treatment Group D (retifanlimab plus INCAGN02385) Treatment Group E (retifanlimab plus INCAGN02385 plus INCAGN02390) Total treatment duration is a maximum of 10 weeks to reflect a window of opportunity before radical cystectomy. The study is a platform study design, which allows for addition of future treatment groups. Each treatment group will undergo an initial fresh biopsy (while undergoing TURBT) followed by neoadjuvant treatment, depending on the treatment group assigned, the treatment will be at least 4 weeks, followed by surgery (radical cystectomy). The treatment duration will be a maximum of 10 weeks. In all treatment groups, tissue from the surgical specimen(s) will be collected and will be compared with the initial biopsy samples to determine biologic response to the assigned treatment. All participants will then be followed for safety for 90 days after cystectomy or after the last dose of study treatment if cystectomy is not performed.
Estimated Duration of Study Participation	Up to 28 days for screening, continuous treatment for 4 to 10 weeks as long as participants have not met any criteria for study withdrawal, followed by surgery, 30-day safety follow-up after the last dose, and 90 days follow-up after cystectomy. In the event that the participant does not undergo a cystectomy, the follow-up visit will be 90 days after the last dose of study treatment. The estimated duration of study participation is approximately 6 months.
DSMB	A DSMB will be used.
Coordinating Principal Investigator	[redacted] MD

Treatment Groups and Duration:

Figure 1 presents the study design schema, and Table 3 through Table 7 present the SoA.

Figure 1: Study Design Schema



[1]Treatment duration is based on date of radical cystectomy. Participants should receive a minimum of 4 weeks and maximum of 10 weeks of treatment.

The current sample size represents an estimated number of participants per treatment group in order to attain the necessary evaluable paired biopsies. Additional participants will be enrolled in treatment groups to ensure the number of evaluable paired biopsies are obtained. This is a platform design, and additional treatment arms may be added or removed in the future.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

Table 3: Schedule of Activities for Participants Receiving Epacadostat Plus Retifanlimab (Treatment Group A)

Visit Day (Range)	Screening	Treatment (Cycle Is Q4W)			Precystectomy (2 wk Before Cystectomy)	Cystectomy (± 2 wk)	Safety Follow-Up		Notes
		Cycle 1	Cycle 2	Cycle 3			30 Days After Cystectomy (or After Last Dose If Cystectomy Not Performed)	90 Days After Cystectomy (or After Last Dose If Cystectomy Not Performed)	
	Days –28 to –1	Day 1	Day 1 (± 3 d)	Day 1 (± 3 d)					
Informed consent	X								Section 8.1.1.
Inclusion/exclusion criteria	X	X							Section 5.
General and disease medical history	X								Section 8.1.5.
Prior/concomitant medications	X	X	X	X	X		X	X	Section 6.6.
Cystectomy						X			
Safety assessments									
AE assessments	X	X	X	X	X	X	X	X	Body systems with symptoms should be physically examined. AEs should be collected until 90 days after cystectomy or the last dose of either study drug if cystectomy not performed; this may occur via telephone. Section 8.3.1.
Physical examination/height/ body weight	X*	X	X	X	X		X	X	*Comprehensive physical examination (including hearing and peripheral neuropathy assessments) and height at screening only. Section 8.3.2.
Vital signs	X	X	X	X	X		X	X	Section 8.3.3.
12-lead ECG	X	X	X	X	X		X		Section 8.3.4.
ECOG PS	X	X	X	X	X		X		Section 8.3.6.
Postsurgical safety assessments							X		Section 8.3.7 and Appendix D for details.

Table 3: Schedule of Activities for Participants Receiving Epacadostat Plus Retifanlimab (Treatment Group A) (Continued)

Visit Day (Range)	Screening	Treatment (Cycle Is Q4W)			Precystectomy (2 wk Before Cystectomy)	Cystectomy (± 2 wk)	Safety Follow-Up		Notes
		Cycle 1	Cycle 2	Cycle 3			30 Days After Cystectomy (or After Last Dose If Cystectomy Not Performed)	90 Days After Cystectomy (or After Last Dose If Cystectomy Not Performed)	
	Days –28 to –1	Day 1	Day 1 (± 3 d)	Day 1 (± 3 d)					
Efficacy assessments									
Radiologic tumor assessments	X				X			X	CT/MRI of the abdomen and pelvis and CT scan of the thorax (RECIST v1.1).
Pathological tumor assessments	X					X			Pathological tumor assessments include pathological complete response, major pathological response, [redacted] Section 8.2.1.
Tumor tissue sampling	X					X			Section 8.5.2.
Laboratory assessments									
Blood chemistry	X	X*	X	X	X		X		Locally tested. *Not necessary if screening assessment performed within 7 days of C1D1. Section 8.3.5.
Hematology	X	X*	X	X	X		X		Locally tested. *Not necessary if screening assessment performed within 7 days of C1D1. Section 8.3.5.
Thyroid function	X		X	X	X		X		Locally tested.
Lipid panel	X		X						Locally tested.
Coagulation parameters	X		X	X	X		X		Locally tested.
Urinalysis	X		X	X	X		X		Locally tested.

Table 3: Schedule of Activities for Participants Receiving Epacadostat Plus Retifanlimab (Treatment Group A) (Continued)

Visit Day (Range)	Screening	Treatment (Cycle Is Q4W)			Precystectomy (2 wk Before Cystectomy)	Cystectomy (± 2 wk)	Safety Follow-Up		Notes
		Cycle 1	Cycle 2	Cycle 3			30 Days After Cystectomy (or After Last Dose If Cystectomy Not Performed)	90 Days After Cystectomy (or After Last Dose If Cystectomy Not Performed)	
	Days –28 to –1	Day 1	Day 1 (± 3 d)	Day 1 (± 3 d)					
Laboratory assessments (continued)									
Pregnancy testing (women of childbearing potential)	X	X	X	X	X		X		Locally tested. Serum at screening and precystectomy, and urine or serum before cystectomy, before the first dose on D1 of each cycle, and at 30-day safety follow-up. Pregnancy testing will be conducted as medically indicated or per country or institutional requirements. Section 8.3.5.1.
Hepatitis screening (HBV and HCV)	X								Results obtained within the last 3 months before C1D1 are acceptable.
HIV screening and management testing HIV viral load CD4+ cell count	X				X		X		Locally tested. Section 8.3.5.
Other assessments									
[redacted]									
Serum sample for ADA		X	X				X		Preinfusion and safety follow-up 30 days after last dose. Section 8.4.1 and Table 20.

Table 3: Schedule of Activities for Participants Receiving Epacadostat Plus Retifanlimab (Treatment Group A) (Continued)

Visit Day (Range)	Screening: Days –28 to –1	Treatment (Cycle Is Q4W): Cycle 1 Day 1	Cycle 2 Day 1 (± 3 d)	Cycle 3 Day 1 (± 3 d)	Precystectomy (2 wk Before Cystectomy)	Cystectomy (± 2 wk)	Safety Follow-Up: 30 Days After Cystectomy (or After Last Dose If Cystectomy Not Performed)	Safety Follow-Up: 90 Days After Cystectomy (or After Last Dose If Cystectomy Not Performed)	Notes
Other assessments (continued)									
[redacted]									
Dispensing and administration of study drug									
Dispense epacadostat		X	X	X					Epacadostat will be administered daily until cystectomy. Section 6 and Pharmacy Manual.
Administer retifanlimab		X	X	X					Section 6 and Pharmacy Manual.
Distribute reminder cards		X	X	X					Section 8.1.4.

Table 4: Schedule of Activities for Participants Receiving Retifanlimab Monotherapy (Treatment Group B)

Visit Day (Range)	Screening	Treatment (Cycle Is Q4W)			Precystectomy (2 wk Before Cystectomy)	Cystectomy (± 2 wk)	Safety Follow-Up		Notes
		Cycle 1	Cycle 2	Cycle 3			30 Days After Cystectomy (or After Last Dose If Cystectomy Not Performed)	90 Day After Cystectomy (or Post Last Dose If Cystectomy Not Performed)	
	Days –28 to –1	Day 1	Day 1 (± 3 d)	Day 1 (± 3 d)					
Informed consent	X								Section 8.1.1.
Inclusion/exclusion criteria	X	X							Section 5.
General and disease medical history	X								Section 8.1.5.
Prior/concomitant medications	X	X	X	X	X		X	X	Section 6.6.
Cystectomy						X			
Safety assessments									
AE assessments	X	X	X	X	X	X	X	X	Body systems with symptoms should be physically examined. AEs should be collected until 90 days after cystectomy or the last dose of either study drug if cystectomy not performed; this may occur via telephone. Section 8.3.1.
Physical examination/height/ body weight	X*	X	X	X	X		X	X	*Comprehensive physical examination (including hearing and peripheral neuropathy assessments) and height at screening only. Section 8.3.2.
Vital signs	X	X	X	X	X		X	X	Section 8.3.3.
12-lead ECG	X	X	X	X	X		X		Section 8.3.4.
ECOG PS	X	X	X	X	X		X		Section 8.3.6.
Postsurgical safety assessments							X		Section 8.3.7 and Appendix D for details.

Table 4: Schedule of Activities for Participants Receiving Retifanlimab Monotherapy (Treatment Group B) (Continued)

Visit Day (Range)	Screening	Treatment (Cycle Is Q4W)			Precystectomy (2 wk Before Cystectomy)	Cystectomy (± 2 wk)	Safety Follow-Up		Notes
		Cycle 1	Cycle 2	Cycle 3			30 Days After Cystectomy (or After Last Dose If Cystectomy Not Performed)	90 Day After Cystectomy (or Post Last Dose If Cystectomy Not Performed)	
	Days –28 to –1	Day 1	Day 1 (± 3 d)	Day 1 (± 3 d)					
Efficacy assessments									
Radiologic tumor assessments	X				X			X	CT/MRI of the abdomen and pelvis and CT scan of the thorax (RECIST v1.1).
Pathological tumor assessments	X					X			Pathological tumor assessments include pathological complete response, major pathological response, [redacted] Section 8.2.1.
Tumor tissue sampling	X					X			Section 8.5.2.
Laboratory assessments									
Blood chemistry	X	X*	X	X	X		X		Locally tested. *Not necessary if screening assessment performed within 7 days of C1D1. Section 8.3.5.
Hematology	X	X*	X	X	X		X		Locally tested. *Not necessary if screening assessment performed within 7 days of C1D1. Section 8.3.5.
Thyroid function	X		X	X	X		X		Locally tested.
Lipid panel	X		X						Locally tested.
Coagulation parameters	X		X	X	X		X		Locally tested.
Urinalysis	X		X	X	X		X		Locally tested.

Table 4: Schedule of Activities for Participants Receiving Retifanlimab Monotherapy (Treatment Group B) (Continued)

Visit Day (Range)	Screening	Treatment (Cycle Is Q4W)			Precystectomy (2 wk Before Cystectomy)	Cystectomy (± 2 wk)	Safety Follow-Up		Notes
		Cycle 1	Cycle 2	Cycle 3			30 Days After Cystectomy (or After Last Dose If Cystectomy Not Performed)	90 Day After Cystectomy (or Post Last Dose If Cystectomy Not Performed)	
	Days –28 to –1	Day 1	Day 1 (± 3 d)	Day 1 (± 3 d)					
Laboratory assessments (continued)									
Pregnancy testing (women of childbearing potential)	X	X	X	X	X		X		Locally tested. Serum at screening and precystectomy, and urine or serum before cystectomy, before the first dose on D1 of each cycle, and at 30-day safety follow-up. Pregnancy testing will be conducted as medically indicated or per country or institutional requirements. Section 8.3.5.1.
Hepatitis screening (HBV and HCV)	X								Results obtained within the last 3 months before C1D1 are acceptable.
HIV screening and management HIV viral load CD4+ cell count	X				X		X		Locally tested. Section 8.3.5.
Other assessments									
[redacted]									
Serum sample for ADA		X	X				X		Preinfusion and safety follow-up 30 days after last dose. Section 8.4.1 and Table 20.

Table 4: Schedule of Activities for Participants Receiving Retifanlimab Monotherapy (Treatment Group B) (Continued)

Visit Day (Range)	Screening	Treatment (Cycle Is Q4W)			Precystectomy (2 wk Before Cystectomy)	Cystectomy (± 2 wk)	Safety Follow-Up		Notes
		Cycle 1	Cycle 2	Cycle 3			30 Days After Cystectomy (or After Last Dose If Cystectomy Not Performed)	90 Day After Cystectomy (or Post Last Dose If Cystectomy Not Performed)	
	Days –28 to –1	Day 1	Day 1 (± 3 d)	Day 1 (± 3 d)					
Dispensing and administration of study drug									
Administer retifanlimab*		X	X	X					Section 6 and Pharmacy Manual. *Maximum total treatment duration is 10 weeks.
Distribute reminder cards		X	X	X					Section 8.1.4.

Table 5: Schedule of Activities for Participants Receiving Epacadostat Monotherapy (Treatment Group C)

Visit Day (Range)	Screening	Treatment (Cycle Is Q4W)			Precystectomy (2 wk Before Cystectomy)	Cystectomy (± 2 wk)	Safety Follow-Up		Notes
	Days –28 to –1	Cycle 1 Day 1	Cycle 2 Day 1 (± 3 d)	Cycle 3 Day 1 (± 3 d)			30 Days After Cystectomy (or After Last Dose If Cystectomy Not Performed)	90 Days After Cystectomy (or After Last Dose If Cystectomy Not Performed)	
Informed consent	X								Section 8.1.1.
Inclusion/exclusion criteria	X	X							Section 5.
General and disease medical history	X								Section 8.1.5.
Prior/concomitant medications	X	X	X	X	X		X	X	Section 6.6.
Cystectomy						X			
Safety assessments									
AE assessments	X	X	X	X	X	X	X	X	Body systems with symptoms should be physically examined. AEs should be collected until 90 days after cystectomy or the last dose of either study drug if cystectomy not performed; this may occur via telephone. Section 8.3.1.
Physical examination/height/ body weight	X*	X	X	X	X		X	X	*Comprehensive physical examination (including hearing and peripheral neuropathy assessments) and height at screening only. Section 8.3.2.
Vital signs	X	X	X	X	X		X	X	Section 8.3.3.
12-lead ECG	X	X	X	X	X		X		Section 8.3.4.
ECOG PS	X	X	X	X	X		X		Section 8.3.6.
Postsurgical safety assessments							X		Section 8.3.7 and Appendix D for details.

Table 5: Schedule of Activities for Participants Receiving Epacadostat Monotherapy (Treatment Group C) (Continued)

Visit Day (Range)	Screening	Treatment (Cycle Is Q4W)			Precystectomy (2 wk Before Cystectomy)	Cystectomy (± 2 wk)	Safety Follow-Up		Notes
		Cycle 1	Cycle 2	Cycle 3			30 Days After Cystectomy (or After Last Dose If Cystectomy Not Performed)	90 Days After Cystectomy (or After Last Dose If Cystectomy Not Performed)	
	Days –28 to –1	Day 1	Day 1 (± 3 d)	Day 1 (± 3 d)					
Efficacy assessments									
Radiologic tumor assessments	X				X			X	CT/MRI of the abdomen and pelvis and CT scan of the thorax (RECIST v1.1).
Pathological tumor assessments	X					X			Pathological tumor assessments include pathological complete response, major pathological response, [redacted] Section 8.2.1.
Tumor tissue sampling	X					X			Section 8.5.2.
Laboratory assessments									
Blood chemistry	X	X*	X	X	X		X		Locally tested. *Not necessary if screening assessment performed within 7 days of C1D1. Section 8.3.5.
Hematology	X	X*	X	X	X		X		Locally tested. *Not necessary if screening assessment performed within 7 days of C1D1. Section 8.3.5.
Thyroid function	X		X	X	X		X		Locally tested.
Lipid panel	X		X						Locally tested.
Coagulation parameters	X		X	X	X		X		Locally tested.
Urinalysis	X		X	X	X		X		Locally tested.

Table 5: Schedule of Activities for Participants Receiving Epacadostat Monotherapy (Treatment Group C) (Continued)

Visit Day (Range)	Screening	Treatment (Cycle Is Q4W)			Precystectomy (2 wk Before Cystectomy)	Cystectomy (± 2 wk)	Safety Follow-Up		Notes
		Cycle 1	Cycle 2	Cycle 3			30 Days After Cystectomy (or After Last Dose If Cystectomy Not Performed)	90 Days After Cystectomy (or After Last Dose If Cystectomy Not Performed)	
	Days –28 to –1	Day 1	Day 1 (± 3 d)	Day 1 (± 3 d)					
Laboratory assessments (continued)									
Pregnancy testing (women of childbearing potential)	X	X	X	X	X		X		Locally tested. Serum at screening and precystectomy, and urine or serum before cystectomy, before the first dose on D1 of each cycle, and at 30-day safety follow-up. Pregnancy testing will be conducted as medically indicated or per country or institutional requirements. Section 8.3.5.1.
Hepatitis screening (HBV and HCV)	X								Results obtained within the last 3 months before C1D1 are acceptable.
HIV screening and management testing HIV viral load CD4+ cell count	X				X		X		Locally tested. Section 8.3.5.
Other assessments									
[redacted]									

Table 5: Schedule of Activities for Participants Receiving Epacadostat Monotherapy (Treatment Group C) (Continued)

Visit Day (Range)	Screening	Treatment (Cycle Is Q4W)			Precystectomy (2 wk Before Cystectomy)	Cystectomy (± 2 wk)	Safety Follow-Up		Notes
		Cycle 1	Cycle 2	Cycle 3			30 Days After Cystectomy (or After Last Dose If Cystectomy Not Performed)	90 Days After Cystectomy (or After Last Dose If Cystectomy Not Performed)	
	Days –28 to –1	Day 1	Day 1 (± 3 d)	Day 1 (± 3 d)					
Dispensing and administration of study drug									
Dispense epacadostat		X	X	X*					Section 6 and Pharmacy Manual. Epacadostat will be administered daily until cystectomy. *Cycle 3 is a maximum of 2 weeks of therapy. Maximum total treatment duration is 10 weeks.
Distribute reminder cards		X	X	X					Section 8.1.4.

Table 6: Schedule of Activities for Participants Receiving Retifanlimab Plus INCAGN02385 (Treatment Group D)

Visit Day (Range)	Screening	Treatment (Cycle Is Q4W)					Precystectomy (2 wk before cystectomy)	Cystectomy (± 2 wk)	Safety Follow-Up		Notes
		Cycle 1		Cycle 2		Cycle 3			30 Days After Cystectomy (or After Last Dose If Cystectomy Not Performed)	90 Days After Cystectomy (or After Last Dose If Cystectomy Not Performed)	
	Days –28 to –1	Day 1	Day 15 (± 2 d)	Day 1 (± 3 d)	Day 15 (± 2 d)	Day 1 (± 3 d)					
Informed consent	X										Section 8.1.1.
Inclusion/exclusion criteria	X										Section 5.
General and disease medical history	X										Section 8.1.5.
Prior/concomitant medications	X	X	X	X	X	X	X		X	X	Section 6.6.
Cystectomy								X			
Safety assessments											
AE assessments	X	X	X	X	X	X	X	X	X	X	Body systems with symptoms should be physically examined. AEs should be collected until 90 days after cystectomy or the last dose of either study drug if cystectomy not performed; this may occur via telephone. Section 8.3.1.
Physical examination/height/ body weight	X*	X	X	X	X	X	X		X	X	*Comprehensive physical examination (including hearing and peripheral neuropathy assessments) and height at screening only. Section 8.3.2.
Vital signs	X	X	X	X	X	X	X		X	X	Section 8.3.3.
12-lead ECG	X	X		X		X	X		X		Section 8.3.4.
ECOG PS	X	X		X		X	X		X		Section 8.3.6.
Postsurgical safety assessments									X		Section 8.3.7 and Appendix D.

Table 6: Schedule of Activities for Participants Receiving Retifanlimab Plus INCAGN02385 (Treatment Group D) (Continued)

Visit Day (Range)	Screening	Treatment (Cycle Is Q4W)					Precystectomy (2 wk before cystectomy)	Cystectomy (± 2 wk)	Safety Follow-Up		Notes
		Cycle 1		Cycle 2		Cycle 3			30 Days After Cystectomy (or After Last Dose If Cystectomy Not Performed)	90 Days After Cystectomy (or After Last Dose If Cystectomy Not Performed)	
	Days –28 to –1	Day 1	Day 15 (± 2 d)	Day 1 (± 3 d)	Day 15 (± 2 d)	Day 1 (± 3 d)					
Efficacy assessments											
Radiologic tumor assessments	X						X			X	CT/MRI of the abdomen and pelvis and CT scan of the thorax (RECIST v1.1).
Pathological tumor assessments	X							X			Pathological tumor assessments include pathological complete response, major pathological response, [redacted] Section 8.2.1.
Tumor tissue sampling	X							X			Section 8.5.2.
Laboratory assessments											
Blood chemistry	X	X*	X	X	X	X	X		X		Locally tested. *Not necessary if screening assessment performed within 7 days of C1D1. Section 8.3.5.

Table 6: Schedule of Activities for Participants Receiving Retifanlimab Plus INCAGN02385 (Treatment Group D) (Continued)

Visit Day (Range)	Screening	Treatment (Cycle Is Q4W)					Precystectomy (2 wk before cystectomy)	Cystectomy (± 2 wk)	Safety Follow-Up		Notes
		Cycle 1		Cycle 2		Cycle 3			30 Days After Cystectomy (or After Last Dose If Cystectomy Not Performed)	90 Days After Cystectomy (or After Last Dose If Cystectomy Not Performed)	
	Days –28 to –1	Day 1	Day 15 (± 2 d)	Day 1 (± 3 d)	Day 15 (± 2 d)	Day 1 (± 3 d)					
Laboratory assessments (continued)											
Troponin I or T measurements	X	X*	X	X		X	X				To be performed predose on C1D1 (*only if not done at screening) and C1D15. Predose is defined as within 3 calendar days prior to dosing. All laboratory values should be checked prior to dosing. Day 15 laboratory values should be checked as soon as possible. In case of high troponin levels, see management guidelines in Table 15 and Table 18.
Hematology	X	X*	X	X	X	X	X		X		Locally tested. *Not necessary if screening assessment performed within 7 days of C1D1. Section 8.3.5.
Thyroid function	X			X		X	X		X		Locally tested.
Lipid panel	X			X							Locally tested.

Table 6: Schedule of Activities for Participants Receiving Retifanlimab Plus INCAGN02385 (Treatment Group D) (Continued)

Visit Day (Range)	Screening	Treatment (Cycle Is Q4W)					Precystectomy (2 wk before cystectomy)	Cystectomy (± 2 wk)	Safety Follow-Up		Notes
		Cycle 1		Cycle 2		Cycle 3			30 Days After Cystectomy (or After Last Dose If Cystectomy Not Performed)	90 Days After Cystectomy (or After Last Dose If Cystectomy Not Performed)	
	Days –28 to –1	Day 1	Day 15 (± 2 d)	Day 1 (± 3 d)	Day 15 (± 2 d)	Day 1 (± 3 d)					
Laboratory assessments (continued)											
Coagulation parameters	X			X		X	X		X		Locally tested.
Urinalysis	X			X		X	X		X		Locally tested.
Pregnancy testing (women of childbearing potential)	X	X		X		X	X		X		Locally tested. Serum at screening and precystectomy, and urine or serum before cystectomy, before the first dose on D1 of each cycle, and at 30-day safety follow-up. Pregnancy testing will be conducted as medically indicated or per country or institutional requirements. Section 8.3.5.1.
Hepatitis screening (HBV and HCV)	X										Results obtained within the last 3 months before C1D1 are acceptable.
HIV screening and management HIV viral load CD4+ cell count	X						X		X		Locally tested. Section 8.3.5.
Other assessments											
[redacted]											

Table 6: Schedule of Activities for Participants Receiving Retifanlimab Plus INCAGN02385 (Treatment Group D) (Continued)

Visit Day (Range)	Screening	Treatment (Cycle Is Q4W)					Precystectomy (2 wk before cystectomy)	Cystectomy (± 2 wk)	Safety Follow-Up		Notes
		Cycle 1		Cycle 2		Cycle 3			30 Days After Cystectomy (or After Last Dose If Cystectomy Not Performed)	90 Days After Cystectomy (or After Last Dose If Cystectomy Not Performed)	
	Days –28 to –1	Day 1	Day 15 (± 2 d)	Day 1 (± 3 d)	Day 15 (± 2 d)	Day 1 (± 3 d)					
Other assessments (continued)											
Serum sample for ADA		X		X					X		Preinfusion and safety follow-up 30 days after last dose. Section 8.4.1 and Table 20.
Dispensing and administration of study drug											
Administer retifanlimab		X		X		X					Retifanlimab administered on D1 of each cycle. Section 6.1.
Administer INCAGN02385		X	X	X	X	X					INCAGN02385 is administered Q2W. Section 6.1.
Distribute reminder cards		X	X	X	X	X					Section 8.1.4.

Table 7: Schedule of Activities for Participants Receiving Retifanlimab Plus INCAGN02385 Plus INCAGN02390 (Treatment Group E)

	Screening	Treatment (Cycle Is Q4W)					Precystectomy (2 wk Before Cystectomy)	Cystectomy (± 2 wk)	Safety Follow-Up		
		Cycle 1		Cycle 2+		Cycle 3			30 Days After Cystectomy (or After Last Dose If Cystectomy Not Performed)	90 Days After Cystectomy (or After Last Dose If Cystectomy Not Performed)	
Visit Day (Range)	**Days –28 to –1**	**Day 1**	**Day 15 (± 2 d)**	**Day 1 (± 3 d)**	**Day 15 (± 2 d)**	**Day 1 (± 3 d)**					**Notes**
Informed consent	X										Section 8.1.1.
Inclusion/exclusion criteria	X										Section 5.
General and disease medical history	X										Section 8.1.5.
Prior/concomitant medications	X	X	X	X	X	X	X		X	X	Section 6.6.
Cystectomy								X			
Safety assessments											
AE assessments	X	X	X	X	X	X	X	X	X	X	Body systems with symptoms should be physically examined. AEs should be collected until 90 days after cystectomy or the last dose of either study drug if cystectomy not performed; this may occur via telephone. Section 8.3.1.
Physical examination/height /body weight	X*	X	X	X	X	X	X		X	X	Comprehensive physical examination (including hearing and peripheral neuropathy assessments) and height at screening only. Section 8.3.2.
Vital signs	X	X	X	X	X	X	X		X	X	Section 8.3.3.
12-lead ECG	X	X		X		X	X		X		Section 8.3.4.

Table 7: Schedule of Activities for Participants Receiving Retifanlimab Plus INCAGN02385 Plus INCAGN02390 (Treatment Group E) (Continued)

Visit Day (Range)	Screening	Treatment (Cycle Is Q4W)					Precystectomy (2 wk Before Cystectomy)	Cystectomy (± 2 wk)	Safety Follow-Up		Notes
		Cycle 1		Cycle 2+		Cycle 3			30 Days After Cystectomy (or After Last Dose If Cystectomy Not Performed)	90 Days After Cystectomy (or After Last Dose If Cystectomy Not Performed)	
	Days –28 to –1	Day 1	Day 15 (± 2 d)	Day 1 (± 3 d)	Day 15 (± 2 d)	Day 1 (± 3 d)					
Safety assessments (continued)											
ECOG PS	X	X		X		X	X		X		Section 8.3.6.
Postsurgical safety assessments									X		Section 8.3.7 and Appendix D.
Efficacy assessments											
Radiologic tumor assessments	X						X			X	CT/MRI of the abdomen and pelvis and CT scan of the thorax (RECIST v1.1).
Pathological tumor assessments	X							X			Pathological tumor assessments include pathological complete response, major pathological response, [redacted] Section 8.2.1.
Tumor tissue sampling	X							X			Section 8.5.2.
Laboratory assessments											
Blood chemistry	X	X*	X	X	X	X	X		X		Locally tested. *Not necessary if screening assessment performed within 7 days of C1D1. Section 8.3.5.

Table 7: Schedule of Activities for Participants Receiving Retifanlimab Plus INCAGN02385 Plus INCAGN02390 (Treatment Group E) (Continued)

Visit Day (Range)	Screening	Treatment (Cycle Is Q4W)					Precystectomy (2 wk Before Cystectomy)	Cystectomy (± 2 wk)	Safety Follow-Up		Notes
		Cycle 1		Cycle 2+		Cycle 3			30 Days After Cystectomy (or After Last Dose If Cystectomy Not Performed)	90 Days After Cystectomy (or After Last Dose If Cystectomy Not Performed)	
	Days –28 to –1	Day 1	Day 15 (± 2 d)	Day 1 (± 3 d)	Day 15 (± 2 d)	Day 1 (± 3 d)					
Laboratory assessments (continued)											
Troponin I or T measurements	X	X*	X	X		X	X				To be performed predose on C1D1 (*only if not done at screening) and C1D15. Predose is defined as within 3 calendar days prior to dosing. All laboratory values should be checked prior to dosing. Day 15 laboratory values should be checked as soon as possible. In case of high troponin levels, see management guidelines in Table 15 and Table 18.
Hematology	X	X*	X	X	X	X	X		X		Locally tested. *Not necessary if screening assessment performed within 7 days of C1D1. Section 8.3.5.
Thyroid function	X			X		X	X		X		Locally tested.
Lipid panel	X			X							Locally tested.
Coagulation parameters	X			X		X	X		X		Locally tested.
Urinalysis	X			X		X	X		X		Locally tested.

Table 7: Schedule of Activities for Participants Receiving Retifanlimab Plus INCAGN02385 Plus INCAGN02390 (Treatment Group E) (Continued)

Visit Day (Range)	Screening	Treatment (Cycle Is Q4W)					Precystectomy (2 wk Before Cystectomy)	Cystectomy (± 2 wk)	Safety Follow-Up		Notes
		Cycle 1		Cycle 2+		Cycle 3			30 Days After Cystectomy (or After Last Dose If Cystectomy Not Performed)	90 Days After Cystectomy (or After Last Dose If Cystectomy Not Performed)	
	Days –28 to –1	Day 1	Day 15 (± 2 d)	Day 1 (± 3 d)	Day 15 (± 2 d)	Day 1 (± 3 d)					
Laboratory assessments (continued)											
Pregnancy testing (women of childbearing potential)	X	X		X		X	X		X		Locally tested. Serum at screening and precystectomy, and urine or serum before cystectomy, before the first dose on D1 of each cycle, and at 30-day safety follow-up. Pregnancy testing will be conducted as medically indicated or per country or institutional requirements. Section 8.3.5.1.
Hepatitis screening (HBV and HCV)	X										Results obtained within the last 3 months before C1D1 are acceptable.
HIV screening and management HIV viral load CD4+ cell count	X						X		X		Locally tested. Section 8.3.5.
Other assessments											
[redacted]											

Table 7: Schedule of Activities for Participants Receiving Retifanlimab Plus INCAGN02385 Plus INCAGN02390 (Treatment Group E) (Continued)

	Screening	Treatment (Cycle Is Q4W)							Safety Follow-Up		
		Cycle 1		Cycle 2+		Cycle 3					
Visit Day (Range)	Days –28 to –1	Day 1	Day 15 (± 2 d)	Day 1 (± 3 d)	Day 15 (± 2 d)	Day 1 (± 3 d)	Precystectomy (2 wk Before Cystectomy)	Cystectomy (± 2 wk)	30 Days After Cystectomy (or After Last Dose If Cystectomy Not Performed)	90 Days After Cystectomy (or After Last Dose If Cystectomy Not Performed)	Notes
Other assessments (continued)											
Serum sample for ADA		X		X					X		Preinfusion and safety follow-up 30 days after last dose. Section 8.4.1 and Table 20.
Dispensing and administration of study drug											
Administer retifanlimab		X		X		X					Retifanlimab administered on D1 of each cycle. Section 6.1.
Administer INCAGN02385		X	X	X	X	X					INCAGN02385 is administered Q2W. Section 6.1.
Administer INCAGN02390		X	X	X	X	X					INCAGN02390 is administered Q2W Section 6.1.
Distribute reminder cards		X	X	X	X	X					Section 8.1.4.

2. INTRODUCTION

2.1. Study Rationale

This is an umbrella study to investigate the biological rationale and outcomes for selected monotherapy and combination therapies in order to inform of potential neoadjuvant treatment combinations to be further tested in miUBC in cisplatin-ineligible participants or those refusing cisplatin therapy and are awaiting radical cystectomy.

2.1.1. Scientific Rationale for Study Design

Bladder cancer was the 11th most common cancer based on 2018 estimates, accounting for approximately 549,000 new cases and 200,000 deaths globally (Global Cancer Observatory 2019). In the US, bladder cancer is the fourth most common cancer, with over 70,000 new cases each year (CDC 2019). Urothelial carcinoma is the predominant histologic type of bladder cancer in the US and Western Europe, where it accounts for approximately 90% of bladder cancers. Approximately 25% of patients will have muscle-invasive disease and either present with or later develop metastases (von der Maase et al 2005).

Early stage localized disease can be treated initially by TURBT. Unfortunately, up to 50% of patients will have a recurrence of the cancer within 12 months. Due of this high recurrence rate, adjuvant therapy is usually recommended (Cao et al 2015). Neoadjuvant chemotherapy yields Level 1 evidence in the National Comprehensive Cancer Network guidelines (NCCN 2020). However, modest improvements are seen with neoadjuvant therapy over radical cystectomy. In the MRC/EORTC trial of 976 patients, only 6% absolute increase in OS at 5 years was observed over radical cystectomy. Therefore, there is a need for improved outcomes with use of neoadjuvant therapy (International Collaboration of Trialists 1999). This study will be conducted in participants with miUBC who are routinely candidates for radical cystectomy alone. These patients are good candidates for biologic studies, because patients undergo a short course of neoadjuvant treatment that precedes surgery without prolonging the routine waiting time (usually in the range of 8-10 weeks; Poletajew et al 2014).

In a SEER-Medicare analysis performed by Gore et al (2009), time from diagnosis to radical cystectomy ranged from 4 to 52 weeks in 441 patients with Stage 2 bladder cancer who underwent radical cystectomy between 1992 and 2001. Eighty-nine percent of these patients underwent definitive surgical extirpation within 24 weeks of diagnosis, of whom 73% underwent cystectomy within 12 weeks.

Patients who achieve a pCR (pT0) have a better long-term outcome. In recent meta-analyses, the absolute risk reduction in OS is approximately 30%; therefore, pathological downstaging is a potential surrogate marker for efficacy and increased survival in neoadjuvant therapies for miUBC (Rosenblatt et al 2012).

In a 50-patient cohort study, the anti–PD-1 antibody pembrolizumab as single-agent therapy, given as neoadjuvant therapy in patients with T2-3b bladder cancer, demonstrated a 42% pT0 rate. Those with PD-L1 CPS > 10 achieved a 54% pT0 rate, whereas those with PD-L1 CPS < 10 achieved a 13.3% pT0 rate (Necchi et al 2018).

A growing body of data supports that the key to generating immune responses in tumor, triggered by administration of immunotherapy, is the expansion and tumor invasion of T lymphocytes and the focus of many clinical studies aimed at delivering effective immunotherapy for cancer patients has been on the expansion of the T lymphocyte population. Vaccine studies have demonstrated the ability to boost tumor specific T cells in the peripheral blood, but the key to obtaining tumor regression appears to be TILs (Liakou et al 2007).

A high prevalence of TILs has been shown to be associated with a favorable response to chemotherapy in bladder cancer, even in the setting of more invasive disease (Liakou et al 2007). The presence of intratumoral CD8 T cells has shown to predict better disease-free survival and OS in bladder cancer patients with muscle invasive disease (Sharma et al 2007). Liu et al (2018) also reported that higher TILs were associated with disease-free survival, with the association stronger in muscle invasive as compared with non–muscle invasive disease. Huang et al (2018) demonstrated a significant increase in median OS in patients with metastatic bladder cancer having intense TILs infiltration. Subgroup analysis showed that TILs were prognostic for both urothelial carcinoma of bladder and upper tract urothelial carcinoma. Sharma et al (2007) found that CD8 tumor-infiltrating lymphocytes are predictive of survival in muscle-invasive urothelial carcinoma.

The tumor-infiltrating lymphocyte population consists of multiple T-cell populations, including CD4+ helper cells, CD8+ cytotoxic T cells, and FoxP3+ Tregs. This study will use a multiplex CD8/FoxP3/granzyme B IHC assay to monitor the overall influx and activation state of these populations into the tumor. Subsequent immunohistochemical and transcriptional analyses will further characterize the infiltrating T-cell subpopulations.

Differential response to immunotherapy in urothelial bladder cancer can be based on various factors such as the following:

- T-cell inflamed versus non–T-cell inflamed groups
- Tumor subtype (luminal vs basal) – where luminal 1,2 are less responsive to immunotherapy versus basal subtypes

This umbrella design study that will test the biological rationale for use of targeted and immunotherapy agents for neoadjuvant treatment of cisplatin-ineligible miUBC and potential for subsequent efficacy benefit, as shown with other anti–PD-1 inhibitors and at doses shown to add minimal/acceptable risk from AEs (ie, positive benefit/risk). The translational endpoints will inform which therapies are viable candidates for further investigation in miUBC.

The purpose of this study is to examine various treatments (either monotherapy or combination therapy) given in the neoadjuvant setting before radical cystectomy. Study treatment groups include the following:

- Group A: Epacadostat in combination with retifanlimab
- Group B: Retifanlimab monotherapy
- Group C: Epacadostat monotherapy
- Group D: Retifanlimab plus INCAGN02385
- Group E: Retifanlimab plus INCAGN02385 plus INCAGN02390

2.1.2. Treatment Group Rationale

Treatment Group A (epacadostat in combination with retifanlimab): A dose-finding study combining epacadostat with retifanlimab is being conducted (INCMGA 0012-102) and determined the preliminary RP2D as 600 mg BID. [redacted]

Treatment Group B (retifanlimab monotherapy): Pembrolizumab was approved for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy based on efficacy results observed in KEYNOTE-052 (Balar et al 2017). An ORR of 29% was observed in all participants. However, PD-L1 CPS ≥ 10 had higher ORR versus those with PD-L1 CPS < 10 (47% vs 21%). Based on these results, pembrolizumab was approved in front-line cisplatin-ineligible locally advanced/metastatic urothelial cancer of the bladder in patients with PD-L1 CPS ≥ 10. The rationale for including this arm in the study is to investigate the biological immunological changes when a checkpoint inhibitor is administered to participants. In POD1UM-203, retifanlimab was investigated in advanced solid tumors, including cisplatin-ineligible locally advanced/metastatic urothelial cancer with PD-L1 CPS > 10%. A total of 29 participants demonstrated an ORR of 38% and a disease control rate of 55%. The median duration of response was not reached when the results of the study were reported (Maio et al 2021).

Treatment Group C (epacadostat): Epacadostat monotherapy is well-tolerated at doses ranging up to 700 mg BID in participants with refractory solid tumors (Beatty et al 2017). The rationale for including a monotherapy group is to investigate tumor immunologic biological changes and plasma and tumor kynurenine level changes when it is administered as a monotherapy agent at a dose that optimally inhibits production of the immunosuppressive metabolite, kynurenine, by the alternate tryptophan pathway mediated by the enzyme IDO1.

Treatment Group D (retifanlimab plus INCAGN02385): 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). Further, in murine models, it has been demonstrated that PD-1 and LAG-3 act synergistically to promote tumor immune escape, and simultaneous blockade of LAG-3 and PD-1 results in synergistic inhibition of tumor growth (Woo et al 2012). Combined blockade of these 2 inhibitory receptors markedly improved CD8+ T-cell responses (INCAGN02385 IB, Jin et al 2010).

Treatment Group E (retifanlimab plus INCAGN02385 plus INCAGN02390): Early clinical evidence of the efficacy of these combinations in patients whose disease failed to respond to anti–PD-(L)1 therapy has been evolving. Blockade of the PD-(L)1 axis in combination with blockade of either LAG-3 or TIM-3 has resulted in only modest responses in patients whose disease failed to respond to anti–PD-1 therapy alone (Ascierto et al 2017, Davar et al 2018). Potentially, multiple checkpoint inhibitors are potentially required in order to restore antitumor T-cell effector function in situ. Evidence for this approach was presented by Kauffman et al (2018). Evidence for synergy of anti–PD-1 and anti–TIM-3 was shown in an in vivo murine model of chronic infection resulting in T-cell exhaustion characterized by coexpression of TIM-3 and PD-1. 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 plus LAG-3 or PD-1 plus TIM-3 in a murine model. In addition, the combination of all 3 antibodies resulted

in greater restoration of function to TILs isolated from patients with ovarian cancer. This suggests a requirement for inhibition of all 3 checkpoints in concert is more relevant for returning immune function and tumor growth.

As this is an umbrella study (FDA 2018, CTFG 2019), additional agents may be included in this study (as monotherapy or as combinations) via Protocol amendment based on emerging PK, pharmacodynamic, and/or safety data once the RP2D for the combination has been established by the sponsor.

2.1.3. Retifanlimab

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

In vitro studies with retifanlimab have demonstrated high affinity binding to both recombinant human and cynomolgus monkey PD-1 as well as to PD-1 that is naturally expressed on the cell surface, including on T cells. Consistent with its intended mechanism of action and functional properties, retifanlimab has been shown to inhibit the binding of PD-L1 and PD-L2 to PD-1, to disrupt the PD-1/PD-L1 inhibitory axis, and to enhance IFN-γ secretion in staphylococcal enterotoxin B–stimulated human peripheral blood mononuclear cells with activity comparable to pembrolizumab and nivolumab replicas (generated by MacroGenics, Inc based on the published sequences of these antibodies). Retifanlimab does not induce antibody-dependent cellular cytotoxicity or complement-dependent cytotoxicity, mitogenic activity, hemolysis, or cytokine release.

Retifanlimab is currently being investigated in locally advanced or metastatic bladder cancer in participants who are not eligible for cisplatin therapy and whose tumors express PD-L1 with a CPS ≥ 10 (INCMGA 0012-203 [POD1UM-203]).

2.1.3.1. Rationale for Retifanlimab Dose

Retifanlimab will be administered at 500 mg Q4W. The selection of this dose is based on modeling of clinical PK data from the first-in-human monotherapy study, INCMGA 0012-101, in which 37 participants were treated with doses of 1 mg/kg Q2W, 3 mg/kg Q2W, 3 mg/kg Q4W, 10 mg/kg Q2W, and 10 mg/kg Q4W.

Pharmacokinetic data were obtained from 15 participants who received retifanlimab 500 mg Q4W in Study INCMGA 0012-101. The observed $AUC_{0-\infty}$ for 500 mg Q4W is close to the steady-state AUC_{0-t} based on the population PK analysis of weight-based doses, as is the estimated clearance. The 500 mg Q4W dose has approximately 58% probability to obtain a steady-state trough plasma concentration ≥ 21 µg/mL, which is associated with maximum target engagement and greatest probability of efficacy. Based on these observations, 500 mg Q4W has been chosen as the dose regimen. In addition, retifanlimab 375 mg Q3W was investigated and selected as a RP2D and is utilized in clinical trials. For further details, refer to the retifanlimab IB.

2.1.4. Epacadostat

IDO1 is an enzyme in an alternative tryptophan metabolism pathway that reduces tryptophan levels and generates metabolites (eg, kynurenine and others) that contribute to tumor-derived immune suppression. IDO1-mediated oxidation of tryptophan results in a strong inhibitory effect on the development of T-cell responses by blocking T-cell activation and inducing T-cell apoptosis (Mellor et al 2003). IDO1 activity also promotes the differentiation of naive T cells to cells with a regulatory phenotype (ie, Tregs; Fallarino et al 2006). In preclinical models, IDO1 inhibition has been shown to synergize with blockade of anti–PD-1/PD-L1 in delaying tumor growth and increasing survival (Spranger et al 2014). This effect was shown to be T-cell–dependent, lead to enhanced T-cell proliferation and IL-2 production within the tumor, and produce a marked increase in the effector-to-regulatory T-cell ratios in the tumors, suggesting that the results are the consequence of disabling immunosuppressive mechanisms that exist within the tumor microenvironment. Based on this rationale, combinations of epacadostat with a PD-1 or PD-L1 inhibitor are being extensively studied across multiple tumor types (epacadostat IB, Fallarino et al 2006, Mellor et al 2003, Spranger et al 2014).

2.1.4.1. Rationale for Epacadostat Dose

Epacadostat monotherapy is well-tolerated at doses of up to 700 mg BID in participants with refractory solid tumors (Beatty et al 2017). Pharmacodynamic inhibition of plasma IDO1 was observed at doses of 100 mg BID or greater, although clinical responses were not observed. Specifically, a monotherapy dose of epacadostat 100 mg BID achieved an exposure that exceeded the IC_{50} at steady state, which resulted in optimum efficacy in nonclinical models. However, intratumoral pharmacodynamics (eg, changes in the kynurenine/tryptophan ratio) were not assessed. Given the results of the Phase 3 randomized study (ECHO-301/KEYNOTE-252), higher doses of epacadostat were investigated in Study POD1UM-102 (see Section 2.1.5 and refer to the epacadostat IB) to maintain a steady-state concentration that exceeds the IC_{90} at all times in tumor tissue and in the setting of PD-(L)1 combination therapy, which has been shown to induce IDO1.

2.1.5. Combination of Epacadostat Plus Retifanlimab

The combination of retifanlimab and epacadostat has been assessed in a dose-finding study (INCMGA 0012-102, NCT03589651). As of 13 DEC 2021, 100 participants had been treated with the combination of retifanlimab 500 mg Q4W and epacadostat at doses of 100, 400, 600, and 900 mg BID. Epacadostat 900 mg BID exceeded the MTD based on the development of Grade 3 rash in 2 of 3 participants, with the third participant developing rash after the Protocol-defined DLT window.

Paired biopsies were collected to measure tumor T-cell infiltration by IHC and intratumoral kynurenine by quantitative mass spectrometry imaging. Increases in total T cells, CD8 T cells, and Treg infiltration were observed in the on-treatment biopsies in the majority of the 10 samples tested. Results of the quantitative mass spectrometry imaging analysis showed that intratumoral kynurenine levels decreased in 4 of 5 paired samples analyzed. In addition, epacadostat 600 mg BID resulted in durable normalization of plasma kynurenine levels (epacadostat IB, Smith et al 2020).

Based on these observations, 600 mg BID was chosen as the RP2D for epacadostat in combination with retifanlimab and is the dose regimen being used in this study. It is also the monotherapy dose that is being investigated in this study. Refer to the epacadostat IB for further information.

In Study INCMGA 0012-102, the frequency of proliferating T cells in the circulation and the concentration of CXCL9 and CXCL10 was monitored. Participants presented an early increase on treatment in the frequency of proliferating and activated T cells. These changes were consistent with the changes observed in the monotherapy study. Refer to the epacadostat IB for further information.

2.1.6. INCAGN02385

INCAGN02385 is an Fc-modified $IgG_1\kappa$ monoclonal antibody that binds to human LAG-3 with an estimated affinity of 1.7 nM and was chosen for clinical development based on its selectivity for human LAG-3, with no cross-reactivity to related Ig superfamily proteins. INCAGN02385 functions as a potent LAG-3 antagonist antibody via its ability to inhibit LAG-3 binding to major histocompatibility complex class II, leading to enhanced T-cell receptor signaling. Additional information regarding preclinical and in vitro experience with INCAGN02385 can be found in the INCAGN02385 IB.

2.1.6.1. Rationale for INCAGN02385 Dose

As of 21 MAR 2021, a total of 22 unique participants had been enrolled and received at least 1 dose of INCAGN02385 at doses of 25, 75, 250, 350, and 750 mg Q2W IV in an open-label, nonrandomized, dose-escalation, and cohort-expansion study (NCT03538028). All doses were well-tolerated; no DLTs were observed, and there were no treatment-related deaths. INCAGN02385 PK was independent of dose after the first dose and showed moderate to high interindividual variability. At a dose of 350 mg Q2W (N = 3), the steady-state AUC was 30,200 µg/mL·h. The dose of 350 mg Q2W was chosen for INCAGN02385 based on the results that the receptor on the surface of the cells was fully occupied at trough concentration and that the pharmacodynamic marker supported this dose to be pharmacologically active as measured by an increase in peripheral T-cell activation observed at doses > 250 mg. Refer to the INCAGN02385 IB for further information.

2.1.7. INCAGN02390

INCAGN02390 is a recombinant, aglycosylated, fully human IgG1κ monoclonal antibody that binds to the extracellular domain of the TIM-3 receptor. Antagonist TIM-3 antibodies have demonstrated enhanced antitumor activity in several mouse tumor models when combined with blockade of the PD-1/PD-L1 pathway (Ngiow et al 2011, Sakuishi et al 2010). Additional information regarding preclinical and in vitro experience with INCAGN02390 can be found in the INCAGN02390 IB.

2.1.7.1. Rationale for INCAGN02390 Dose

As of 28 JUN 2021, a total of 40 unique participants had been enrolled and received at least 1 dose of INCAGN02390 at doses of 10, 30, 100, 200, 400, 800, and 1600 mg IV Q2W in the open-label, nonrandomized, dose-escalation, and cohort expansion study (NCT03652077)

evaluating INCAGN02390 monotherapy. All doses were well-tolerated, no DLTs were observed, and there were no treatment-related deaths. INCAGN02390 showed supraproportional PK after first dose from 30 mg to 800 mg Q2W and low interindividual variability on PK exposures. At a dose of 400 mg Q2W, the mean steady-state AUC determined in 4 participants was 43,400 µg/mL·h. The dose of 400 mg was chosen for INCAGN02390 based on the results that the TIM-3 receptor was fully occupied on the surface of circulating monocytes. Refer to the INCAGN02390 IB for further information.

2.1.8. Combination of Retifanlimab Plus INCAGN02385

It has been demonstrated in murine models that PD-1 and LAG-3 act synergistically to promote tumor immune escape, and simultaneous blockade of LAG-3 and PD-1 results in synergistic inhibition of tumor growth (Woo et al 2012). Evidence for synergy of anti–PD-1 and anti–TIM-3 was shown in an in vivo murine model of chronic infection resulting in 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).

RELATIVITY-047, a Phase 3 study in patients with previously untreated unresectable or metastatic melanoma, demonstrated an improvement in PFS when nivolumab was combined with relatlimab (10.1 vs 4.63 months; Lipson et al 2021). Additional clinical activity was demonstrated with the combination of pembrolizumab and eftilagimod in patients with PD-L1 unselected metastatic second-line treatment for head and neck squamous cell carcinoma (ORR: 31.4%; Peguero et al 2019). As such, this study investigates the combination of retifanlimab and INCAGN02385 in cisplatin-ineligible urothelial carcinoma.

2.1.9. Combination of Retifanlimab Plus INCAGN02385 Plus INCAGN02390

Early clinical evidence of the efficacy of retifanlimab plus INCAGN02385 plus INCAGN02390 in patients with disease that has failed to respond to anti–PD-(L)1 therapy has been evolving. Blockade of the PD-(L)1 axis in combination with blockade of either LAG-3 or TIM-3 has resulted in only modest responses in patients with disease that has failed to respond to anti–PD-1 therapy alone (Ascierto et al 2017, Davar et al 2018). Potentially, multiple checkpoint inhibitors may be required in order to restore antitumor T-cell effector function in situ (Kaufmann et al 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 plus LAG-3 or PD-1 plus TIM-3 in a murine model. In addition, the combination of all 3 antibodies resulted in greater restoration of function to TILs isolated from patients with ovarian cancer. This suggests a requirement for inhibition of all 3 checkpoints in concert is more relevant for returning immune function and tumor growth inhibition

2.1.10. Combination of Retifanlimab Plus INCAGN02385 and Combination of Retifanlimab Plus INCAGN02385 Plus INCAGN02390

INCAGN 2385-201 in an ongoing Phase 1/2 study evaluating the safety and preliminary efficacy of combinations of the Phase 1 doses of INCAGN02385 and INCAGN02390 together with retifanlimab 500 mg Q4W. As of 28 JUN 2021, a total of 21 unique participants had been enrolled and received at least 1 dose of INCAGN02385 at a dose of 350 mg Q2W IV in combination with INCAGN02390 400 mg Q2W (N= 10) or INCAGN02390 400 mg Q2W plus

retifanlimab 500 mg Q4W (N = 11) in this open-label, nonrandomized, safety evaluation and cohort expansion study. During Phase 1 of INCAGN 2385-201, no DLTs were observed; 19 participants had at least 1 TEAE. Based on the results from the monotherapy trials as well as the INCAGN 2385-201 study, the dose for Treatment Group D will be retifanlimab 500 mg Q4W IV in combination with INCAGN02385 350 mg Q2W IV. For Treatment Group E, the dose will be retifanlimab 500 mg Q4W IV in combination with INCAGN02385 350 mg Q2W IV and INCAGN02390 400 mg Q2W IV.

2.2. Benefit/Risk Assessment

2.2.1. Monotherapy Risks

2.2.1.1. Retifanlimab

PD-1 inhibitors have proven efficacy against a wide variety of cancer types, including neoadjuvant treatment of muscle invasive bladder cancer (Necchi et al 2018). The available preclinical and clinical data strongly suggest that the pharmacology and clinical activity of retifanlimab are similar to experience with other drugs of this class (Chen et al 2019, Condamine et al 2019, Lakhani et al 2017, Mehnert et al 2018). Thus, it is logical to study retifanlimab in this disease as monotherapy and in combinations in which PD-1 inhibitors are the backbone therapy.

As of the data cutoff date of 23 SEP 2021, 660 unique participants have been exposed to retifanlimab as monotherapy. Results from the dose-escalation and dose-expansion portion of the retifanlimab monotherapy study (POD1UM-101) 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. Refer to the retifanlimab IB for further information.

2.2.1.2. Epacadostat

A total of 216 participants have been treated with epacadostat monotherapy, including healthy participants (INCB 24360-102, INCB 24360-103, INCB 24360-104, INCB 24360-105, INCB 24360-106, and INCB 24360-107) and participants with advanced malignancies (INCB 24360-101 and INCB 24360-210). In the Phase 1 clinical study in participants with refractory solid tumors (INCB 24360-101), doses up to 700 mg BID were given without an MTD determined.

2.2.2. Combination Therapy Risks

2.2.2.1. Epacadostat and Retifanlimab

Retifanlimab and epacadostat are immunomodulatory agents; therefore, irAEs may be associated with their coadministration. Experience with other immuno-oncology agents that target endogenous immunosuppressive mechanisms has demonstrated that irAEs can affect any organ or tissue but most frequently occur in the skin (rash), gastrointestinal system (diarrhea/colitis), liver (hepatitis), lungs (pneumonitis), endocrine system (endocrinopathies due to inflammation of the pituitary, thyroid and adrenal glands), and kidneys (nephritis). Management of irAEs should follow the general approach that has been used for other immuno-oncology agents. See Section 6.5.3 for the irAE dose modification and monitoring guidance.

There is a rare chance that epacadostat, when administered alone or in combination with other serotonergic agents, could cause an increase in serotonin levels in the brain that might trigger serotonin syndrome (Boyer and Shannon 2005). This syndrome has been most closely associated with use of MAOIs, meperidine, linezolid, or methylene blue. Selective serotonin reuptake inhibitors, SNRIs, and MAOIs are permitted in the study. Serotonin syndrome usually manifests with autonomic changes, mental status changes, and neurological findings. Procedures for participants in the epacadostat groups exhibiting serotonin syndrome are presented in Section 6.5.5.

Treatment-emergent AEs reported in > 10% of participants included fatigue, nausea, decreased appetite, abdominal pain, pruritus, maculopapular rash, anemia, rash, dyspnea, constipation, pyrexia, and diarrhea. Serious TEAEs occurred in 39 participants (39%). The most frequently reported serious TEAEs were dyspnea (6%), maculopapular rash (5%), and pleural effusion (3%). Treatment-emergent AEs led to discontinuation of epacadostat for 16 participants (16.0%). The most frequently reported TEAE leading to discontinuation of epacadostat was maculopapular rash (7.0%). The MTD of epacadostat in combination with retifanlimab 500 mg was determined to be 600 mg BID. Epacadostat 900 mg BID exceeded the MTD based on the occurrence of Grade 3 maculopapular rash in 2 of 3 participants during the DLT evaluation period. Overall, the following DLTs were reported:

- 400 mg BID: 1 DLT of Grade 3 maculopapular rash
- 600 mg BID: 1 DLT of Grade 3 maculopapular rash, 1 DLT of Grade 3 acneiform dermatitis, and 1 DLT of Grade 3 abdominal pain
- 900 mg BID: 2 DLTs of Grade 3 maculopapular rash

Five participants (5.0%) had fatal TEAEs: acute respiratory distress syndrome and COVID-19 pneumonia (1 participant) and ascites, cardiovascular disorder, respiratory failure, and thrombocytopenia (1 participant each). None of the fatal TEAEs were considered related to epacadostat. For further information, refer to the epacadostat IB.

2.2.2.2. Retifanlimab, INCAGN02385, and INCAGN02390

For the combination of INCAGN02385 and INCAGN02390, 5 participants had serious TEAEs (asthenia, pancreatitis, dyspnea and hypoxia and rectal hemorrhage, vulval hemorrhage, pyrexia, vasculitis, COVID-19, and sepsis). Of these TEAEs, only 1 (vasculitis) was considered related to both study drugs by the investigator. One participant had a fatal TEAE (sepsis), which was considered not related to INCAGN02385 or INCAGN02390 by the investigator.

For the combination of retifanlimab, INCAGN02385, and INCAGN02390, 2 participants experienced TEAEs (1 participant had acute respiratory failure, and another had pericardial effusion and myocarditis). The pericardial effusion (Grade 2) and myocarditis (Grades 2 and 3) were considered related to INCAGN02385, INCAGN02390, and retifanlimab by the investigator and resolved following interruption of study drugs. This participant discontinued from the study due to progressive disease.

2.2.3. Risks of Delayed Cystectomy

Overall survival has been associated with the pathological tumor stage of radical cystectomy. The 5-year OS estimates range from 81% to 93% for patients with pT0 disease but decrease to

46% to 48% in patients with PT3 disease (Hautmann et al 2012). The impact of the time to definitive treatment with radical cystectomy after completion of neoadjuvant therapy is not well-studied, with various results mainly from single-institution experiences. In an analysis by Park et al (2016), the timing of radical cystectomy had no impact on OS, whereas Alva et al (2012) demonstrated that delays of up to 5 months between the end of neoadjuvant chemotherapy and radical cystectomy served as potential thresholds that conferred worse outcomes after radical cystectomy. Gore et al (2009) established from a Surveillance, Epidemiology, and End Results Medicare Program analysis that there is an increase in mortality when radical cystectomy is delayed for more than 12 weeks from time to diagnosis to radical cystectomy in patients who had not received neoadjuvant therapy. A recent analysis by Chu et al (2019) with more than 1500 participants demonstrated that compared with timely surgery, delays in radical cystectomy longer than 11 weeks after the completion of neoadjuvant chemotherapy significantly compromised patient survival. It should be noted that delays in radical cystectomy were not necessarily due to AEs from neoadjuvant chemotherapy. In fact, in the study by Chu et al (2019), 13% of participants who did not have neoadjuvant chemotherapy versus 22% of those who received neoadjuvant therapy experienced delays in radical cystectomy > 12 weeks, defined as more than 12 weeks for patients proceeding directly to radical cystectomy if no neoadjuvant therapy was provided or 11 weeks after the completion of treatment for those treated with neoadjuvant therapy.

2.2.3.1. Treatment-Emergent Adverse Events of Special Interest

Based on the review of outcomes in patients who had delays in radical cystectomy > 12 weeks, it is imperative that there are minimal treatment delays > 11 weeks after completion of neoadjuvant therapy to radical cystectomy in this study. To better understand the rates of AEs in the first 12 weeks of treatment with the agents (3 cycles of treatment) to be administered in this study as well as the time to resolution for these AEs, an analysis was conducted on drug-related TEAOSI. The TEAOSI were chosen based on the likelihood that they may delay surgery. Since this study uses investigational agents, the rate of resolution of these TEAOSI within 12 weeks from start of treatment was also calculated. This conservative timeframe was chosen as opposed to 11 weeks after neoadjuvant therapy to simulate the potential risk for patients not receiving any neoadjuvant therapy.

An analysis was conducted after 12 weeks from start of treatment on select studies that include retifanlimab or epacadostat to further characterize their safety profiles, as detailed in the SAP (see Appendix E). Table 8 and Table 9 provide summaries from the data on file in the SAP. The TEAOSI were selected based on the likelihood they may cause potential delay in surgery. As such, TEAOSI was defined as any of the following:

- Select Grade 3 or higher AEs
  - Cardiac disorders; ear and labyrinth disorders; endocrine disorders; gastrointestinal disorders; hepatobiliary disorders; infections/infestations; injury/bleeds; hemorrhages; metabolism and nutrition disorders; musculoskeletal and connective tissue disorders; benign/malignant neoplasms; nervous system disorders; psychiatric disorders; renal/urinary disorders; reproductive system and breast disorders; respiratory, thoracic, and mediastinal disorders; skin and subcutaneous tissue disorders; and vascular disorders

- Adverse events leading to hospitalization
- Fatal AEs
- Grade 2 or higher irAEs

2.2.3.1.1. Retifanlimab and Epacadostat

The studies that were selected had completed data at the time of analysis. They included participants who had recurrent disease of various metastatic solid tumors. Studies included monotherapy treatments with retifanlimab and epacadostat. For combination regimens, the dose-finding study with epacadostat in combination with retifanlimab in solid tumors as well as epacadostat in combination with pembrolizumab were included (see Appendix E). Of note, 2 trials of epacadostat in combination with pembrolizumab in recurrent urothelial cancer were included, but these had halted accrual early due to the lack of benefit observed in the completed ECHO-301 trial in recurrent melanoma (Long et al 2019).

Table 8: Summary of TEAOSI for Select Studies With Retifanlimab and Epacadostat That Occurred Within the First 12 Weeks of Treatment

	Retifanlimab (N = 647)	Epacadostat (N = 159)
Number (%) of participants with select Grade 3 or higher AEs related to study drug	8 (1.2)	4 (2.5)
Probability (95% CI) of unresolved Grade 3 or higher AEs related to study drug at week 12 (all participants)	0.01 (0.00, 0.01)	0.02 (0.01, 0.05)
Median (95% CI) time (in weeks) from start of treatment to resolution of Grade 3 or higher AEs related to study drug (among participants with Grade 3 or higher AEs, n = 8 for retifanlimab, n = 4 for epacadostat)	9.0 (4.0, NE)	14.1 (9.9, NE)
Number of participants with at least 1 AE related to study drug leading to hospitalization (%)	20 (3.1)	4 (2.5)
Probability (95% CI) of unresolved AEs related to study drug that led to hospitalization (all participants)	0.01 (0.00, 0.02)	0.02 (0.01, 0.05)
Median (95% CI) time (in weeks) to resolution of AEs related to study drug that led to hospitalization (among participants with AEs leading to hospitalization)	7.7 (4.4, 10.3)	13.7 (9.9, 42.4)
Number (%) of fatal AEs related to study drug	2 (0.3)[a]	0 (0)
Number (%) of Grade 2 or higher irAEs	41 (6.3)	17 (10.7)
Probability (95% CI) of unresolved Grade 2 or higher irAEs (all participants)	0.03 (0.02, 0.05)	0.08 (0.05, 0.13)
Median (95% CI) time (in weeks) to resolution of Grade 2 or higher irAEs (among participants with Grade 2 or higher irAEs)	12.3 (9.0, 18.7)	NE (9.9, NE)

NE = not estimable.
Note: Kaplan-Meier estimates based on time from start of treatment.
[a] For retifanlimab, fatal outcomes were due to progression of disease.

The overall rates of Grade 3/4 SAEs related to study drug are favorable when compared with cisplatin-based chemotherapy, in particular, in the Phase 3 SWOG 1817 trial in neoadjuvant miUBC, in which at least one-third of participants had severe hematologic or gastrointestinal effects (Grossman et al 2003). The rates of such SAEs were not observed in Incyte-sponsored trials. In addition, the participant population for our trials is those with recurrent metastatic solid tumors who have undergone multiple lines of treatment and are more likely to experience higher rates of hospitalization or fatal outcomes predominantly due to progression of disease.

Among participants with Grade 2 or higher irAEs, the median time to resolution of these AEs is > 12 weeks. However, not all of these irAEs would result in delay in surgery. In particular, Grade 2 immune-related TEAEs that were not resolved in 12 weeks did not typically delay surgery. Taking this into account, only 10 of 647 participants (1.5%) treated with retifanlimab and 9 of 159 participants (5.7%) treated with epacadostat experienced a Grade 3 to 5 immune-related TEAE that was unresolved in 12 weeks and potentially delayed surgery. It should be noted that the epacadostat-containing regimen was in combination with other immune checkpoint inhibitors (pembrolizumab and nivolumab). However, 8 of these 9 participants (88.9%) received epacadostat in combination with pembrolizumab and only 1 participant received epacadostat monotherapy.

Table 9: Grade 2 or Higher Immune-Related TEAEs for Studies With Retifanlimab and Epacadostat (Multiple Tumor Types)

	Resolved at Week 12 From Start of Treatment N (%)	Unresolved[a] at Week 12 From Start of Treatment N (%)	Death at Week 12 N (%)	Total N (%)
Retifanlimab (N = 647)				
Participants with any Grade 2 or higher immune-related TEAEs	18 (43.9)	21 (51.2)	2 (4.9)	41 (6.3)
Participants with Grade 2 immune-related TEAEs	7 (33.3)	14 66.7)	0 (0.0)	21 (3.2)
Participants with Grade 3/4 immune-related TEAEs	14 (63.6)	8 (36.4)	0 (0.0)	22 (3.4)
Participants with Grade 5 (fatal) immune-related TEAEs	0 (0.0)	0 (0.0)	2 (100.0)	2 (0.3)
Epacadostat (N = 159)				
Participants with any Grade 2 or higher immune-related TEAEs	4 (23.5)	13 (76.5)	0 (0.0)	17 (10.7)
Participants with Grade 2 immune-related TEAEs	2 (20.0)	8 (80.0)	0 (0.0)	10 (6.3)
Participants with Grade 3/4 immune-related TEAEs	3 (25.0)	9 (75.0)	0 (0.0)	12 (7.5)
Participants with Grade 5 (fatal) immune-related TEAEs	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Note: Participants who had Grade 2 as well as Grade 3 or higher immune-related TEAEs are reported.
[a] Includes participants with immune-related TEAEs that started before Week 12 and resolved/recovered after Week 12.

The rates of treatment-related grade 3/4 SAEs as well as SAEs that require hospitalization were considerably low (1.2% and 2.5% for retifanlimab and epacadostat, respectively), and a population-level median time to resolution is not estimable. The estimated probabilities (95% CI) of unresolved treatment-related grade 3/4 SAEs and SAEs that required hospitalizations in a treated population were 0.01 (0.00, 0.01) and 0.01 (0.00, 0.02) for retifanlimab and 0.02 (0.01, 0.05) and 0.02 (0.01, 0.05) for epacadostat, respectively.

Also, in the PURE-01 study investigating pembrolizumab as neoadjuvant treatment in miUBC, there were a few irAEs that subsequently did not delay planned surgery (Necchi et al 2018).

2.2.3.1.2. INCAGN02385 and INCAGN02390 Monotherapy and in Combination With Retifanlimab

Three dose-finding studies were conducted investigating the safety and tolerability of INCAGN02385 monotherapy (INCAGN 2385-101, NCT 03538028; N = 22), INCAGN02390 monotherapy (INCAGN 2390-101, NCT03652077; N = 40), and doublet therapy with INCAGN02385/INCAGN02390 (N = 10) and triplet therapy with retifanlimab/INCAGN02385 and INCAGN02390 (N = 11; –INCAGN 2385-201, NCT04370704). In total, 83 participants were enrolled between the 3 studies (see Appendix E). In the INCAGN02385 monotherapy study, 8 participants had serious TEAEs, none of which were considered related to INCAGN02385 by the investigator. In the INCAGN02390 monotherapy study, the only drug-related TEAOSI observed within the first 12 weeks of treatment was Grade 2 or higher irAE in 2 participants (1 case of diarrhea that resolved in 9 days and 1 case of lymphopenia). Also, no participants experienced a Grade 3 or higher TEAOSI in the INCAGN02385 monotherapy study. One participant in the INCAGN02385 plus INCAGN02390 plus retifanlimab arm experienced a Grade 3 pericardial effusion and myocarditis that were related to treatment per the investigator and resolved following interruption of study drugs. This participant discontinued from the study due to progressive disease (see Table 10).

Table 10: Grade 2 or Higher Immune-Related TEAEs for Studies With INCAGN02385, INCAGN02390, and Retifanlimab

	INCAGN02385 Monotherapy (N = 22)	INCAGN02390 Monotherapy (N = 40)	INCAGN02385 Plus INCAGN02390 (N = 10)	INAGN02385 Plus INCAGN02390 Plus Retifanlimab (N = 11)
Participants with any Grade 2 or higher immune-related TEAEs	0	2	0	1
Participants with Grade 2 immune-related TEAEs	0	2	0	0
Participants with Grade 3/4 immune-related TEAEs	0	0	0	1
Participants with Grade 5 (fatal) immune-related TEAEs	0	0	0	0

In conclusion, the lower rates of Grade 3/4 SAEs of interest compared to those with cisplatin-based treatments, the reasonable time to resolution of both overall SAEs and those leading to hospitalization, as well as the lower overall Grade 3/4 immune-related TEAEs that were not resolved in 12 weeks from start of treatment, which is typically the timeframe observed for patients not on neoadjuvant chemotherapy as opposed to the more generous timeframe of 11 weeks after the last dose of neoadjuvant therapy, all provide a favorable safety profile for these agents that would warrant further investigation of their utility in the neoadjuvant setting for miUBC.

2.2.4. Benefits

Greater immunomodulatory effects in the tumor microenvironment could potentially enhance the clinical benefit in participants with miUBC. By providing broader inhibition of the immunosuppressive environment driven by myeloid-deprived suppressor cells, Tregs, and other immune cells and factors, it is hypothesized that this additional benefit may not come at the cost of additional toxicity or that additional immune toxicities (by incidence or severity) will be manageable by drug interruption and temporary use of immunosuppressive therapies (eg, corticosteroids).

More detailed information about the known and expected benefits and risks and reasonably expected AEs of each compound may be found in the respective Investigator's Brochures (epacadostat IB, INCAGN02385 IB, INCAGN02390 IB, and retifanlimab IB).

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

Participants to be enrolled into this study have advanced or metastatic malignancies 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 malignancies are limited and no effective therapies or standards of care exist. 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).

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. Potential participants with known or suspected active COVID-19 infection are ineligible as per Exclusion Criterion 14. It is at the principal investigator's discretion to balance the risk/benefit while considering the participant's safety, existing comorbidities, and current malignancy.

Participants who are diagnosed with COVID-19 during the study 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 and strategy for participant management during the dynamic pandemic as applicable is described in Appendix G.

3. OBJECTIVES AND ENDPOINTS

Table 11 presents the objectives and endpoints.

Table 11: Objectives and Endpoints

Objectives	Endpoints
Primary	
To determine biologic response in participants with muscle-invasive cisplatin-ineligible or those refusing cisplatin therapy, urothelial carcinoma of the bladder.	For each treatment group, the primary endpoint is the change from baseline in CD8+ lymphocytes within resected tumor.
Secondary	
To evaluate the safety and tolerability of each of the treatment groups.	• Safety and tolerability assessed by monitoring the frequency and severity of AEs, including delay in cystectomy due to AEs.
To evaluate the preliminary efficacy of each of the treatment groups.	• pCR rate, defined as percentage of participants with ypT0N0 in each treatment group. • Major pathological response, defined as residual ypT0/1/a/isN0M0.
[redacted]	

Table 11: Objectives and Endpoints (Continued)

Objectives	Endpoints
[redacted]	

4. STUDY DESIGN

4.1. Overall Design

This is an open-label, randomized, Phase 2 umbrella study of various neoadjuvant therapies for miUBC (ie, Galsky et al 2011) undergoing radical cystectomy.

This study will test the biological rationale for use of targeted and immuno-oncology agents for neoadjuvant treatment of cisplatin-ineligible or participants refusing cisplatin therapy miUBC and potential for subsequent efficacy benefit, as shown with other anti–PD-1 inhibitors and at doses shown to add minimal/acceptable risk from side effects (ie, positive benefit/risk). The translational endpoints will inform which therapies are viable candidates for further investigation in miUBC. This study is an umbrella design where future treatment arms may be added or removed at the discretion of the sponsor.

Participants will be randomized into 1 of the following treatment groups:

- Treatment Group A: epacadostat in combination with retifanlimab
- Treatment Group B: retifanlimab monotherapy
- Treatment Group C: epacadostat (IDO1 inhibitor) monotherapy
- Treatment Group D: retifanlimab plus INCAGN02385
- Treatment Group E: retifanlimab plus INCAGN02385 plus INCAGN02390

Tumor tissue will be tested centrally to determine PD-L1 CPS score.

Participants will be randomized into treatment groups according to the schema in Figure 1. Participants with PD-L1 CPS < 10 or PD-L1 CPS ≥ 10 will be randomized at a 2:2:1:2:2 ratio into Groups A, B, C, D and E, respectively. Participants who passed screening for PD-L1 CPS < 10 will not be randomized into a group once that group has reached the allowed number

of participants with PD-L1 CPS < 10. Similarly, participants with PD-L1 CPS ≥ 10 will be randomized into a group once that group has reached the allowed number of participants with PD-L1 CPS ≥ 10. This will ensure that the desired proportion of participants who have PD-L1 CPS < 10 and PD-L1 CPS ≥ 10 within each group will be enrolled.

For Treatment Group C, the subgroup of participants with PD-L1 CPS < 10 or PD-L1 CPS ≥ 10 that reaches 5 participants will hold enrolling participants to that particular subgroup and will continue to enroll until 4 participants in the other subgroup are enrolled.

After signing the ICF, screening assessments may be completed over a period of up to 28 days. Treatment cycles are 28 days unless otherwise noted. Each participant enrolled in the study will receive a minimum of 1 treatment cycle if, in the judgment of the investigator, the participant has not met any criteria for study withdrawal. The treatment duration will be approximately 4 to 10 weeks. The radical cystectomy is typically scheduled 8 to 10 weeks with an average of 8 weeks from the TURBT (ie, approximately Day 56; Poletajew et al 2014).

Precystectomy assessments will be performed within 2 weeks before surgery. Participants are followed for safety as well as radiographic imaging for 90 days after cystectomy or the last dose of study treatment in the event cystectomy is not performed.

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 scheduled procedure shown in the SoA of the last participant in the study globally.

A participant is considered to have completed the study if he/she has completed all parts of the study including the last scheduled procedure shown in the SoA.

The estimated duration of study participation is approximately 6 months from start of study treatment.

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 DSMB. 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 DSMB will recommend termination of the study if warranted, as described in Section 5.6.

5. STUDY POPULATION

Deviations from eligibility criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability, and/or participant safety. Therefore, adherence to the criteria as specified in the Protocol is essential. Prospective approval of Protocol deviations to recruitment and enrollment criteria, also known as Protocol waivers or exemptions, are not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1. Ability to comprehend and willingness to sign a written ICF for the study.
2. Men or women aged 18 years or older.
3. Histologically confirmed transitional cell urothelial carcinoma. Participants with mixed histologies are required to have a dominant (ie, 50% at least) transitional cell pattern.
4. Clinical stage T2-T3b, N0, M0 muscle invasive urothelial carcinoma by CT (or MRI) (Stage II-IIIA per AJCC 2018).
    a. Concomitant upper tract tumors should be excluded. However, previous history of surgery for upper tract tumors may be allowed, provided that it was a noninvasive pT (ie, pT < 2N0M0 stage).
5. Refuse cisplatin therapy (does not apply in France) or are ineligible for cisplatin therapy per modified Galsky criteria with exclusion of ECOG PS 2 participants (see Appendix C).
    a. Participants with CTCAE v4 ≥ Grade 2 audiometric hearing loss (Galsky Criteria).
    b. Participants with CTCAE v4 ≥ Grade 2 peripheral neuropathy (Galsky Criteria).
    c. Creatinine clearance of < 60 mL/min but ≥ 30 mL/min (measured by the Cockcroft-Gault formula or 24-hour urine).
    d. New York Heart Association Class III heart failure.
6. Eligible for radical cystectomy by the following:
    a. Fit and planned for radical cystectomy according to local guidelines.
    b. Able to receive a minimum of 4 weeks of neoadjuvant treatment on study before date of scheduled radical cystectomy.
    c. Willing and able to delay surgery by a maximum of 12 weeks, if necessary.
7. Removed during Protocol Amendment 4.
8. ECOG PS 0 or 1.
9. Pretreatment tumor biopsy must be a tumor block or 20 unstained slides from biopsy of primary tumor containing at least 20% tumor.

10. Willingness to avoid pregnancy or fathering children based on the criteria below.
    a. Male participants with childbearing potential must agree to take appropriate precautions to avoid fathering children (with at least 99% certainty) from screening through 100 days in the US and 190 days in Europe after the last dose of study drug and must refrain from donating sperm during this period. Permitted methods that are at least 99% effective in preventing pregnancy (see Appendix A) should be communicated to the participants and their understanding confirmed.
    b. Women participants with childbearing potential must have a negative serum and/or pregnancy test at screening and before the first dose of study drug on Day 1 and must agree to take appropriate precautions to avoid pregnancy (with at least 99% certainty) and from donating oocytes from screening through 100 days in the US and 190 days in Europe after the last dose of study drug. Permitted methods that are at least 99% effective in preventing pregnancy (see Appendix A) should be communicated to the participants and their understanding confirmed.
    c. Women participants without childbearing potential (ie, surgically sterile with a hysterectomy and/or bilateral oophorectomy OR ≥ 12 months of amenorrhea).
    d. Women participants without childbearing potential should refrain from donating oocytes from screening through 190 days after the last dose of study drug.

5.2. Exclusion Criteria

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

1. Participation in any other study in which receipt of an investigational study drug or device occurred within 28 days or 5 half-lives (whichever is longer) before first dose. For investigational agents with long half-lives (eg, 5 days), enrollment before the fifth half-life requires medical monitor approval.
2. Previously received systemic therapy for bladder cancer or received prior treatment with checkpoint inhibitor agents (such as anti–PD-1, anti–PD-L1, anti–PD-L2, or anti–CTLA-4).
3. Evidence of measurable nodal or metastatic disease.
4. Concurrent anticancer therapy (eg, chemotherapy, radiation therapy, surgery, immunotherapy, biologic therapy, hormonal therapy, investigational therapy, intravesical therapy or tumor embolization).
5. Has had major surgery within 4 weeks before enrollment (C1D1).
6. Has had known additional malignancy other than miUBC 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, prostate intraepithelial neoplasm, carcinoma in situ of the cervix, or other noninvasive or indolent malignancy, or cancers from which the participant has been disease-free for > 1 year, after treatment with curative intent.

7. Has active autoimmune disease requiring systemic immunosuppression with corticosteroids (> 10 mg daily doses of prednisone or equivalent) or immunosuppressive drugs within 2 years of Day 1 of study treatment.
8. Participants with laboratory values at screening defined in Table 12.

Table 12: Exclusionary Laboratory Values

Laboratory Parameter		Exclusion Criterion
Hematology		
a	Platelets	$< 100 \times 10^9$/L
b	Hemoglobin	< 8 g/dL
c	ANC	$< 1.5 \times 10^9$/L
Hepatic		
d	ALT	≥ 2 × ULN
e	AST	≥ 2 × ULN
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.
Renal		
g	CrCl	< 30 mL/min calculated by Cockcroft-Gault equation (glomerular filtration rate can also be used in place of CrCl)
Coagulation		
h	INR or PT	> 1.5 × ULN unless on therapeutic anticoagulants
i	aPTT	> 1.5 × ULN
Cardiac		
j	Treatment Groups D and E only: troponin I or troponin T	> 2 × institutional ULN Participants with troponin I or troponin T levels between > 1 and 2 × ULN will be permitted if repeat levels within 24 hours are ≤ 1 × ULN.[a]

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

9. Active autoimmune disease requiring systemic immunosuppression in excess of physiologic maintenance doses of corticosteroids (> 10 mg/day of prednisone or equivalent).

   Notes:

   - Physiologic corticosteroid replacement therapy at doses > 10 mg daily doses of prednisone or equivalent for adrenal or pituitary insufficiency and in the absence of active autoimmune disease is permitted.
   - Participants with a condition that require 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, 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 are permitted.

10. Has known active hepatitis B or C (defined as follows) or HIV, HBV, HCV, or hepatitis D virus coinfection:

    a. Active hepatitis B infection is defined by positive HBsAg and positive total anti-HBc results. The following exceptions are allowed:

       - Participants with results positive for HBsAg and total anti-HBc and negative for IgM anti-HBc with a sustained viral response that is HBV DNA level $\leq$ 1000 IU/mL for at least 12 months after the end of antiviral therapy with no pre-existing cirrhosis are eligible for this study. The following conditions should be followed:
         - Initiate a prophylactic antiviral therapy and remain on it for the study duration and for 6 months after the last dose of study treatment.
         - Assess the potential risk of drug-drug interaction with the prescribed antiviral therapy and assigned study drug.
         - Monitor every 2 cycles by performing HBV viral load and HBsAg serology test. The need for additional serology tests (eg, total anti-HBc, IgM anti-HBc, anti-HBs) is per the investigator's discretion.
         - Consider increasing monitoring of LFTs (ie, at least every other week) for the first 3 months of antiviral therapy to allow proactive management of potential hepatitis flare risk on antiviral therapy.
       - Participants with results positive for HBsAg and total anti-HBc and negative for IgM anti-HBc who are receiving antiviral therapy at study entry but show undetectable HBV DNA ($\leq$10 IU/mL under the limit of detection per laboratory) are eligible for the study. The following conditions should be followed:
         - Monitor every 2 cycles by performing HBV viral load and HBsAg serology test. The need for additional serology tests (eg, total anti-HBc, IgM anti-HBc, anti-HBs) is per the investigator's discretion.

- Consider increasing monitoring of LFTs (ie at least every other week) for the first 3 months of antiviral therapy to allow proactive management of potential hepatitis flare risk on antiviral therapy.
- Assess the potential of drug-drug interaction with the prescribed antiviral therapy and assigned study drug.

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

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

11. Participants who are known to be HIV-positive, unless all of the following criteria are met:
    a. CD4+ count ≥ 300/μL.
    b. Undetectable viral load.
    c. Receiving antiretroviral therapy that is not a potential risk for a drug-drug interaction with the assigned study drugs.
12. Has known carcinomatous meningitis.
13. Active infection requiring systemic antibiotics ≤ 14 days from first dose of study drug.
    Note: A short course of antibiotics as part of the regimen for TURBT is permitted.
14. Participants with known or suspected active COVID-19 infection.
15. Use of probiotics within 28 days from first dose of study drug.
16. Current use of prohibited medication as noted in Section 6.6.3.
17. Has not recovered to ≤ Grade 1 from toxic effects of previous therapy and/or complications from previous surgical intervention before starting study therapy.

    Note: Participants with stable chronic AEs (≤ Grade 2) not expected to resolve (eg, alopecia) are exceptions and may enroll.

    Note: Participants with a history of peripheral neuropathy ≥ Grade 2 will be excluded.
18. History or presence of an abnormal ECG that, in the investigator's opinion, is clinically meaningful. A screening QTcF interval > 450 milliseconds is excluded.
19. History of a gastrointestinal condition (eg, inflammatory bowel disease, Crohn disease, ulcerative colitis) that may affect oral drug absorption.
20. Has received a live vaccine within 30 days of planned start of study therapy.

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

21. Participants with impaired cardiac function or clinically significant cardiac disease:
    a. New York Heart Association Class III or IV cardiac disease, including preexisting clinically significant ventricular arrhythmia, congestive heart failure, or cardiomyopathy
    b. Unstable angina pectoris.
    c. Acute myocardial infarction ≤ 6 months before study participation.
    d. Other clinically significant heart disease (eg, ≥ Grade 3 hypertension).
22. Inability or unlikeliness to comply with the dose schedule and study evaluations, in the opinion of the investigator.
23. Prior allogenic tissue/solid organ transplant.
24. **For all participants:**
    a. Evidence of interstitial lung disease or active, noninfectious pneumonitis.
    b. Has known hypersensitivity to any of the study drugs, excipients, including mannitol or another monoclonal antibody which cannot be controlled with standard measures (eg, antihistamines and corticosteroids).
    c. Any ≥ Grade 2 immune-related toxicity while receiving prior immunotherapy.
25. **For all participants:**
    a. History of serotonin syndrome after receiving 1 or more serotonergic drugs.
    b. Concomitant use of medications that are known to be substrates of CYP1A2, CYP2C8, or CYP2C19 with narrow therapeutic window are prohibited (see Section 6.6.3).
    c. Patients who are receiving or required to receive medications that are known to be UGT1A9 inhibitors (see Section 6.6.3).
26. For participants enrolled in France, the following are excluded: vulnerable populations according to article L.1121-6 of the French Public Health Code and adults under legal protection or who are unable to express their consent per article L.1121-8 of the French Public Health Code.

5.3. Lifestyle Considerations

No restrictions are required.

5.3.1. Meals and Dietary Restrictions

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

5.4. Screen Failures

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

Test with results that fail eligibility requirements may be repeated 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 if the investigator believes that there has been a change in eligibility status. Participants who rescreen must be assigned a new participant number.

5.5. Replacement of Participants

Participants in Treatment Groups A, B, D, and E (those with 18 participants per group) who are not able to provide evaluable paired biopsies will be replaced to ensure that there are 8 participants with paired biopsies for each of 2 CPS subgroups (CPS < 10 and CPS ≥ 10) for a total of 16 paired biopsies. Participants in Treatment Group C (epacadostat monotherapy group [9 participants]) who are not able to provide evaluable paired biopsies will be replaced to ensure there are 8 paired biopsies. Additionally, participants who have not received at least 4 weeks of neoadjuvant study treatment will be replaced.

5.6. Data Safety Monitoring Board

This study will use an independent DSMB to monitor safety for all treatment groups as needed throughout the duration of the study as specified in the DSMB charter. In addition, the DSMB will assess safety data for all participants receiving epacadostat plus retifanlimab combination therapy and epacadostat monotherapy (Treatment Groups A and C, respectively) on a regular basis and will make a recommendation related to epacadostat dose adjustments as deemed necessary (see Section 6.5.1.2).

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

6. STUDY TREATMENT

6.1. Study Treatments Administered

Study treatment information for infused study drugs and oral study drug are presented respectively. At visits where oral study drug is administered in the clinic in combination with retifanlimab, the oral study drug should be administered just before the start of the retifanlimab infusion. The order of administration of study drugs should be retifanlimab followed by INCAGN02385 followed by INCAGN02390. For details regarding infusion of study drugs, please refer to the Pharmacy Manual.

Table 13 presents the study treatment information. Retifanlimab, epacadostat, INCAGN02385, and INCAGN02390 will be provided by the sponsor.

Table 13: Study Treatment and Treatment Group Information

	Study Treatment 1	Study Treatment 2	Study Treatment 3	Study Treatment 4
Study treatment name:	Retifanlimab (INCMGA00012)	Epacadostat (INBC024360)	INCAGN02385	INCAGN02390
Mechanism of action:	Inhibitor of PD-1	IDO1 inhibitor	LAG-3 inhibitor	TIM-3 inhibitor
Dosage formulation:	25 mg/mL liquid formulation	300 mg and 100 mg tablets	50 mg/mL Solution for infusion	50 mg/ mL Solution for infusion
Unit dose strength(s) /dosage level(s):	Dose level: 500 mg Q4W	Dose level: 600 mg BID or 400 mg BID	Dose level: 350 mg Q2W	Dose level: 400 mg Q2W
Administration instructions:	Administered IV over 30 minutes (+ 15 min) on Day 1 of each 28-day cycle	For the 600 mg BID dose, two 300 mg tablets BID. For the 400 mg BID dose reduction, one 300 mg and one 100 mg tablet. Both dose levels should be administered without regard to food. Drug should be administered daily up to and including day of surgery.	IV (30-minute infusion with filter followed by flush) Q2W	IV (30-minute infusion with filter followed by flush) Q2W
Treatment Group A:	500 mg IV over 30 minutes (+ 15 min) on Day 1 of each 28-day cycle	600 mg BID or 400 mg BID	N/A	N/A
Treatment Group B:	500 mg IV over 30 minutes (+ 15 min) on Day 1 of each 28-day cycle	N/A	N/A	N/A
Treatment Group C:	N/A	600 mg BID or 400 mg BID	N/A	N/A

Table 13: Study Treatment and Treatment Group Information (Continued)

	Study Treatment 1	Study Treatment 2	Study Treatment 3	Study Treatment 4
Treatment Group D:	500 mg IV over 30 minutes (+ 15 min) on Day 1 of each 28-day cycle followed by 10 minute flush	N/A	350 mg IV over 30 minutes (−5/+10 min) Q2W followed by 10 minute flush	N/A
Treatment Group E:	500 mg IV over 30 minutes (+ 15 min) on Day 1 of each 28-day cycle followed by 10 minute flush	N/A	350 mg IV over 30 minutes (−5/+10 min) Q2W followed by 10 minute flush	400 mg IV over 30 minutes (−5/+10 min) Q2W followed by 10 minute flush
Route of administration:	IV	PO	IV	IV
Packaging and labeling:	Study drug will be provided in vials. Each vial will be labeled as required per country requirement.	Study drug will be provided in bottles. Each bottle will be labeled as required per country requirement.	Study drug will be provided in vials. Each vial will be labeled as required per country requirement.	Study drug will be provided in vials. Each vial will be labeled as required per country requirement.
Storage:	Stored upright under refrigeration at 2°C to 8°C (36°F-46°F) and protected from light	Stored at room temperature at 15°C-30°C (59°F-86°F)	Stored upright under refrigeration at 2°C to 8°C (36°F-46°F) and protected from light	Stored upright under refrigeration at 2°C to 8°C (36°F-46°F) and protected from light
Status of treatment in participating countries:	Investigational	Investigational	Investigational	Investigational

6.2. Preparation, Handling, and Accountability

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

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

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

- Delivery of study drug(s) to the study site.
- Inventory of study drug(s) at the site.
- Participant use of the study drug(s) including tablet and/or vial counts as applicable from each supply dispensed.
- For participants receiving retifanlimab, INCAGN02385, and INCAGN02390: Lot numbers and/or vial numbers (as applicable) of study drug used to prepare the infusion solution.
- Return of study drug(s) to the investigator or designee by participants receiving epacadostat.

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

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

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

6.3. Measures to Minimize Bias: Randomization and Blinding

This is an open-label, stratified randomized study with a translational primary endpoint of change in CD8+. Post PD-L1 testing, participants will be randomized to Treatment Group A, B, C, D, or E based on PD-L1 CPS value (see Figure 1) at a 2:2:1:2:2 ratio, respectively, if participants are eligible for Treatments D and E based on exclusionary criteria. If participants are not eligible for Treatments D and E based on exclusionary criteria, participants will be randomized to Treatment Group A, B, or C based on PD-L1 CPS value (see Figure 1) at a 2:2:1 ratio. This will ensure that the planned number of participants will be enrolled into each treatment group with PD-L1 CPS balanced within each treatment group. Additional details on randomization will be included in the IRT specifications document.

6.4. Study Treatment Compliance

The site personnel must emphasize compliance with all study-related treatments to the participant. Appropriate steps should be taken to optimize compliance during the study. Participants in the epacadostat treatment groups will be instructed to bring all unused study drugs with them to the study visits in order for site personnel to conduct tablet counts to assess study drug accountability. The drug accountability documentation will be used by the sponsor to calculate treatment compliance.

For participants in the retifanlimab, INCAGN02385, and INCAGN02390 treatment groups, compliance will be calculated by the sponsor based on study drug accountability and infusion records documented by the site staff and monitored by the sponsor/designee.

6.5. Dose Modifications

6.5.1. Criteria and Procedures for Dose Interruptions and Adjustments of Study Drugs

6.5.1.1. Retifanlimab, INAGN02385, and INCAGN02390

Dose modification of retifanlimab, INCAGN02385, or INCGN02390 is not permitted. If a dose interruption is necessary for management of drug-related TEAEs, study drugs will be reinitiated at the starting doses.

Individual decisions regarding dose modifications of study treatment should be made using clinical judgment in consultation with the medical monitor (whenever possible), taking into account relatedness of the AE to the study treatment and the participant's underlying condition. 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-interruption rules.

Decisions regarding these dose interruptions and restarts of retifanlimab, INCAGN02385, or INCAGN02390 will be made according to Table 14 for suspected infusion reactions, Table 15 for irAEs, and Table 16 for non-irAEs.

Safety concerns should be discussed with the sponsor immediately upon occurrence or awareness.

6.5.1.2. Epacadostat

Epacadostat may be reduced to 400 mg BID per guidance in Table 15 for irAEs. If dose interruption is necessary for management of treatment-related TEAEs, retifanlimab will be reinitiated at 500 mg Q4W and epacadostat at 600 mg or 400 mg BID. Only 1 dose reduction of epacadostat is permitted. If the same AE that required epacadostat dose reduction reoccurs at the same severity or greater, regardless of the causality to epacadostat, epacadostat should be discontinued. If a participant who is being treated with epacadostat 400 mg BID has a different AE that is considered unrelated to epacadostat by the investigator, the participant may resume study treatment at 400 mg BID when the AE resolves. Once a participant is started on the 400 mg BID dose of epacadostat, dose escalation to the 600 mg BID dose is not permitted. Additionally, information regarding management of participants receiving the epacadostat combination who experience serotonin syndrome is presented in Section 6.5.5.

6.5.1.3. All Study Treatments

Decisions on any treatment dose reduction, interruption, or restart can also be jointly made, when needed, by the investigator and medical monitor on a case-by-case basis.

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

To reduce the risk of delays in radical cystectomy due to TEAEs, if treatment is withheld for more than 2 weeks in any treatment arm, then the participant will discontinue study treatment.

Study treatment should only be resumed if it allows for a minimum of an additional 2 weeks of therapy before radical cystectomy.

6.5.2. Management of Suspected Infusion Reactions

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

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

Table 14: Guidelines for Management of Suspected Infusion Reactions

Grade	Description[a]	Treatment	Subsequent Infusions
1	Mild reaction; interruption or slowed rate of infusion indicated; intervention not indicated.	Monitor vital signs closely until medically stable.	Premedication with antipyretics (eg, acetaminophen/paracetamol) and a histamine blocker (eg, diphenhydramine) should be considered for participants who have had previous systemic reactions to protein product infusions or when recommended by institutional policy.
2	Requires infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hours.	**First occurrence:** Stop infusion and initiate appropriate medical measures (eg, IV fluids, antihistamines, NSAIDs, antipyretics, narcotics, per institutional preferences). Monitor vital signs until medically stable. If symptoms resolve within 1 hour, infusion may be resumed at 50% of the original infusion rate. **Subsequent occurrences (after recommended prophylaxis):** Permanently discontinue study treatment.	Premedicate at least 30 minutes before infusion with antihistamines (eg, diphenhydramine 50 mg PO) and antipyretics (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 medical therapy (eg, IV fluids, antihistamines, NSAIDs, antipyretics, narcotics, oxygen, pressors, epinephrine, corticosteroids, per institutional preferences). Monitor vital signs frequently until medically stable. Hospitalization may be indicated.	Permanently discontinue study treatment. If rapidly responsive to symptomatic medication and/or to brief interruption of infusion, study drug does not need to be permanently discontinued, per NCI CTCAE v5.

[a] Per NCI CTCAE v5.0, appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of study treatment administration.

6.5.3. Procedures for Participants Exhibiting Immune-Related Adverse Events

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

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

Recommendations for the management of specific immune-mediated AEs known to be associated with other PD-1 inhibitors are detailed in Table 15 and Section 6.5.6. Algorithms for the evaluation of selected immune toxicities that have previously been attributed to PD-1 inhibitors and management guidelines for irAEs not detailed elsewhere in the Protocol should follow the ASCO or ESMO Clinical Practice Guidelines (Brahmer et al 2018, Haanen et al 2018).

If an irAE warrants study treatment interruption, all study drugs should be withheld.

Dose modification and toxicity management guidelines for irAEs are provided in Table 15.

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

irAE	Toxicity Grade or Conditions (CTCAE v5.0)	Action Taken With Study Treatment	AE 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 *Clostridium 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 > 3 × ULN	Permanently discontinue	

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

irAE	Toxicity Grade or Conditions (CTCAE v5.0)	Action Taken With Study Treatment	AE 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 hypothyroidism, hyperthyroidism, or Type 1 diabetes mellitus	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 standard of care.
	Grades 3 or 4 hyperthyroidism	Withhold until ≤ Grade 1 or is otherwise clinically stable	Initiate symptomatic management.
	Grades 3 or 4 Type 1 diabetes mellitus (or hyperglycemia)	Withhold until ≤ Grade 1 or is otherwise clinically stable	Initiate treatment with antihyperglycemics or insulin as clinically indicated.
	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 (asymptomatic) hypophysitis	• Withhold until ≤ Grade 1 • May restart study drug after controlled by hormone replacement therapy	Initiate treatment with hormone replacement therapy.
	Grade 2 (symptomatic; eg, headaches, visual disturbances) hypophysitis	• 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 (symptomatic)	Permanently discontinue	
Nephritis and renal dysfunction	Grade 1	No action	None.
	Grades 2 or 3 increased blood creatinine	Withhold until ≤ Grade 1	Administer corticosteroids per local practice followed by taper.
	Grade 4 increased blood creatinine	Permanently discontinue	

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

irAE	Toxicity Grade or Conditions (CTCAE v5.0)	Action Taken With Study Treatment	AE Management With Corticosteroid and/or Other Supportive Care Therapies[a]
Skin (eg, SJS, TEN)	Grade 1	No action	None.
	Grade 2	No action	Manage with topical corticosteroids with or without drug interruption.
	Grade 3[b], persistent Grade 2 (≥ 2 weeks), or suspected SJS[c]	Withhold until ≤ Grade 1 after corticosteroid taper to ≤ 10 mg/day prednisone or equivalent	• Administer corticosteroids per local practice followed by taper. Additionally, oral histamine 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 confirmed Grade 4 SJS[c] or TEN[d]	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	Permanent discontinuation of study drug	• 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 standard of care and with guidance from cardiology. Consider cardiac MRI and myocardial biopsy for diagnosis.
	Grades 3 or 4	Permanently discontinue	

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

irAE	Toxicity Grade or Conditions (CTCAE v5.0)	Action Taken With Study Treatment	AE Management With Corticosteroid and/or Other Supportive Care Therapies[a]
Troponin I or troponin T increase	All troponin elevations (including asymptomatic elevations)	Withhold INCMGA00012, INCAGN02385, INCAGN02390, and epacadostat until resolved to baseline	• All troponin elevations (including asymptomatic elevations) will require a dose delay in order for the participant to undergo a cardiac evaluation via prompt cardiology consult and diagnostic workup including, at minimum, ECG and echocardiogram (plus cardiac MRI and further relevant biological markers [brain natriuretic peptide, creatine kinase] per the cardiologist's recommendation) and a confirmatory test repeated within 24 hours. – If troponin elevation is not confirmed within 24 hours in an asymptomatic participant, the dose delay may not be needed provided that the cardiac evaluation is completed and a cardiologist has made the recommendation to proceed with treatment. – Otherwise, if troponin elevation is confirmed, continue serial monitoring until recovery. Consider corticosteroids per treating physician. Dosing may resume when troponin level resolves to baseline provided that the cardiac evaluation is completed and a cardiologist has made the recommendation to proceed with treatment.
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 standard of care and with guidance from neurology.
	Grades 3 or 4	Permanently discontinue	

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

irAE	Toxicity Grade or Conditions (CTCAE v5.0)	Action Taken With Study Treatment	AE 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 Grades 2 or Grade 3	Permanently discontinue	
	Grade 4[e] (excluding endocrinopathies)	Permanently discontinue	

[a] As general instructions, the following should be followed: if treatment-related toxicity does not resolve to Grade 0-1 within 12 weeks after 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] 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.

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

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

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

6.5.4. Procedures for Participants Exhibiting Drug-Related, Non–Immune-Related Adverse Events

The guidance presented in Table 16 should be followed as best practice for decisions regarding management of non-irAEs for participants receiving retifanlimab as monotherapy or in combination with epacadostat.

Table 16: Management Guidelines for Drug-Related, Non–Immune-Related Adverse Events

Drug-Related, Non-Immune–Related	Grade	Action Taken With Study Treatment
Any drug-related, non–immune-related AE	1	No action
	2	No action
	3	Withhold until ≤ Grade 1[a]
	4	Permanently discontinue[a]

[a] For Treatment Group A, if retifanlimab dosing is held, dosing for epacadostat must also be held. Participants are allowed, however, to receive retifanlimab monotherapy if epacadostat is discontinued due to drug-related, non-irAEs. For Treatment Groups D and E, in all cases where retifanlimab dosing is held, dosing for the other combination drug must also be held. Participants are allowed, however, to receive retifanlimab monotherapy if INCAGN02385 and/or INCAGN02390 is discontinued.

6.5.5. Procedures for Participants in the Epacadostat Groups Exhibiting Serotonin Syndrome

There is a rare chance that epacadostat, when administered alone or in combination with other serotonergic agents, could cause an increase in serotonin levels in the brain that might trigger serotonin syndrome (Boyer and Shannon 2005). This syndrome has been most closely associated with use of MAOIs, meperidine, linezolid, or methylene blue. Preclinical data suggest that serotonin syndrome is unlikely after treatment with either epacadostat alone or in combination with MAOIs such as linezolid (Zhang et al 2019). For more information, refer to the epacadostat IB.

Selective serotonin reuptake inhibitors, SNRIs, and MAOIs are permitted in the study. Serotonin syndrome usually manifests with autonomic changes, mental status changes, and neurological findings. These mild, moderate, and severe signs and symptoms of serotonin syndrome (summarized in Table 17) should be evaluated in the context of possible comorbid conditions as well. A neurology consult is recommended to diagnose or confirm serotonin syndrome or to rule out other etiologies.

The following procedures will be implemented if participants exhibit the signs/symptoms of serotonin syndrome, including tremor; hyperreflexia; spontaneous, ocular, or inducible clonus; together with agitation, fever, diaphoresis, or muscle rigidity:

- Immediately interrupt all study treatment administration.
- Immediately interrupt any MAOI, SSRI, or SNRI administration.

- Provide appropriate medical management of the participant until all signs/symptoms are resolved (eg, IV fluids and/or sympathomimetic amines for hypotension, benzodiazepines for agitation, administration of 5-hydroxytryptamine antagonists such as cyproheptadine).
- If etiologies other than serotonin syndrome are excluded, study treatment administration may be resumed unless other AE management guidelines apply for the specific event.
- If participant chooses to remain in the study, restart treatment with epacadostat after the MAOI, SSRI, or SNRI has been discontinued, no sooner than 5 half-lives have elapsed for the specific MAOI, SSRI, or SNRI in question, and after resolution of signs/symptoms of serotonin syndrome. The MAOI, SSRI, or SNRI administration MAY NOT be restarted.
- If participant chooses to withdraw from the study or must restart treatment with the MAOI, SSRI, or SNRI, the participant should be scheduled for a follow-up visit. Treatment with the MAOI, SSRI, or SNRI may be initiated 2 weeks after resolution of signs and symptoms of serotonin syndrome.
- If a participant had experienced moderate or severe unconfounded serotonin syndrome in the opinion of the investigator, without concomitant MAOI, SSRI, or SNRI usage or serotonergic concomitant medications, study treatment should be permanently discontinued.

Table 17: Signs and Symptoms of Serotonin Syndrome

Seriousness	Autonomic Signs	Neurologic Signs	Mental Status	Other
Mild	• Afebrile or low-grade fever • Tachycardia • Mydriasis • Diaphoresis or shivering	• Intermittent tremor • Akathisia • Myoclonus • Mild hyperreflexia	• Restlessness • Anxiety	Not applicable
Moderate	• Increased tachycardia • Fever (up to 41°C) • Diarrhea with hyperactive bowel sounds • Diaphoresis with normal skin color	• Hyperreflexia • Inducible clonus • Ocular clonus (slow continuous lateral eye movements) • Myoclonus	• Easily startled • Increased confusion • Agitation and hypervigilance	• Rhabdomyolysis • Metabolic acidosis • Renal failure • Disseminated intravascular coagulopathy (secondary to hyperthermia)
Severe	Temperature often more than 41°C (Secondary to increased tone)	• Increased muscle tone (lower limb > upper) • Spontaneous clonus • Substantial myoclonus or hyperreflexia	• Delirium • Coma	As above

Source: Boyer and Shannon 2005.

6.5.6. Criteria for Permanent Discontinuation of Study Drug

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 study treatment for more than 2 weeks (14 days) unless a greater delay has been approved by the sponsor.
- Any AE defined in the dose modification guidelines requiring that the study drug be discontinued.

The following criteria will require permanent discontinuation of a treatment group and evaluation by the DSMB:

- A maximum of 4 out of 18 participants in Treatment Groups A, B, D, or E or 2 out of 9 participants in Treatment Group C who experience Grade 3 to Grade 5 SAEs in vital organs (eg, lung, heart, liver, kidney) clearly attributable to treatment-related AEs.
- A maximum of 4 out of 18 participants in Treatment Groups A, B, D, or E or 2 out of 9 participants in Treatment Group C who require a delay in surgery of > 11 weeks from the start of therapy (see Section 2.2.3). The delay of surgery should be clearly attributable to side effects of study treatment rather than other non–treatment-related factors (eg, operating room availability).
- A maximum of 4 out of 18 participants in Treatment Groups A, B, D, or E or 2 out of 9 participants in Treatment Group C who experience postsurgical complications due to study treatment.

See Section 6 for study drug and study treatment discontinuation/modifications.

6.6. Concomitant Medications and Procedures

All concomitant medications and treatments (including over-the-counter or prescription medicines, vitamins, vaccines, and/or herbal supplements) must be recorded in the eCRF. Any prior medication received up to 30 days before the first dose of study treatment and 90 days after radical cystectomy (unless associated with the treatment of an AE, which should be collected regardless of timing), or until the participant begins a new anticancer therapy, whichever occurs first, will be recorded in the eCRF. If radical cystectomy is not performed then concomitant medications must be recorded up to 30 days from the last dose of study treatment. Any addition, deletion, or change in the dose of these medications will also be recorded. Concomitant medications administered for the management of SAEs as defined in Section 9.2 should be recorded regardless of when they were provided. Concomitant treatments/procedures that are required to manage a participant's medical condition during the study will also be recorded in the eCRF. The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.6.1. Permitted Medications and Procedures

Recommended supportive measures for specific toxicities are described in Section 6.5. Growth factors, bisphosphonates, anticoagulants, and transfusional support will also be permitted but should be discussed with the medical monitor before implementing.

Antiretroviral therapy should be continued for participants who are known to be HIV-positive. ***Note:*** Participants must be receiving antiretroviral therapy that is not a potential risk for a drug-drug interaction with the assigned study drugs.

The use of corticosteroids is permitted in the following situations:

- Acute treatment for an AE.
- 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.
- Participants with asthma who require intermittent use of bronchodilators, inhaled steroids, or local steroid injections.
- Topical, ocular, intra-articular, or intranasal steroids (with minimal systemic absorption).
- Brief course of corticosteroids for prophylaxis (eg, < 3 weeks for contrast dye allergy), study treatment–related premedication as per standard, chronic obstructive pulmonary disease exacerbation, or for treatment of nonautoimmune conditions (eg, delayed-type hypersensitivity reaction caused by a contact allergen).
- As described in Section 6.5.5, SSRIs, SNRIs, and MAOIs are permitted in the study.

6.6.2. Restricted Medications and Procedures

Radiation therapy to a symptomatic solitary lesion or to the brain may be considered on an exceptional case-by-case basis after consultation with the medical monitor. The participant must have clear measurable disease outside the radiated field.

For participants in epacadostat-containing treatment groups (Treatment Groups A and C), an epacadostat metabolite is a moderate in vitro inhibitor of CYP1A2; thus, it is recommended to avoid or limit caffeine consumption (eg, no more than 1 cup of coffee per day).

6.6.3. Prohibited Medications and Procedures

The following medications and measures are prohibited:

- Other anticancer therapies, including investigational treatments.
- Systemic immunosuppression for active autoimmune disease using immunosuppressive drugs or corticosteroids (> 10 mg daily of prednisone or equivalent) within 2 years of Day 1 of study treatment and throughout the treatment period (with the exception of acute treatment for an AE).
- Chronic use of systemic steroids (> 10 mg daily of prednisone or equivalent). Exceptions for steroid use are outlined in Section 6.6.1.

- Live vaccines within 28 days before the first administration of study drug, during the study and for a duration of 5 half-lives (approximately 90 days) after the last dose of study treatment.
- Chronic doses of products containing acetyl-para-aminophenol (also known as APAP, acetaminophen, or paracetamol) in excess of 2 g or 2000 mg total daily dose.
- Prohibited medications and procedures for epacadostat-containing treatment groups (Treatment Groups A and C):
  - Use of any UGT1A9 inhibitors, including acitretin, amitriptyline, androsterone, cyclosporine, dasatinib, diclofenac, diflunisal, efavirenz, erlotinib, flutamide, gefitinib, gemfibrozil, glycyrrhetinic acid glycyrrhizin, imatinib, imipramine, ketoconazole (systemic), mycophenolic acid, niflumic acid, nilotinib, phenobarbital, phenylbutazone, phenytoin, probenecid, quinidine, ritonavir, sorafenib, sulfinpyrazone, valproic acid, and verapamil.
  - Use of warfarin for participants receiving epacadostat doses greater than 300 mg BID. An alternative to warfarin should be considered. If an alternate cannot be found, the participant may not be enrolled. If anticoagulation is needed during the conduct of the study and nonwarfarin regimens are not feasible, the participant must discontinue study therapy.
  - Chronic use of systemic antibiotics (> 14 days) unless medical monitor review and approval.
- Due to the potential concern for epacadostat metabolite inhibition of CYP1A2, CYP2C8 and CYP2C19, and OATP1B1 and OATP1B3 transporters with doses of epacadostat ≥ 600 mg BID, the medications listed in Appendix F are prohibited for concomitant use.
- Participants should seek alternatives that are not in the class. If alternatives cannot be found, the medical monitor should be contacted to discuss if enrollment is appropriate.

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:

- 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.
- If, during the course of the study, a participant is found not to have met eligibility criteria, the participant should be withdrawn from study treatment.
- Further participation would be injurious to the participant's health or well-being, in the investigator's medical judgment.
- Unacceptable toxicity as noted in Section 6.5.
- Investigator's decision to withdraw the participant from study treatment.
- The participant becomes pregnant, confirmed by a positive serum pregnancy test.
- The participant must discontinue if he/she has suspected or confirmed disease progression or is not responding to treatment.
- The treatment group is terminated by the DSMB; see Section 6.5.6.
- 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:

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

7.1.2. Discontinuation Procedures

In the event that the decision is made to permanently discontinue the study treatment, the 30-day post–last dose safety follow-up visit and the 90-day post-cystectomy safety follow-up visits should be conducted. In the event the participant does not undergo a cystectomy, the last follow-up visit will be 90 days post last dose of study treatment. Reasonable efforts should be made to have the participant return for the follow-up visits. These visits are described in Table 3 through Table 7. The last date of the last dose of study drug(s)/treatment and the reason for discontinuation of study treatment will be recorded in the eCRF.

If a participant is discontinued from study treatment:

- The study monitor or sponsor must be notified.
- The reason(s) for withdrawal must be documented in the participant's medical record and the primary reason for withdrawal must be included in the eCRF.
- The Safety Follow-up visits should be performed and dates recorded.
- The status of the participant should be updated to EOT in the IRT.
- Participants must be followed for safety until the time of the follow-up visit or until study drug/treatment–related toxicities resolve, return to baseline, or are deemed irreversible, whichever is longest.

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.

See Table 3 through Table 7 for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

7.3. Lost to Follow-Up

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

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

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

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Administrative and General Procedures

8.1.1. Informed Consent Process

- The informed consent process will include 2 separate consent forms for this study; the screening consent and treatment consent, which is inclusive of all treatment groups. Participants will be required to sign both consents if they are deemed eligible and are enrolled into the study.
- 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(ies) 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.

A participant who is rescreened is not required to sign another ICF if the rescreening occurs within 28 days from the previous ICF signature date.

8.1.2. Screening Procedures

For each participant, the diagnostic biopsy or sample from the TURBT procedure shall be provided to the sponsor's central testing laboratory for analysis at the time of screening.

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). Screening laboratory assessments must be performed within 28 days of Cycle 1 Day 1. If chemistry and hematology laboratory assessments were 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. Results of a test performed before the participant signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified timeframe. For participants who are enrolled in the study, information associated with eligibility requirements must be entered into the appropriate eCRF pages.

Tests with results that fail eligibility requirements may be repeated 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 if the investigator believes that there has been a change in eligibility status. Participants who rescreen must be assigned a new participant number.

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. Site staff will also be asked to enter the outcome of the participant's PD-L1 CPS testing during screening into the IRT to obtain the treatment assignment. The treatment assignment will be done as described in Section 4.1, and any participants who do not meet study inclusion/exclusion criteria will fail screening. 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. Distribution of Reminder Cards

All participants will be provided with reminder cards. Participants in Treatment Groups A, B, and C will be provided with a reminder card at Day 1 of each treatment cycle, while participants

in Groups D and E will be provided with a reminder card at Day 1 of each cycle and Day 15 of Cycles 1 and 2. The reminder card will indicate the date/time of the next visit as well as other visit-specific procedures and reminders (ie, not take their morning dose of oral study drug before the next visit). [redacted]

8.1.5. Demography and Medical History

8.1.5.1. Demographics and General Medical History

Demographic data and general medical history will be collected at screening by the investigator or qualified designee and will include 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.

8.1.5.2. Disease Characteristics and Treatment History

A disease-targeted medical and treatment history will be collected at screening. Details regarding the participant's malignancy under study, including date of diagnosis, initial and current cancer stage, tumor histology, and relevant disease characteristics, and prior treatments, including systemic treatments, radiation, and surgical procedures, will be recorded.

8.2. Efficacy Assessments

The primary translational endpoint of this study is the change in tumor-infiltrating immune CD8+ T effector cells at the time of cystectomy compared to pretreatment. Subsequent immunohistochemical and transcriptional analysis will further characterize the infiltrating T-cell subpopulations.

8.2.1. Pathological Complete Response, Major Pathological Response, [redacted]

Efficacy analysis for the pCR rate [redacted] will include all participants who met the eligibility criteria, had at least 1 cycle of study treatment, and underwent cystectomy or withdrew for progression of disease. pCR is defined as pT0 and in situ cancer on the basis of histological evaluation of the TURBT and cystectomy samples by local institutional analysis. Major pathological response is defined as residual ypT0/1/a/isN0M0 on the basis of histological evaluation of the TURBT and cystectomy samples. [redacted]

8.2.2. Health Economics

Not applicable.

8.3. Safety Assessments

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

8.3.1. Adverse Events

Adverse events will be monitored from the time the participant signs the ICF until 90 days after cystectomy or the last dose of either study drug if cystectomy not performed. If cystectomy is not performed, then AEs are collected at least 28 days after the last dose of study treatment or until the start of new anticancer therapy, whichever occurs first. Adverse events that begin or worsen after informed consent should be recorded on the Adverse Events Form in the eCRF regardless of the assumption of a causal relationship with the study treatment(s). Conditions that were already present at the time of informed consent should be recorded on the Medical History Form in the eCRF. Adverse events (including laboratory abnormalities that constitute AEs) should be described using a diagnosis whenever possible rather than by individual underlying signs and symptoms.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative). The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following-up on AEs that are serious, considered related to the study treatment/procedures, or that caused the participant to discontinue the study treatment. Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant, such as "How are you feeling?" is the preferred method to inquire about AE occurrences. Adverse events may also be detected when they are volunteered by the participant during the screening process or between visits or through physical examinations, laboratory tests, or other assessments. The definition, reporting, and recording requirements for AEs are described in Section 9.

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

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

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 (with the exception of abnormalities associated with disease progression). Investigators should pay special attention to clinical signs related to previous serious illnesses.

At the screening visit, a comprehensive physical examination should be conducted. The comprehensive physical examination will include height and body weight, and assessment of the following organ or body systems: skin; head, eyes, ears, nose, and throat; thyroid; lungs; cardiovascular system; abdomen (liver, spleen); extremities; and lymph nodes; as well as a brief neurological examination. Audiometric hearing and peripheral neuropathy will be assessed as

per Galsky criteria (Galsky et al 2011). Height will be measured at the screening only. Weight should be assessed at the study visits as indicated in the SoA.

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

8.3.3. Vital Signs

Vital sign measurements (should be taken before blood collection for laboratory tests) include blood pressure, pulse, respiratory rate, and body temperature and are to be taken as specified in the SoA. 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, semi recumbent, or sitting position after 5 minutes of rest. Abnormal vital sign results identified after the first dose of study treatment constitute an AE if they are considered clinically meaningful, induce clinical signs or symptoms, require concomitant therapy, or require changes in study treatment.

8.3.4. Electrocardiograms

Single 12-lead ECG will be obtained as outlined in the SoA using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. All 12-lead ECGs will be performed with the participant in a recumbent or semirecumbent position after 5 minutes of rest. Electrocardiograms will be conducted predose.

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.

8.3.5. Laboratory Assessments

See Table 18 for the list of clinical laboratory tests to be performed and the SoAs 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, thyroid function, lipid panel, serology, 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 for specific combinations or if clinically indicated.

Clinically significant abnormal laboratory findings are those which 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 do not need to be repeated 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.

Laboratory checks of HIV viral load and CD4+ cell count will be performed at screening, before cystectomy, and then at the 30-day safety follow-up visit.

Table 18: Required Laboratory Analytes

<table>
<tr><th>Serum Chemistries</th><th>Hematology</th><th>Urinalysis</th><th>Serology</th><th>Coagulation</th></tr>
<tr><td rowspan="3">Albumin
Alkaline phosphatase
ALT
AST
Amylase
Bicarbonate or CO_2[a] or HCO_3 (if clinically indicated)
Blood urea nitrogen or urea
Calcium
Chloride
Creatinine
Glucose
Lactate dehydrogenase
Lipase
Potassium
Sodium
Total bilirubin
Direct bilirubin (if total bilirubin is elevated above ULN)
Total protein
Uric acid
Troponin I or T (All treatment groups for screening, Treatment Groups D and E only during treatment cycles, per local standard)</td><td rowspan="3">Complete blood count, including:
• Hemoglobin
• Hematocrit
• Platelet count
• Red blood cell count
• White blood cell count

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

Absolute values must be provided for:
• WBC differential laboratory results</td><td>Color and appearance
pH and specific gravity
Bilirubin
Glucose
Ketones
Leukocytes
Nitrite
Occult blood
Protein
Microscopic examination (if blood or protein is abnormal)</td><td>HIV screening and management:
HIV viral load
CD4+ cell count

Hepatitis B surface antigen
Hepatitis B surface antigen antibody
Hepatitis B core antibody
HBV-DNA
HCV antibody
HCV-RNA</td><td>PT
PTT or aPTT
INR</td></tr>
<tr><th>Thyroid Panel</th><th>Pregnancy Testing</th><th>Lipid Panel</th></tr>
<tr><td>TSH
T4
T3/FT3 (based on local availability)</td><td>Female participants of childbearing potential only require a serum test at screening and precystectomy. A urine or serum pregnancy test is required before cystectomy, before the first dose on Day 1 of every cycle before dose administration, and at the 30-day safety follow-up visit; in Europe, a urine or serum pregnancy test is also required 190 days after the last dose of study treatment.
Pregnancy tests (serum or urine) should be repeated if required by local regulations.</td><td>Total cholesterol
Triglycerides
Low-density lipoprotein cholesterol
High-density lipoprotein cholesterol</td></tr>
</table>

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

8.3.5.1. Pregnancy Testing

A serum pregnancy test will be required for all women of childbearing potential at screening and at the precystectomy visit. The serum pregnancy test performed at screening must be performed within 72 hours before the first dose of study treatment. Urine or serum pregnancy tests will be performed locally as outlined in Table 3 to Table 7, as medically indicated (eg, in case of loss of menstrual cycle, when pregnancy is suspected), or per country-specific requirements. Additionally, monthly telephone visits should take place to check pregnancy status (via testing, including home urine pregnancy tests) during the period when contraception is mandatory, which is 190 days after the last dose of study treatment for European sites. 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 9.7 for reporting requirements.

8.3.6. Eastern Cooperative Oncology Group Performance Status

Eastern Cooperative Oncology Group PS will be assessed according to the criteria in Table 19.

Table 19: Eastern Cooperative Oncology Group Performance Status

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

Source: Oken et al 1982.

8.3.7. Postsurgical Criteria for Adverse Events

In the PURE-01 study, where pembrolizumab was administered as neoadjuvant therapy before radical cystectomy in patients with miUBC, the medical and surgical reported AEs are listed in Table 2 of Necchi et al (2018). Postsurgical complications were consistent with previously reported findings. Clavien Dindo > Grade II complications (see Appendix D) occurred in 15 participants (30%), and the most frequent complications were sepsis (n = 10; 20%) and subocclusion (n = 8; 16%). However, there were a few delayed immune-related AEs, including pyrexia (n = 3; 6%), pruritus (n = 3; 6%), and xerostomia (n = 2; 4%). All of the latter AEs occurred within 2 months postoperatively, and three participants required corticosteroid treatment.

As noted in Mitropoulos et al (2012), a more rigid criteria of measuring postsurgical complications may have resulted in perceived higher rates of complications. The following

quality criteria will be followed for postsurgical AEs at 30 days after cystectomy (or after last dose if cystectomy is not performed) for accurate and comprehensive reporting:

- Define the method of accruing data: retrospective/ prospective; through chart review/telephone interview/face to face interview/other.
- Define who collected the data: medical doctor/nurse/data manager/other, and whether he or she was involved in the treatment.
- Indicate the duration of follow-up: 30 days.
- Include outpatient information.
- Include mortality data and causes of death.
- Include definitions of complications.
- Define procedure-specific complications.
- Report intraoperative and postoperative complications separately.
- Use a severity grading-system for postoperative complications (avoiding the distinction minor/major); the Clavien-Dindo systems is recommended.
- Postoperative complications should be presented in a table either by grade or by complications type (specific grades should always be provided; grouping in not accepted).
- Include risk factors: American Society of Anesthesiologists score, Charlson score, ECOG PS, other.
- Include readmissions and causes.
- Include reoperations, types, and causes.
- Include the percentage of participants lost to follow-up.

All Grade 3 and Grade 4 AEs reported and any reported postsurgical complication will be added for internal analysis of data.

8.4. [redacted] Immunogenicity Assessments

[redacted]

Participants in Treatment Group A receiving combination therapy should take their scheduled oral dose of epacadostat immediately before the start of retifanlimab infusion. The exact date and time of the dose administered at the clinic should be recorded and entered into the EDC.

[redacted]

[redacted] Instructions for sample preparation and shipping will be provided in the Laboratory Manual.

Any changes in the timing or addition of timepoints for any planned study assessments must be documented and approved by the relevant study team member and then archived in the sponsor and site study files but will not constitute a Protocol Amendment. The IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICF.

8.4.1. Blood Sample Collection for Monoclonal Antibodies

Blood samples for [redacted] ADA analysis will be obtained at the visits indicated in the appropriate SoA. Timing of [redacted] ADA assessments for retifanlimab, INCAGN02385, and INCAGN02390 are outlined in Table 20. [redacted] Predose is defined as within 24 hours before administration of study drug. [redacted]

Table 20: Timing of [redacted] Antidrug Antibody Serum Sample Collection

Study Visit	Assessment	Timing of Sample Collection
Cycle 1 Day 1 for Treatment Groups A and B	[redacted] ADA	Preinfusion
	[redacted]	[redacted]
Cycle 2 Day 1 for Treatment Groups A and B	[redacted] ADA	Preinfusion
	[redacted]	[redacted]
Safety follow-up (30-day) for Treatment Groups A and B	ADA	Untimed ADA sample
Cycle 1 Day 1 for Treatment Groups D and E	[redacted] ADA	Predose/preinfusion of INCAGN02385 and/or INCAGN02390 and retifanlimab Sample must be collected before dose/infusion of other agents
	[redacted]	[redacted]
Cycle 2 Day 1 for Treatment Groups D and E	[redacted] ADA	Predose/preinfusion
30-day safety follow-up for Treatment Groups D and E	ADA	Untimed sample

8.4.1.1. Immunogenicity (Antidrug Antibody) Assessments

Blood samples will be assessed for antibodies binding to retifanlimab, INCAGN02385, and INCAGN02390 and the titer of confirmed positive samples will be reported. Other analyses may be performed to verify the stability of antibodies to retifanlimab, INCAGN02385, and INCAGN02390 and/or further characterize the immunogenicity of study drug.

The detection and characterization of antibodies to retifanlimab, INCAGN02385, and INCAGN02390 will be performed using a validated assay method by or under the supervision of the sponsor or designee. All samples collected for detection of antibodies to study drugs will also be evaluated for concentration to enable interpretation of the antibody data. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of the study drug.

[redacted]

8.4.3. Bioanalytical Methodology and Sample Analysis

All the bioanalysis work will be performed by Incyte or its designee. Serum concentrations of retifanlimab monotherapy or in combination with other oral therapies will be measured using a quantitative sandwich ELISA method. Plasma concentrations of epacadostat will be measured using validated liquid chromatography–tandem mass spectrometry assays.

The generation of ADA directed against retifanlimab will be monitored using a bridging ELISA method.

8.5. Pharmacodynamic and Translational Assessments

8.5.1. Timing of Assessments

[redacted].

The tumor infiltrating lymphocyte population consists of multiple T cell populations, including CD4+ helper cells, CD8+ cytotoxic T cells, and FoxP3+ Tregs. The primary translational endpoint of this study is the change in tumor-infiltrating immune CD8+ T effector cells at the time of cystectomy compared to pretreatment. This study will use a multiplex CD8/FoxP3/granzyme B IHC assay to monitor the overall influx and activation state of these populations into the tumor. Subsequent immunohistochemical and transcriptional analyses will further characterize the infiltrating T-cell subpopulations.

[redacted]

[redacted]

8.5.2. Tissue Biopsy Collection Requirements

All tumors will have an initial assessment for PD-L1 CPS score for participant stratification. The PD-L1 IHC 22C3 pharmDx assay must be used for PD-L1 CPS score testing, which will be done centrally.

[redacted]

Screening sample and PD-L1 testing will be performed via the sample collected from the TURBT procedure. Tumor tissue must be formalin-fixed, paraffin-embedded and contain a minimum of 20% tumor cells. Tumor block or 20 unstained slides are necessary for the planned analysis to be conducted after the initial PD-L1 assessments.

Mandatory tumor biopsies will be collected as specified below:

- **Screening:** Pretreatment biopsies will be obtained when the participant undergoes TURBT.
  - At sites where the participant had TURBT performed elsewhere, pretreatment biopsy will be obtained from the TURBT or other diagnostic procedure.
  - At study sites where the TURBT is conducted, a portion of the biopsy will also be immediately flash-frozen on dry ice to allow for amino acid metabolite analysis. The remaining tissue will be collected and stored as formalin-fixed, paraffin-embedded samples.

- **Cystectomy:** If a flash-frozen biopsy was obtained during the TURBT and the participant was randomized to Treatment Groups A, B, or C, then a portion of the biopsy at cystectomy will also be immediately flash-frozen on dry ice to allow for amino acid metabolite analysis. This will be done during the grossing period with a maximum of 30 minutes of ischemic time. If a flash-frozen biopsy was not obtained during TURBT, one is not needed during cystectomy. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

8.6. Unscheduled Visits

Unscheduled study visits may occur at any time if medically warranted. Any assessments performed at those visits should be recorded in the eCRF.

8.7. End of Treatment and/or Early Termination

When the participant permanently discontinues study treatment, whether the participant is terminating the study early or the participant has completed the study, the precystectomy visit should be conducted. If the treatment visit is within 2 weeks of the cystectomy visit, then all the evaluations for both the treatment visit and the precystectomy visit should be conducted. 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 cystectomy and the scheduled 90-day safety follow-up visit. All participants will have the safety follow-up visits at 30 days after radical cystectomy (or last dose if cystectomy procedure is not performed) and 90 days after cystectomy. In the event the participant does not undergo a cystectomy, the follow-up visit will be 90 days after last dose of study treatment. If radical cystectomy is not performed, then AEs and SAEs must be reported up until 1) at least 28 days after the last dose of study treatment or the start of a new anticancer therapy or 2) until toxicities resolve, return to baseline, or are deemed irreversible, whichever is longer. Reasonable efforts should be made to have the participant return for the follow-up visit and report any AEs that may occur during this period. If the participant cannot return to the site for the safety follow-up visit (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 eCRF.

If a participant is scheduled to begin a new anticancer therapy before the end of the 30- or 90-day safety follow-up period, then the safety follow-up visit should be performed before the new anticancer therapy is started.

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

9.1. Definition of Adverse Event

Adverse Event Definition
• An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not it is considered drug-related. • An AE can therefore be any unfavorable or unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study treatment.
Additional Guidance for Events Meeting the Adverse Event Definition
• Any safety assessments (eg, ECG, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease) are to be reported as an AE. • Abnormal laboratory test results are to be reported as an AE if they are considered clinically meaningful, induce clinical signs or symptoms, require concomitant therapy, or require changes in study drug. Whenever possible, a diagnosis (eg, anemia, thrombocytopenia) should be recorded in the eCRF rather than the abnormal laboratory result (eg, low hemoglobin, platelet count decreased). • Exacerbation of a chronic or intermittent pre-existing condition/disease, including either an increase in the frequency and/or intensity of the condition, is to be reported as an AE. • New conditions detected or diagnosed after the start of study treatment administration even though they may have been present before the start of the study are to be reported as AEs. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction are to be reported as AEs. • Signs and/or symptoms from dosing errors of a study drug/treatment (eg, overdose) or a concomitant medication are to be reported as an AE. • "Lack of efficacy," "disease progression," or "failure of expected pharmacological action" will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. • [redacted] The SAE and AE reporting from the TURBT procedure will be recorded as part of medical history. A secondary consent specific to the treatment arm is also signed prior to the patient starting study treatment. • Pre-existing diseases or conditions with expected fluctuations in signs or symptoms should be reported as an AE only if the investigator judges the fluctuation to have worsened more than expected during study participation.

9.2. Definition of Serious Adverse Event

If an event is not an AE per the 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 occurs. 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 (involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment or planned surgery (eg, stent replacement, hip surgery) is not considered an SAE. Hospitalization for medical interventions in which no unfavorable medical occurrence occurred (ie, elective procedures or routine medical visits) are not considered SAEs.
d. Results in persistent or significant disability/incapacity • The term "disability" means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle), that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Is an important medical event An important medical event is an event that may not result in death, be immediately life-threatening, or require hospitalization but may be considered serious when, based on appropriate medical judgment, the event may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in the above definition. Examples of such events include new invasive or malignant cancers, 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, or suspected transmission of an infectious agent via a medicinal product. Secondary malignancies should always be considered as 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 diagnostic 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 Adverse Event Form in the eCRF.
- There may be rare 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 by the site staff on the copies of the medical records before submission. These records can be submitted to Incyte Pharmacovigilance by email/fax per the contact information listed in the Study Reference Manual or as per SAE completing guidelines
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate AE/SAE.

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

- 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 (including study drug[s] and/or reference therapy): suspected (yes) or not suspected (no). See below for further instructions on the assessment of causality.
- The start and end dates, unless unresolved at the final safety follow-up visit.
- The action taken with regard to study drug and/or reference therapy 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/reference therapy must be assessed (ie, for the Incyte product[s] and for the other product[s] that are 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 medical 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 possibility of a relationship.
- The investigator will also consult the RSI in the IB or Product Information for study drug/treatment, or marketed products, respectively, in making his/her assessment.
- Alternative causes, such as underlying or concurrent 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 based on the available information 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 submit 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.
- Once an AE is detected, it should be followed in the AE eCRFs until it has resolved or until it is judged to be permanent; assessment should be made at each visit (or more frequently if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat the event, and the outcome.
- When the severity of an AE changes over time for a reporting period (eg, between visits), each change in severity will be reported as a separate AE until the event resolves.

- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor with a copy of any postmortem findings, including histopathology
- Updated SAE information will be recorded in the originally completed eCRF and reported to Incyte Pharmacovigilance (either via email/fax if paper SAE form is used or in the SAE EDC CRF) until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up.
- Any updated SAE data (including SAEs being downgraded to nonserious) will be submitted to the sponsor (or designee) within 24 hours of receipt of the information.

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 90 days after the last dose of study treatment ***or*** until 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. 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 SAE information after the safety follow-up visit or 90 days after the last dose of study drug/treatment. If the investigator learns of any SAE, including death, at any time after a participant has been withdrawn from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, then 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 AESIs (as defined in Section 9.5) will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

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

If the SAE is not documented in the Reference Safety Information of the respective IB (retifanlimab IB, epacadostat IB, INCAGN02385 IB, and 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 expedited 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 an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate, according to local requirements.

Serious Adverse Event Reporting

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

9.5. Adverse Events of Special Interest

No specific AEs are expected to be sent to the sponsor within an expedited manner outside the AEs that meet the seriousness category as described in Section 9.2. Adverse events of special interest will include irAEs that will be coded according to MedDRA along with all other AEs, as well as postsurgical complications using Clavien-Dindo Grading System (see Appendix D). Immune response AEs will be tabulated by preferred term and system organ class and by events of Grade 3 or higher.

As suggested by CIOMS VI, Management of Safety Information from Clinical Trials (CIOMS 2005), an AESI is described as follows: an AESI (serious or nonserious) is one of scientific and medical concern specific to the sponsor's product or program, which requires ongoing monitoring and rapid communication by the investigator to the sponsor. Such events may require further investigation in order to characterize and understand them. Depending on the nature of the event, rapid communication by the trial sponsor to other parties may also be necessary (eg, regulators).

CIOMS VI further elaborates that an AESI is a noteworthy event for the particular product or class of products that a sponsor wishes to monitor carefully. It could be serious or nonserious (eg, hair loss, loss of taste, impotence) and could include events that might be potential precursors or prodromes for more serious medical conditions in susceptible individuals. Such events should be described in Protocols or Protocol Amendments, and instructions should be provided for investigators as to how and when they should be reported to the sponsor.

The description of the AESI should include the following:

- The definition of the event
- Whether it is a measurable quantity. If so, how will the measurement be done?
- Whether it is a clinical event. If so, how will it be confirmed?

AESIs should be captured in the eCRF. Data management should be alerted to the presence of any AESIs so that the correct form can be included. If special communication needs are required (eg, reporting within a specific timeframe), the investigator will need to determine and describe the mechanism (paper form or a trigger in the eCRF for a new form to be generated in the system to collect additional data) and exact timeframe (number of days) for expedited reporting.

9.6. Emergency Unblinding of Treatment Assignment

Not applicable.

9.7. Pregnancy

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

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

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

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 its designee.

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

9.8. Warnings and Precautions

Special warnings or precautions for the study treatment, derived from safety information collected by the sponsor or its designee, are presented in the IB for each study drug (retifanlimab IB, epacadostat IB, INCAGN02385 IB, and 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.

9.9. Product Complaints

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

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

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

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

10. STATISTICS

10.1. Sample Size Determination

Approximately 81 participants will be enrolled in this study. Per treatment group, the evaluable paired biopsies in Table 22 are needed.

Table 22: Sample Size Determination

Treatment Group	Number of Participants	Estimated Number of Paired Biopsies
A: Epacadostat plus retifanlimab	18	16
B: Retifanlimab monotherapy	18	16
C: Epacadostat monotherapy	9	8
D: Retifanlimab plus INCAGN02385	18	16
E: Retifanlimab plus INCAGN02385 plus INCAGN02390	18	16
Total	81	72

For each group, the power consideration is based on the change from baseline in CD8+ T effector cells. Eight evaluable paired biopsies in Treatment Group C will provide 80% power to detect a mean change from baseline in the degree of 1 standard deviation of the change variable at 2-sided alpha = 0.10 level.

For Treatment Groups A and B, the 16 evaluable paired biopsies will provide > 95% power to detect the same degree of the mean change for the entire group and 80% power at 2-sided alpha = 0.10 level for both PD-L1 subgroups combined (PD-L1 CPS < 10 and PD-L1 CPS ≥ 10).

10.2. Populations for Analysis

Table 23 presents the populations for analysis.

Table 23: Populations for Analysis

Population	Description
Translational evaluable population[a]	The translational evaluable population includes all participants enrolled in the study who have the following: • Completed a baseline scan. • Received at least 4 weeks of neoadjuvant study treatment. – Treatment Groups A and C need to receive epacadostat dosing up to and including day of surgery. • Provided evaluable paired biopsies (pretreatment core biopsy and surgical resection biopsy).
Safety evaluable	The safety evaluable population includes all enrolled participants who received at least 1 dose of study drug. All safety analyses will be conducted using the safety evaluable population.
Efficacy evaluable	The efficacy evaluable population will include participants with efficacy endpoint data available. • For endpoints that are change from baseline, participants with assessments both at baseline and at the time of cystectomy will be included. • For endpoints that are evaluated at the time of cystectomy, participants with assessments at cystectomy will be included.
[redacted]/pharmacodynamic evaluable	[redacted] The pharmacodynamic evaluable population will include all participants who received at least 1 dose of any study treatment and provided at least 1 plasma sample (1 pharmacodynamic measurement).

[a] The sponsor determines whether the samples are sufficiently evaluable for primary, secondary, [redacted] analysis.

10.3. Level of Significance

The level of significance for the primary end point is 2-sided 10%. The mean change from baseline will be assessed using a paired t-test in each treatment group for the primary endpoint. The significance of all secondary [redacted] analyses will be assessed at 2-sided 10% level. All CIs will be reported at 80%. No multiplicity control will be applied to the assessments.

10.4. Statistical Analyses

10.4.1. Primary Analysis

For each treatment group, the primary endpoint is change from baseline in immune (CD8+ T effector) cells. The mean paired difference will be calculated as [post treatment] – [pretreatment]. The difference will be testing using a paired t-test with n – 1 degrees of freedom, where n is the number of evaluable paired samples. The CI for the mean paired difference will be reported based on the t-distribution with n – 1 degrees of freedom. A summary of reasons for excluding participants from the analysis will be provided.

10.4.2. Secondary Analysis

Safety and tolerability assessed by monitoring the frequency and severity of AEs, including delay in cystectomy due to AEs.

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 drug) 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. Participants exhibiting clinically notable ECG abnormalities will be listed.

Pathological CR rates as well as major pathological response rates at the time of radical cystectomy will be assessed as secondary endpoints. For pCR, the percentage of participants with ypT0N0, and for major pathological response, the percentage of participants with ypT0/1/a/isN0 in each treatment group, respectively, will be calculated, and its 80% CI will be estimated using the Clopper-Pearson method. Assessments will be performed by the pathologist using the biopsies from radical cystectomy.

10.5. Interim Analysis

No formal interim analysis for evaluating efficacy or futility is planned in this study. Periodic safety reports will be produced in accordance with the DSMB charter (see Section 5.6).

11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

11.1. Investigator Responsibilities

- The Protocol, Protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- The investigator is responsible for ensuring that the safety reports provided by the sponsor are reviewed and processed in accordance with regulatory requirements, the policies and procedures established by the IRB/IEC, and institutional requirements.
- Any amendments to the Protocol will require approval from both Health Authorities and 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 without receiving approval from the sponsor. The investigator must notify the sponsor or its designee in the event of accidental loss or destruction of any study records. If the investigator leaves the institution where the study was conducted, the sponsor or its designee must be contacted to arrange alternative record storage options.

- All eCRF data entered by the site (including audit trail), as well as computer hardware and software (for accessing the data), will be maintained or made available at the site in compliance with applicable record retention regulations. The sponsor will retain the original eCRF data and audit trail.

11.1.1. Identification of the Coordinating Principal Investigator

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

11.2. Data Management

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

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

The sponsor (or designee) will be responsible for:

- 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:

- Recording, or ensuring the recording of, all relevant data relating to the study in the eCRF.
- Delivering, or ensuring the delivery of, all other results, documents, data, know-how, or formulas relating to the study to the sponsor or designee electronically and/or centrally (eg, laboratory data, imaging data, [redacted], photographs, diary data), or as otherwise specified in the Protocol.
- Verifying that data entries are accurate and correct by physically or electronically signing the eCRF.

- Maintaining accurate documentation (source data) that supports the information entered in the eCRF, or sent to a central vendor designated by the sponsor, or as described in other study and data flow manuals.
  - Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
  - 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. Also, current applicable medical records must be available.
- May have responsibility for sending participants' data, either as unique samples, or copies, or photographs, to be evaluated centrally or analyzed centrally, or both, by a qualified vendor designated by the sponsor.
- Permitting study-related monitoring, sponsor audits, IRB/IEC review, and regulatory inspections by providing direct access to source data and other relevant clinical study documents.
  - Monitoring: Qualified representatives of the sponsor or its designee, study monitors, will monitor the study according to a predetermined plan. The investigator must allow the study monitors to review any study materials and participant records at each monitoring visit.
  - Auditing: Qualified representatives of the sponsor or its designee may audit the clinical study site and study data to evaluate compliance with the Protocol, applicable local clinical study regulations, and overall study conduct. The investigator must allow the auditors to review original source records and study documentation for all participants.
  - Regulatory inspection: Regulatory authorities may conduct an inspection of the study and the site at any time during the development of an investigational product. The investigator and staff are expected to cooperate with the inspectors and allow access to all source documents supporting the eCRFs and other study-related documents. The investigator must immediately notify the sponsor when contacted by any regulatory authority for the purposes of conducting an inspection.

11.3. Data Privacy and Confidentiality of Study Records

The investigator and the sponsor or its designee must adhere to applicable data protection laws and regulations. The investigator and the sponsor or its designee are responsible for ensuring that sensitive personal information is handled in accordance with local data protection laws (including but not limited to HIPAA and GDPR) as applicable. Appropriate consent for collection, use and disclosure and/or transfer (if applicable) of personal information must be obtained in accordance with local data protection laws.

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

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 10 years after study completion unless local regulations require otherwise. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

11.4. Financial Disclosure

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

Any new clinical investigators added to the covered clinical study during its conduct must also submit a completed Investigator Financial Disclosure Form. During a covered clinical study, any changes to the financial information previously reported by a clinical investigator must be reported to the sponsor or its designee. At the conclusion of the covered clinical study, the clinical investigators will be reminded of their obligations. In the event that the clinical investigator is not reminded, they nevertheless will remain obligated to report to the sponsor or its designee any changes to the financial information previously reported, as well as any changes in their financial information for a period of 1 year after completion of the covered clinical study.

11.5. Publication Policy

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

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

The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of

multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

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

11.6. Study and Site Closure

The sponsor 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:

All male participants must use a condom from screening through 100 days (in the US) and 190 days (in Europe) after the end of systemic exposure. If a male participant has a partner that is of childbearing potential, the partner should also use contraception through 100 days (in the US) and 190 days (in Europe) after the end of relevant systemic exposure. In addition, male participants must refrain from donating sperm from screening through 100 days (in the US) and 190 days (in Europe) after the end of relevant systemic exposure. Male participants who have had a vasectomy and have received medical assessment of the surgical success qualify as having met the requirement for a highly effective birth control method.

For female participants in the study:

From screening through 100 days (in the US) and 190 days (in Europe) after the last dose of study treatment, women of childbearing potential must have a negative pregnancy test at screening and before the first dose of study treatment on Day 1, must agree to take appropriate precautions to avoid pregnancy (with at least 99% certainty), and refrain from oocyte donation.

The following methods that can achieve a failure rate of < 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
  - oral
  - intravaginal
  - transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation
  - oral
  - injectable
  - implantable[a]
- Intrauterine device[a]
- Intrauterine hormone-releasing system[a]
- Bilateral tubal occlusion[a]
- Vasectomized partner[b]
- Sexual abstinence[c]

  Note: Hormonal contraception may be susceptible to interaction with study drugs, which may render hormonal contraception ineffective, and hormonal methods are not methods that can achieve in this study a failure rate of < 1% per year.

Note: Female participants should also refrain from oocyte donation through 100 days (in US) and 190 days (in Europe) after the last dose of study treatment.

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

[b] 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.

[c] 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 Trials Facilitation and Coordination Group 2020.

APPENDIX B. THE AMERICAN JOINT COMMITTEE ON CANCER STAGING SYSTEM 8TH EDITION, 2017

Primary tumour (T)	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Ta	Non-invasive papillary carcinoma
Tis	Carcinoma in situ: 'flat tumour'
T1	Tumour invades subepithelial connective tissue
T2	Tumour invades muscularis propria
pT2a	Tumour invades superficial muscularis propria (inner half)
pT2b	Tumour invades deep muscularis propria (outer half)
T3	Tumour invades perivesical tissue
pT3a	Microscopically
pT3b	Macroscopically (extravesical mass)
T4	Tumour invades any of the following: prostatic stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall
T4a	Tumour invades prostatic stroma, uterus, vagina
T4b	Tumour invades pelvic wall, abdominal wall
Regional lymph nodes (N)	
NX	Lymph nodes cannot be assessed
N0	No lymph node metastasis
N1	Single regional lymph node metastasis in the true pelvis (hypogastric, obturator, external iliac or presacral lymph node)
N2	Multiple regional lymph node metastasis in the true pelvis (hypogastric, obturator, external iliac or presacral lymph node metastasis)
N3	Lymph node metastasis to the common iliac lymph nodes
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis

APPENDIX C. CRITERIA DEFINING CISPLATIN INELIGIBILITY

Proposed Working Group Eligibility Criteria for Clinical Trials Enrolling Patients With Metastatic Urothelial Carcinoma "Unfit" for Cisplatin-Based Chemotherapy

Eligibility Criteria (at least 1 of the following):
WHO or ECOG PS of 2 or Karnofsky PS of 60%-70%
Creatinine clearance (calculated or measured) < 60 mL/min
CTCAE v4 ≥ Grade 2 audiometric hearing loss
CTCAE v4 ≥ Grade 2 peripheral neuropathy
NYHA Class III heart failure

Source: Galsky et al 2011.

APPENDIX D. CLAVIEN-DINDO GRADING SYSTEM FOR THE CLASSIFICATION OF SURGICAL COMPLICATIONS

Grades	Definitions
I	Any deviation from the normal postoperative course without the need for pharmacologic treatment or surgical, endoscopic, and radiologic interventions. Acceptable therapeutic regimens are drugs such as antiemetics, antipyretics, analgesics, diuretics, and electrolytes, and physiotherapy. This grade also includes would infections opened at the bedside.
II	Requiring pharmacologic treatment with drugs other than those allowed for Grade 1 complications. Blood transfusions and total parental nutrition are also included.
III	Requiring surgical, endoscopic, or radiologic intervention.
IIIa	Intervention not under general anaesthesia.
IIIb	Intervention under general anaesthesia.
IV	Life-threatening complication (including central nervous system complications; brain haemorrhage, ischaemic stroke, subarachnoid bleeding but excluding transient ischaemic attacks) requiring intermediate care/intensive care unit management.
IVa	Single-organ dysfunction (including dialysis).
IVb	Multiorgan dysfunction.
V	Death of a patient.
Suffix "d"	If the patient suffers from a complication at the time of discharge, the suffix "d" (for disability) is added to the respective grade of complication. This label indicates the need for a follow-up to evaluation the complication fully.

Source: Dindo et al 2004.

APPENDIX E. STUDIES AND PARTICIPANT GROUPS INCLUDED IN SAFETY ANALYSIS

Below is a brief overview of the studies and treatment groups included for the analysis of safety in support of Protocol INCB 24360-901.

Study Drug	Study Number	Title	Treatment Groups Included	Participant Groups
Epacadostat	INCB 24360-101	A Phase I, Open-Label, Dose-Escalation Study to Determine the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of INCB024360 in Patients with Advanced Malignancies	1) INCB024360 50 mg QD 2) INCB024360 50 mg BID 3) INCB024360 100 mg BID 4) INCB024360 300 mg BID	All participants who received at least 1 dose of INCB024360
	INCB 24360-210	A Randomized, Open-Label, Phase 2 Study of the IDO inhibitor INCB024360 versus Tamoxifen for Subjects with Biochemical-Recurrent-Only Epithelial Ovarian Cancer, Primary Peritoneal Carcinoma, or Fallopian Tube Cancer Following Complete Remission with First-Line Chemotherapy	1) INCB024360 600 mg BID	All participants who received at least 1 dose of INCB024360
	INCB 24360-303	A Phase 3 Randomized, Double-Blind Clinical Study of Pembrolizumab + Epacadostat vs Pembrolizumab + Placebo as a Treatment for Recurrent or Progressive Metastatic Urothelial Carcinoma in Patients who have Failed a First-Line Platinum-containing Chemotherapy Regimen for Advanced/Metastatic Disease	1) INCB024360 100 mg BID + pembrolizumab 200 mg IV Q3W	All participants who received at least 1 dose of INCB024360 as a monotherapy or in combination with pembrolizumab
	INCB 24360-307	A Phase 3 Randomized, Double- blind Trial of Pembrolizumab (MK-3475) in Combination with Epacadostat (INCB024360) or Placebo in Participants with Cisplatin ineligible Urothelial Carcinoma	1) INCB024360 100 mg BID + pembrolizumab 200 mg IV Q3W	All participants who received at least 1 dose of INCB024360 as a monotherapy or in combination with pembrolizumab
Retifanlimab	INCMGA 0012-101	A Phase 1 Study of the Safety, Tolerability, and Pharmacokinetics of INCMGA00012 (Formerly MGA012) in Patients With Advanced Solid Tumors	1) INCMGA00012 3 mg/kg Q2W 2) INCMGA00012 3 mg/kg Q4W 3) INCMGA00012 10 mg/kg Q2W 4) INCMGA00012 10 mg/kg Q4W 5) INCMGA00012 375 mg Q3W 4) INCMGA00012 500 mg Q4W 4) INCMGA00012 750 mg Q4W	All participant who received at least 1 dose of INCMGA00012 underweight-based dosing or flat-dosing schemes

Study Drug	Study Number	Title	Treatment Groups Included	Participant Groups
	INCMGA 0012-102	A Phase 1b Study of INCMGA00012 in Combination With Other Therapies in Patients With Advanced Solid Tumors	1) INCMGA00012 500 mg Q4W + INCB24360 50 mg BID 2) INCMGA00012 500 mg Q4W + INCB24360 100 mg BID 3) INCMGA00012 500 mg Q4W + INCB24360 300 mg BID 4) INCMGA00012 500 mg Q4W + INCB24360 400 mg BID 5) INCMGA00012 500 mg Q4W + INCB24360 600 mg BID 6) INCMGA00012 500 mg Q4W + INCB24360 900 mg BID 7) INCMGA00012 500 mg Q4W + INCB24360 1200 mg BID	All participants who received at least 1 dose of INCMGA00012 as a monotherapy or in combination with INCB24360
	INCMGA 0012-201	A Phase 2 Study of INCMGA00012 in Participants With Metastatic Merkel Cell Carcinoma	1) INCMGA00012 500 mg Q4W	All participants who received at least 1 dose of INCMGA00012
	INCMGA 0012-202	A Phase 2 Study of INCMGA00012 in Participants With Squamous Carcinoma of the Anal Canal Who Have Progressed Following Platinum-Based Chemotherapy	1) INCMGA00012 500 mg Q4W	All participants who received at least 1 dose of INCMGA00012
	INCMGA 0012-203	A Phase 2 Study of INCMGA00012 (PD-1 Inhibitor) in Participants With Selected Solid Tumors (POD1UM-203)	1) INCMGA00012 500 mg Q4W	All participants who received at least 1 dose of INCMGA00012
INCAGN02385	INCAGN 2385-101	A Safety and Tolerability Study of INCAGN02385 in Select Advanced Malignancies	INCAGN02385 25 mg Q2W INCAGN02385 75 mg Q2W INCAGN02385 250 mg Q2W INCAGN02385 350 mg Q2W INCAGN02385 750 mg Q2W	All participants who received at least 1 dose of INCAGN02385
INCAGN02390	INCAGN 2390-101	A Safety and Tolerability Study of INCAGN02390 in Select Advanced Malignancies	INCAGN02390 10 mg Q2W INCAGN02390 30 mg Q2W INCAGN02390 100 mg Q2W INCAGN02390 200 mg Q2W INCAGN02390 400 mg Q2W INCAGN02390 800 mg Q2W INCAGN02390 1600 mg Q2W	All participants who received at least 1 dose of INCAGN02390

Study Drug	Study Number	Title	Treatment Groups Included	Participant Groups
Retifanlimab INCAGN02385 INCAGN02390	INCAGN 2385-201	Study of Combination Therapy With INCMGA00012 (Anti-PD-1), INCAGN02385 (Anti-LAG-3), and INCAGN02390 (Anti-TIM-3) in Participants With Select Advanced Malignancies	Part 1: INCAGN02385 Q2W plus INCAGN02390 Q2W Part 2: INCAGN02385 Q2W plus INCAGN02390 Q2W plus retifanlimab 500 mg Q4W	All participants who received at least 1 dose of INCAGN02385 and INCAGN02390 in Part 1 and all participants who received at least 1 dose of INCAGN02385, INCAGN02390, and retifanlimab in Part 2

QD = once daily; BID = twice daily; IV = intravenous; Q3W = every 3 weeks; Q4W = every 4 weeks.

APPENDIX F. CYP1A2, CYP2C8, AND CYP2C19 SUBSTRATES OR OATP1B1 AND OATP1B3 TRANSPORTERS

The medications listed below are prohibited for participants receiving doses of epacadostat ≥ 600 mg BID, and alternatives should be sought. If alternatives cannot be found, the medical monitor should be contacted to discuss whether enrollment is appropriate.

OATP1B1 and OATP1B3 Transporters	**CYP1A2 Substrates**	**CYP2C8 Substrates**	**CYP2C19 Substrates**
• Atorvastatin • Bosentan • Cerivastatin • Danoprevir • Docetaxel • Fexofenadine • Glyburide • Nateglinide • Paclitaxel • Repaglinide • Pitavastatin • Pravastatin • Rosuvastatin • Simvastatin acid • Fimasartan • Glecaprevir • Maraviroc • Tacrolimus • Voxilaprevir	**Sensitive:** • Alosetron • Caffeine • Duloxetine • Melatonin • Pirfenidone • Ramelteon • Selegiline • Tacrine • Tasimelteon • Theophylline • Tizanidine	**Sensitive:** • Repaglinide • Daprodustat • Dasabuvir • Montelukast • Pioglitazone • Rosiglitazone	**Sensitive:** • S-mephenytoin • Lansoprazole • Omeprazole • Tilidine • Pantoprazole • Hexobarbital • Diazepam • Gliclazide • Rabeprazole • Voriconazole • Proguanil

APPENDIX G. COVID-19 PANDEMIC MITIGATION STRATEGIES AND INSTRUCTION

The COVID-19 global pandemic presents challenges to the ongoing conduct of clinical trials. In line with regulatory guidance regarding clinical trial 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 trial, 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.

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 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 in the eCRF.

Participant SARS-CoV-2 Infection and Study Treatment

An event of active SARS-CoV-2 infection by a participant in the study should be reported as an AE or SAE and appropriate medical intervention provided. For participants with active SARS-CoV-2 infection, study treatment should be delayed until the resolution of symptoms and until it is allowable for the participant to return to the clinic per institutional guidelines. Prior to restarting treatment, the participant should be afebrile for 72 hours and the treating physician

should determine that the participant's condition is stable enough to resume study treatment. The study physician should also consider if the participant is SARS-CoV-2 negative (by test) before restarting study treatment if COVID-19 was diagnosed during the trial. The study team should be notified when the study treatment is restarted. Safety monitoring following COVID-19 should be implemented as per institutional guidance or clinical judgment (eg, coagulation factors).

COVID-19 Vaccination

Participants may receive the COVID-19 vaccine as long as it is not a live vaccine, which is prohibited per protocol (see Section 5.2, Exclusion Criterion 20). COVID-19 vaccination will be captured in the eCRF as a concomitant medication. Administration of study treatment may be delayed to ensure vaccination is completed.

Clinical Trial 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 the local laboratory visit(s), the costs of local [proximate] laboratory tests).

APPENDIX H. PROTOCOL AMENDMENT SUMMARY OF CHANGES

Document	Date
Amendment 1:	04 SEP 2020
Amendment 2:	02 FEB 2021
Amendment 3:	10 MAY 2021
Amendment 2-IT:	14 JUL 2021
Amendment 4:	01 MAR 2022

Amendment 4 (01 MAR 2022)

Overall Rationale for the Amendment:

The primary purpose of this amendment is to add 2 new treatment groups to the Protocol (retifanlimab plus INCAGN02385 as well as retifanlimab plus INCAGN02385 plus INCAGN02390) and to clarify the radiologic tools used for tumor imaging.

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

   Description of change: Revised the number of evaluable participants, the number of treatment groups, and the number of participants in each treatment group.

   Rationale for change: To provide updated information based on the addition of 2 new treatment groups.

2. **Section 1, Protocol Summary (Table 2: Key Study Design Elements; Figure 1: Study Design Schema; Table 6: Schedule of Activities for Participants Receiving Retifanlimab Plus INCAGN02385 [Treatment Group D]; Table 7: Schedule of Activities for Participants Receiving Retifanlimab Plus INCAGN02385 Plus INCAGN02390 [Treatment Group E]; Section 2.1.1, Scientific Rationale for Study Design; Section 2.1.2, Treatment Group Rationale; Section 2.1.6, INCAGN02385; Section 2.1.6.1, Rationale for INCAGN02385 Dose; Section 2.1.7, INCAGN02390; Section 2.1.7.1, Rationale for INCAGN02390 Dose; Section 2.1.8, Combination of Retifanlimab Plus INCAGN02385; Section 2.1.9, Combination of Retifanlimab Plus INCAGN02385 Plus INCAGN02390; Section 2.1.10, Combination of Retifanlimab Plus INCAGN02385 and Combination of Retifanlimab Plus INCAGN02385 Plus INCAGN02390; Section 2.2.1, Monotherapy Risks; Section 2.2.2, Combination Therapy Risks; Section 2.2.3.1.2, INCAGN02385 and INCAGN02390 Monotherapy and in Combination With Retifanlimab (Table 10: Grade 2 or Higher Immune-Related TEAEs for Studies With INCAGN02385, INCAGN02390, and Retifanlimab); Section 2.2.4, Benefits; Section 3, Objectives and Endpoints (Table 10: Objectives and Endpoints); Section 4.1, Overall Design; Section 5.2, Exclusion Criteria; Section 5.5, Replacement of Participants; Section 6.1, Study Treatment Administered (Table 13: Study Treatment and Treatment Group Information); Section 6.2, Handling, Preparation, and Accountability; Section 6.3, Measures to Minimize Bias: Randomization and Blinding; Section 6.4, Study Treatment Compliance; Section 6.5, Dose Modifications; Section 8.4,**

[redacted] **Immunogenicity Assessments; Section 8.4.1.1, Immunogenicity (Antidrug Antibody) Assessments; Section 9.4, Reporting of Serious Adverse Events; Section 9.8, Warnings and Precautions; Section 10.1, Sample Size Determination; Appendix E, Studies and Participant Groups Included in Safety Analysis**

Description of change: Added information on retifanlimab, INCAGN02385, and INCAGN02390.

Rationale for change: To incorporate the 2 new treatment groups into the Protocol.

3. **Section 1, Protocol Summary (Table 3: Schedule of Activities for Participants Receiving Epacadostat Plus Retifanlimab [Treatment Group A]; Table 4: Schedule of Activities for Participants Receiving Retifanlimab Monotherapy [Treatment Group B]; Table 5: Schedule of Activities for Participants Receiving Epacadostat Monotherapy [Treatment Group C])**

   Description of change: Added that treatment cycle is Q4W, revised radiologic tumor assessments to remove PET/CT and change wording to "CT/MRI of the abdomen and pelvis and CT scan of the thorax (RECIST v1.1)," [redacted]

   Rationale for change: To clarify the duration of a treatment cycle, update the criteria for imaging for MIBC, [redacted]

4. **Section 1, Protocol Summary (Table 3: Schedule of Activities for Participants Receiving Epacadostat Plus Retifanlimab [Treatment Group A]; Table 4: Schedule of Activities for Participants Receiving Retifanlimab Monotherapy [Treatment Group B]; Table 5: Schedule of Activities for Participants Receiving Epacadostat Monotherapy [Treatment Group C]; Section 8.3.5, Laboratory Assessments (Table 18: Required Laboratory Analytes); Section 8.3.5.1, Pregnancy Testing**

   Description of change: Revised pregnancy testing so women of childbearing potential only require a serum test at screening and at precystectomy. A urine or serum pregnancy test is required before cystectomy, before the first dose on D1 of every cycle, and at the 30-day safety follow-up visit; in Europe, a urine or serum pregnancy test is also required 190 days after the last dose of study treatment. Pregnancy tests (serum or urine) should be repeated if required by local regulations.

   Rationale for change: Discrepancy in the language for pregnancy testing requirements within the sections and pregnancy testing requirement in Europe.

5. **Section 1, Protocol Summary (Table 4: Schedule of Activities for Participants Receiving Retifanlimab Monotherapy [Treatment Group B]; Section 8.1.4, Distribution of Reminder Cards**

   Description of change: Added information on distribution of reminder cards.

   Rationale for change: Clarification.

6. **Section 2.1.3, Retifanlimab; Section 2.1.3.1, Rationale for Retifanlimab Dose; Section 2.1.4, Epacadostat; Section 2.1.4.1, Rationale for Epacadostat Dose; Section 2.1.5, Combination of Epacadostat Plus Retifanlimab; 2.2.1.1, Retifanlimab; Section 2.2.1.2, Epacadostat; Section 2.2.2.1, Epacadostat and Retifanlimab**

   Description of change: Updated rationale for treatment as well as dose finding for retifanlimab, epacadostat, and the combination of retifanlimab and epacadostat.

   Rationale for change: To provide updated information from the IB and simplify the information in the Protocol.

7. **Section 2.1.1, Scientific Rationale for Study Design; Section 8.5.1, Timing of Assessments**

   Description of change: Removed PanCK as part of the description of the multiplex IHC assay utilized in this study.

   Rationale for change: To correct information on the multiplex assay utilized.

8. **Section 2.2.3, Risks of Delayed Cystectomy; Section 2.2.3.1, Treatment-Emergent Adverse Events of Special Interest; Section 2.2.3.1.2, INCAGN02385 and INCAGN02390 Monotherapy and in Combination With Retifanlimab; Section 6.5.6, Criteria for Permanent Discontinuation of Study Drug**

   Description of change: Timeline for delay in radical cystectomy changed from > 12 weeks from TURBT to > 11 weeks from end of neoadjuvant chemotherapy.

   Rationale for change: Supportive data demonstrate that a compromise in patient outcome occurs if those with no neoadjuvant treatment have delays > 12 weeks from TURBT and those with neoadjuvant treatment have delays > 11 weeks from end of treatment.

9. **Section 4.1, Overall Design**

   Description of change: Clarified that PD-L1 testing will be done centrally and not locally.

   Rationale for change: Administrative correction.

10. **Section 4.1, Overall Design; Section 6.3, Measures to Minimize Bias: Randomization and Blinding**

    Description of change: Changed randomization to 2:2:1:2:2.

    Rationale for change: Addition of treatment groups.

11. **Section 5.1, Inclusion Criteria (Criteria 5 and 7)**

    Description of change: Revised Criterion 5 to include "refuse cisplatin therapy (does not apply in France)" and removed Criterion 7 (residual disease after TURBT [eg, surgical opinion, cystoscopy or radiologic presence]).

    Rationale for change: Clarification and the presence of residual disease will be documented but not as a mandatory inclusion criterion.

12. **Section 5.1, Inclusion Criteria (Criterion 10); Appendix A, Information Regarding Effectiveness of Contraceptive Methods**

    Description of change: Clarified that pregnancy/fathering children should be avoided through 100 days after the last dose of study drug in the US and 190 days after the last dose in Europe.

    Rationale for change: Updated CTFG requirements.

13. **Section 5.2, Exclusion Criteria (Table 12: Exclusionary Laboratory Values)**

    Description of change: Removed neutrophil lymphocyte ratio from exclusionary laboratory values, modified the hemoglobin exclusion criterion from < 9 to < 8 g/dL, and incorporated the monoclonal antibody as well as the epacadostat exclusion criteria to apply to the entire study population.

    Rationale for change: Neutrophil lymphocyte ratio was deemed unnecessary, the criteria for hemoglobin exclusion was changed to < 8 g/dL per advice from investigators, and incorporating the exclusion criteria was deemed a safer option for participants and allows for streamlined screening.

14. **Section 5.2, Exclusion Criteria (Table 12: Exclusionary Laboratory Values); Section 6.5.3, Procedures for Participants Exhibiting Immune-Related Adverse Events (Table 15: Dose Modification and Toxicity Management Guidelines for Immune-Related Adverse Events); Section 8.3.5, Laboratory Assessments (Table 18: Required Laboratory Analytes)**

    Description of change: Added troponin I and T exclusionary values and management.

    Rationale for change: Monitoring and management of troponin I and T values with INCAGN02385 and INCAGN02390.

15. **Section 5.6, Data Safety Monitoring Board**

    Description of change: Added language on DSMB evaluation for all treatment groups and specific information for epacadostat-containing arms.

    Rationale for change: Clarification.

16. **Section 6.5, Dose Modifications; Section 6.5.1.2, Epacadostat**

    Description of change: Revised dose modification parameters for the epacadostat treatment groups.

    Rationale for change: Clarification on starting dose options and dose modification with epacadostat alone or in combination with retifanlimab.

17. **Section 6.5.2, Management of Suspected Infusion Reactions (Table 14: Guidelines for Management of Suspected Infusion Reactions)**

    Description of change: Revised description of Grade 1 reaction and added option to not discontinue study treatment permanently in a participant with Grade 3 or 4 reaction if the participant responds to symptomatic therapy or brief interruption of infusion.

    Rationale for change: Clarification and to provide an option to not permanently discontinue therapy in some participants with infusion reactions.

18. **Section 6.5.3, Procedures for Participants Exhibiting Immune-Related Adverse Events (Table 15: Dose Modification and Toxicity Management Guidelines for Immune-Related Adverse Events)**

    Description of change: Updated Table 15 to reflect updated guidelines.

    Rationale for change: To update guidelines on management of irAEs.

19. **Section 6.5.4, Procedures for Participants Exhibiting Drug-Related, Non–Immune-Related Adverse Events (Table 16: Management Guidelines for Drug-Related, Non–Immune-Related Adverse Events)**

    Description of change: Added information on non-irAEs for all treatment groups.

    Rationale for change: Clarification on management of non-irAEs.

20. **Section 6.6.2, Restricted Medications and Procedures; Section 6.6.3, Prohibited Medications and Procedures; Appendix F, CYP1A2, CYP2C8, and CYP2C19 Substrates or OATP1B1 and OATP1B3 Transporters**

    Description of change: Added restricted and prohibited medications for epacadostat treatment groups.

    Rationale for change: To update restricted and prohibited medications.

21. **Section 6.6.3, Prohibited Medications and Procedures; Appendix F, CYP1A2, CYP2C8, and CYP2C19 Substrates or OATP1B1 and OATP1B3 Transporters**

    Description of change: Removed reference to CYP3A4 inhibitors and inducers and moderate CYP3A4 inducers.

    Rationale for change: Current treatments in the protocol do not have an effect on CYP3A4.

22. **Section 8.1.1, Informed Consent Process**

    Description of change: Changed the consent to a prescreen consent and a screen consent for all treatment arms.

    Rationale for change: To simplify the informed consent and screening process.

23. **Section 8.1.3, Interactive Response Technology Procedure**

    Description of change: Added text that site staff will enter PD-L1 CPS status into the IRT during screening and that participants who do not meet inclusion/exclusion criteria will fail screening.

    Rationale for change: Clarification on when entry of PD-L1 CPS status needs to take place.

24. **Section 8.3.5, Laboratory Assessments (Table 18: Required Laboratory Analytes)**

    Description of change: Removed amino acid panel, removed the phrase "only applicable for participants known to be HIV-positive" for HIV screening and management, clarified use of either blood urea nitrogen or urea, added HCO_3 if clinically indicated, and added microscopic examination under urinalysis if blood or protein is abnormal.

    Rationale for change: To remove unnecessary amino acid panel, correct an administrative error, and clarify additional laboratory analytes needed.

25. **Section 8.4, [redacted] Immunogenicity Assessments**

    Description of change: Added clear liquids to be acceptable for fasting state.

    Rationale for change: To clarify what can be consumed if a participant is fasting.

26. [redacted]

27. **Section 8.5.2, Tissue Biopsy Collection Requirements**

    Description of change: Added information on biopsy collection for cystectomy.

    Rationale for change: Clarification.

28. **Section 8.7, End of Treatment and/or Early Termination**

    Description of change: Changed EOT visit to precystectomy visit and stated that if the treatment visit is same as the precystectomy visit due to cystectomy being performed within 2 weeks of the treatment visit, then evaluations for both the treatment visit and the precystectomy visit should be conducted.

    Rationale for change: Clarified that the precystectomy visit can act as the EOT and associated evaluations for both the treatment visit and the precystectomy visit can be performed at the same time if cystectomy is within 2 weeks of the treatment visit.

29. **Section 10, Statistics**

    Description of change: Deleted sections on [redacted] immunogenicity analysis.

    Rationale for change: Sample collection and details on both [redacted]/pharmacodynamics and immunogenicity are described in Section 8.4. They are not part of secondary or formal [redacted] analyses, and description of statistics is not required.

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

    Description of change: Added the 2 new treatment groups, updated the total number of participants, and added that the power calculation is > 95% at a 2-sided alpha level of 0.01.

    Rationale for change: Addition of the 2 new treatment groups and clarity.

31. **Section 10.2, Populations for Analysis (Table 23: Populations for Analysis)**

    Description of change: Separated pharmacodynamic analysis from [redacted].

    Rationale for change: To clarify that both [redacted] pharmacodynamic analyses will be conducted.

32. **Appendix B, CYP Inhibitors and Inducers**

    Description of change: Deleted appendix.

    Rationale for change: No longer needed.

33. **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-IT (14 JUL 2021)

Overall Rationale for the Amendment:

The primary purpose of this amendment is to address Health Authority comments.

1. **Section 5.1, Inclusion Criteria; Section 8.3.5, Laboratory Assessments (Table 15: Required Laboratory Analytes); Appendix A, Information Regarding Effectiveness of Contraceptive Methods**

   Description of change: Extended contraceptive treatment to 5 half-lives in men and women, corresponding to 190 days.

   Rationale for change: Modification in accordance with 2020 Clinical Trials Facilitation and Coordination Group guidance.

2. **Section 6.5.3, Procedures for Participants Exhibiting Immune-Related Adverse Events (Table 13: Dose Modification and Toxicity Management Guidelines for Immune-Related Adverse Events)**

   Description of change: Removed mention of participants with liver metastasis.

   Rationale for change: Participants with metastatic disease are ineligible to participate in the study.

3. **Section 6.6.3, Prohibited Medications and Procedures; Appendix B, CYP3A4 Inhibitors and Inducers**

   Description of change: Removed text and appendix regarding CYP3A4 inhibitors and inducers and moderate CYP3A4 inducers.

   Rationale for change: Not required with current protocol study drugs.

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

Amendment 3 (10 MAY 2021)

Overall Rationale for the Amendment:

The primary purpose of this amendment is to address requested comments and changes from the French Health Authority Review.

1. **Section 5.1, Inclusion Criteria**

   Description of change: Modified inclusion criteria to remove "Participants who refuse cisplatin-based therapy."

   Rationale for change: This type of criterion is not acceptable for France, as there are standard treatments whose efficacy and safety are known.

2. **Section 5.2, Exclusion Criteria**

   Description of change: Added exclusion of participants with a history of allogenic tissue/solid organ transplant.

   Rationale for change: Immunotherapy may be administered to participants on immunosuppressants as part of transplant treatment regimen.

3. **Section 6.5.3, Procedures for Participants Exhibiting Immune-Related Adverse Events (Table 13, Dose Modification and Toxicity Management Guidelines for Immune-Related Adverse Events)**

   Description of change: Modified a more stringent criteria for Grade 2 and Grade 3 or 4 toxicities for hypophysitis (adrenal insufficiency).

   Rationale for change: Updates based on recent ESMO guidelines on management of hypophysitis or adrenal insufficiency from immunotherapy.

4. **Section 5.1 Inclusion Criteria, Appendix A**

   Description of change: Modified to extend contraceptive treatment to 5 half-lives in men and women, corresponding to 190 days.

   Rationale for change: Modification in accordance with recent recommendations of the CTFG 2020 (Clinical Trial Facilitation Group).

5. **Section 5.6, Data Monitoring Committee**

   Description of change: Changed DSMB from independent DSMB to internal DSMB.

   Rationale for change: Clarification to align with the DSMB charter.

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

   Description of change: Added the following as reasons for discontinuation of treatment: "Participants with disease progression or not responding to treatment must discontinue the trial."

   Rationale for change: Clarification that participants who have suspected or confirmed disease progression or not responding to therapy should discontinue from the study treatment.

Amendment 2 (02 FEB 2021)

Overall Rationale for the Amendment:

The sponsor evaluated its strategy in bladder cancer and made a decision to remove pemigatinib from this study. As such, this amendment removes the 3 treatment groups that contain pemigatinib (pemigatinib monotherapy, pemigatinib plus retifanlimab, and pemigatinib followed by retifanlimab). The removal of information on FGFR is reflected throughout the protocol as detailed below.

1. **Section 1, Protocol Summary; Section 2.1.1, Scientific Rationale for Study Design; Section 3, Objectives and Endpoints; Section 6.3, Measures to Minimize Bias: Randomization and Blinding; Section 8.2, Efficacy Assessments; Section 8.5, Pharmacodynamic and Translational Assessments; Section 10.1, Sample Size Determination; Section 10.4.1, Primary Analysis**

   Description of change: Amended the primary endpoint to change from baseline in CD8+ lymphocytes within resected tumor.

   Rationale for change: There is evidence in the literature (Sharma et al 2007) that changes in CD8+ TILs is associated with favorable survival for patients with muscle-invasive bladder cancer. As such, the study will use a multiplex CD8/FoxP3/granzyme B/panCK IHC assay to monitor the overall influx and activation state of these populations into the tumor.

2. **Section 1, Protocol Summary; Section 2, Introduction; Section 3, Objectives and Endpoints; Section 4, Study Design; Section 5, Study Population; Section 6, Study Treatment; Section 8, Study Assessments and Procedures; Section 10, Statistics; Appendices**

   Description of change: Removed the 3 treatment groups that included pemigatinib as well as information on FGFR and revised the estimated number of participants in this study.

   Rationale for change: The sponsor evaluated its strategy in bladder cancer and made a decision to remove pemigatinib from this study.

3. **Section 1, Protocol Summary (Table 3: Schedule of Activities for Participants Receiving Epacadostat + Retifanlimab [Treatment Group A]; Table 4: Schedule of Activities for Participants Receiving Retifanlimab Monotherapy [Treatment Group B]; Table 5: Schedule of Activities for Participants Receiving Epacadostat Monotherapy [Treatment Group C]; Section 8.1.2, Screening Procedures; Section 8.5.2, Tissue Biopsy Collection Requirements**

   Description of change: Clarified that all pretreatment biopsies for PD-L1 testing [redacted] s will be from the initial TURBT procedure only and not a mix of archival biopsies or those from the TURBT procedure.

   [redacted]

4. **Section 1, Protocol Summary (Table 3: Schedule of Activities for Participants Receiving Epacadostat + Retifanlimab [Treatment Group A]; Table 4: Schedule of Activities for Participants Receiving Retifanlimab Monotherapy [Treatment Group B]; Table 5: Schedule of Activities for Participants Receiving Epacadostat Monotherapy [Treatment Group C]; Section 8.5.2, Tissue Biopsy Collection Requirements**

   Description of change: Removed the need for flash-frozen biopsy from pretreatment tissue biopsy samples and made it optional for sites.

   Rationale for change: In discussion with clinicians, it appeared to be not feasible to obtain a fresh biopsy pretreatment when TURBT had recently been conducted. As such, this requirement was removed.

4. **Section 1, Protocol Summary (Table 3: Schedule of Activities for Participants Receiving Epacadostat + Retifanlimab [Treatment Group A]; Table 4: Schedule of Activities for Participants Receiving Retifanlimab Monotherapy [Treatment Group B]; Table 5: Schedule of Activities for Participants Receiving Epacadostat Monotherapy [Treatment Group C]); Section 8.3.5, Laboratory Assessments (Table 15: Required Laboratory Analytes)**

   Description of change: Added lipid panel, changed "Endocrine panel" to "Thyroid panel," and removed PD-L1 testing.

   Rationale for change: Lipid panel was added to the SoA for consistency with other epacadostat trials. Endocrine panel was reworded to be more specific to thyroid function tests. The PD-L1 CPS score will be measured centrally and thus does not need to be included in the laboratory assessments because it does not require collection of a specific specimen.

[redacted]

8. **Section 1, Protocol Summary (Table 3: Schedule of Activities for Participants Receiving Epacadostat + Retifanlimab [Treatment Group A]; Table 4: Schedule of Activities for Participants Receiving Retifanlimab Monotherapy [Treatment Group B]; Table 5: Schedule of Activities for Participants Receiving Epacadostat Monotherapy [Treatment Group C])**

   Description of change: Removed collection of a whole blood sample at screening for translational analyses.

   Rationale for change: A whole blood sample is no longer needed because sufficient analyses can be conducted on plasma samples.

9. **Section 2.1.1, Scientific Rationale for Study Design; Section 8.5.1, Timing of Assessments**

   Description of change: Revised the text to indicate that this study will use a multiplex CD8/FoxP3/granzyme B/panCK IHC assay to monitor the overall influx and activation state of these populations into the tumor.

   Rationale for change: The revision of the primary endpoint to change from baseline in CD8+ lymphocytes necessitated a change in the panel to be used to measure the primary endpoint as well as other translational endpoints.

10. [redacted]

7. **Section 2.1.6, Rationale for Epacadostat Dose; Section 8.5.2, Tissue Biopsy Collection Requirements**

   Description of change: Clarified that flash-frozen biopsy samples will be obtained at some sites during TURBT and at all sites during radical cystectomy.

   Rationale for change: Several centers will have participants who undergo TURBT at a different institution and thus will not be able to obtain a flash-frozen biopsy, only formalin-fixed, paraffin-embedded slides. Therefore, obtaining a pretreatment flash-frozen biopsy will be optional from sites that perform both TURBT and radical cystectomy.

8. **Section 2.2.1.1, Retifanlimab; Section 2.2.2.1, Epacadostat and Retifanlimab**

   Description of change: Updated information on exposure to epacadostat and retifanlimab.

   Rationale for change: Updated information in the Investigator's Brochure of each compound from current ongoing trials.

9. **Section 2.2.3.1, Treatment-Emergent Adverse Events of Special Interest (Table 6: Summary of TEAOSI for Select Studies With Retifanlimab and Epacadostat That Occurred Within the First 12 Weeks of Treatment; Table 7: Grade 2 or Higher Immune-Related TEAEs for Studies With Retifanlimab and Epacadostat [Multiple Tumor Types])**

   Description of change: Updated background information on TEAOSI with retifanlimab and epacadostat.

   Rationale for change: Updated analysis conducted based on data from the latest Investigator's Brochure for each compound. The original analysis was conducted based on the previous version of each Investigator's Brochure.

10. **Section 2.2.5, Benefit/Risk Assessment During the COVID-19 Pandemic; Appendix H, COVID-19 Pandemic Mitigation Strategies and Instruction**

    Description of change: Added text to address the risk/benefit of participating in this study during the COVID-19 pandemic. Appendix H outlines guidance to sites for potential disruptions that may occur during the COVID-19 pandemic.

    Rationale for change: To provide guidance and instruction to investigators and participants for disruptions to the conduct of the study that may occur as a result of the COVID-19 pandemic.

11. **Section 4.1, Overall Design; Section 8.5.2, Tissue Biopsy Collection Requirements**

    Description of change: Amended PD-L1 testing to be central testing as opposed to local or central testing.

    Rationale for change: The sponsor wanted to accurately reflect the PD-L1 CPS score and minimize potential discordance due to local testing; therefore, all samples will be centrally tested for PD-L1 CPS score.

[redacted]

14. **Section 5.2, Exclusion Criteria (Criterion 14)**

    Description of change: Added criterion to exclude participants with known or suspected COVID-19 infection.

    Rationale for change: Recommendation from clinical advisors to clarify that active or suspected infection with COVID-19 should be an exclusion criteria.

[redacted]

16. **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 (04 SEP 2020)

Overall Rationale for the Amendment:

The primary purpose of this amendment is to address regulatory comments regarding eligibility criteria, secondary objective and endpoints, withdrawal criteria, and study conduct and additional feedback from investigators to clarify several error and omissions.

1. **Title Page; Section 1, Protocol Summary (Table 1: Primary and Secondary Objectives and Endpoints; Table 2: Key Study Design Elements); Section 2.1, Study Rationale; Section 3, Objectives and Endpoints (Table 3: Objectives and Endpoints); Section 4.1, Overall Design**

   Description of change: Removed "Cisplatin-Ineligible" from and added "…Who Are Cisplatin-Ineligible or Refuse Cisplatin Therapy and…" and added "(Optimus)" to study title. Edited study participants to include those refusing cisplatin therapy.

   Rationale for change: Clarification that participants who refuse cisplatin therapy are also included.

2. **Section 1, Protocol Summary (Table 1: Primary and Secondary Objectives and Endpoints); Section 3, Objectives and Endpoints (Table 11: Objectives and Endpoints);** [redacted]

   Description of change: Added preliminary efficacy as a secondary objective and the following as secondary endpoints to Table 1 and Table 11:

   - pCR rate, defined as percentage of participants with ypT0N0 in each treatment group.
   - Major pathological response, defined as residual ypT0/1/a/isN0M0.

   [redacted]

2. **Section 1, Protocol Summary (Table 3: Schedule of Activities for Participants Receiving Pemigatinib Monotherapy [Group A]; Table 4: Schedule of Activities for Participants Receiving Pemigatinib + Retifanlimab [Group B]; Table 5: Schedule of Activities for Participants Receiving Pemigatinib Monotherapy × 2 Weeks Followed by Retifanlimab [Group C]; Table 6: Schedule of Activities for Participants Receiving Epacadostat + Retifanlimab [Group D]; Table 7: Schedule of Activities for Participants Receiving Retifanlimab Monotherapy [Group E]; Table 8: Schedule of Activities for Participants Receiving Epacadostat Monotherapy [Group F]); Section 10.4.2, Secondary Analysis**

   Description of change: Added that major pathological response rates at the time of radical cystectomy will be assessed as a secondary endpoint in addition to pathological CR rates. [redacted] Moved Tumor Tissue Sampling from "Other Assessments" to "Efficacy Assessments." Also clarified the tumor tissue requirements in that there will be 3 tissue requirements (TURBT archival, screening period, and radical cystectomy) for all the treatment groups.

   Rationale for change: To clarify the analysis of major pathological response.

3. **Section 8.2.1, Pathological Complete Response, Major Pathological Response,** [redacted]

   Description of change: Added that major pathological response is defined as residual ypT0/1/a/isN0M0 on the basis of histological evaluation of the TURBT and cystectomy samples. [redacted]

   Rational for change: To clarify the definition of major pathological response.

4. **Section 1, Protocol Summary (Table 3: Schedule of Activities for Participants Receiving Pemigatinib Monotherapy [Group A]; Table 4: Schedule of Activities for Participants Receiving Pemigatinib + Retifanlimab [Group B]; Table 5: Schedule of Activities for Participants Receiving Pemigatinib Monotherapy × 2 Weeks Followed by Retifanlimab [Group C]; Table 6: Schedule of Activities for Participants Receiving Epacadostat + Retifanlimab [Group D]; Table 7: Schedule of Activities for Participants Receiving Retifanlimab Monotherapy [Group E]; Table 8: Schedule of Activities for Participants Receiving Epacadostat Monotherapy [Group F])**

   Description of change: For Treatment Groups A, B, D, E, and F:

   - Added Cycle 3 Day 1, because study treatment is 4 to 10 weeks, allowing for Cycle 3 to start but not complete a cycle (maximum 2 weeks).
   - Cycle 3 Day 1 assessments are similar to Cycle 2 Day 1 assessments for each treatment group. Also clarified Cycle 3 is a maximum of 2 weeks of therapy.
   - Clarified corresponding [redacted]/ADA draws.

   For Treatment Groups A, B, and C: Removed pre-cystectomy ophthalmology eye exam.

For treatment groups D, F: Removed column C1D15 as no tests will be performed then

For Treatment Group C: Clarified that retifanlimab is dispensed in Cycle 1 Day 15 and Cycle 2 Day 15 as well as clarified corresponding [redacted]/ADA draws.

For all treatment groups: Added PD-L1 testing in addition to the FGFR testing. Also added pathological tumor assessment under efficacy assessments.

For all treatment groups: Clarified that 30-day follow-up is for 30 days after cystectomy or after last dose of drug if cystectomy is not performed.

For all treatment groups: Limited postsurgical safety assessments to be performed 30 days after cystectomy and removed 90-day post-cystectomy assessment.

Rationale for change: Clarification based on medical feedback.

5. **Section 8.3.8, Postsurgical Criteria for Adverse Events; Section 8.8.1, Safety Follow-Up**

   Description of change: Removed 90-day post-surgical complications assessment and limited it to 30-day. Overall safety assessment remains at 30 days post cystectomy and at 90 days post last dose.

   Rationale for change: Most publications support a 30-day follow-up and not 90-day follow-up after cystectomy.

6. **Section 8.4, [redacted] Immunogenicity Assessments (Table 21: Timing of [redacted] Antidrug Antibody Serum Sample Collection for Retifanlimab; [redacted]**

   Description of change: Clarified [redacted] ADA draws, and clarified plasma collection time and plasma draws for oral drugs pemigatinib or epacadostat in all treatment groups.

   Rationale for change: For clarification and to decrease participant burden.

7. [redacted]

8. **Section 2.1.1, Scientific Rationale for Study Design**

   Description of change: Added surgical extirpation and cystectomy data from SEER-Medicare analysis.

   Rationale for change: To add a reference detailing the typical time to schedule cystectomies.

9. **Section 5.2, Exclusion Criteria (Criteria 24); Section 6.6.3, Prohibited Medications; Appendix H, CYP1A2, CYP2C8, and CYP2C19 Substrates**

   Description of change: For participants who will receive epacadostat, added the following criteria:

   a. Concomitant use of medications that are known to be substrates of CYP1A2, CYP2C8, or CYP2C19 with narrow therapeutic window are prohibited.
   b. Patients who are receiving or required to receive medications that are known to be UGT1A9 inhibitor.

   Added Appendix H CYP1A2, CYP2C8 and CYP2C19 substrates listing prohibited medications for participants receiving doses of epacadostat greater than 300 mg BID. Also, participants should avoid caffeine consumption.

   Rationale for change: To exclude participants who are receiving medications that may cause potential drug-drug interactions.

10. **Section 6, Study Treatment (Table 13: Study Treatment Information)**

    Description of change: Clarified that for Treatment Group C, retifanlimab is first administered on Cycle 1 Day 15 to correspond with the schedule of assessment Table 5.

    Rationale for change: Clarification of retifanlimab administration for Treatment Group C.

11. **Section 6.5.1, Criteria and Procedures for Dose Interruptions and Adjustments of Study Drugs (Table 14: Guidelines for Dose Modification)**

    Description of change: Clarified for handling of TEAEs that if treatment is withheld for more than 2 weeks in any treatment arm, the participant will discontinue from study treatment. Added clarification that if TEAE is not resolved within 2 weeks, then retifanlimab will be discontinued for Treatment Groups B, C, D, and E.

    Rationale for change: To reduce the risk of potential delays in radical cystectomy due to TEAEs.

12. **Section 8.5.2, Tissue Biopsy Collection Requirements**

    Description of change: Added that only one commercial assay 22C3 is acceptable for PD-L1 CPS testing and that FGFR testing can be performed using commercially available assays. Portion of the tissue sample will be flash frozen to allow for amino acid analyses. This was implemented on all samples. Also, clarified the number of tissues samples that are required as well as the requirement for flash-frozen biopsy to be over dry ice.

    Rational for change: To clarify acceptable PD-L1 and FGFR testing, and to clarify the requirement for flash frozen biopsy. Participants are not yet randomized into treatment arms during TURBT and the procedure of flash freezing tissue sample needs to be done during/right after the procedure. Therefore, this procedure cannot be selectively done on samples for participants randomized to a treatment arm and will be performed on all samples.

13. **Section 10.2, Population for Analysis (Table 24: Populations for Analysis)**

    Description of change: Added the efficacy evaluable population will include participants with efficacy endpoint data available.

    - For endpoints that are change from baseline, participants with assessments both at baseline and at the time of cystectomy will be included.
    - For endpoints that are evaluated at the time of cystectomy, participants with assessments at cystectomy will be included.

    Rationale for change: To clarify the definition of the efficacy evaluable population.

[redacted]

16. **Section 1, Protocol Summary (Table 3: Schedule of Activities for Participants Receiving Pemigatinib Monotherapy [Group A]; Table 4: Schedule of Activities for Participants Receiving Pemigatinib + Retifanlimab [Group B]; Table 5: Schedule of Activities for Participants Receiving Pemigatinib Monotherapy × 2 Weeks Followed by Retifanlimab [Group C]; Table 6: Schedule of Activities for Participants Receiving Epacadostat + Retifanlimab [Group D]; Table 7: Schedule of Activities for Participants Receiving Retifanlimab Monotherapy [Group E]; Table 8: Schedule of Activities for Participants Receiving Epacadostat Monotherapy [Group F]); Section 4.3 Study Termination; Section 5.2, Exclusion Criteria; Section 7.1.2, Discontinuation Procedures; Section 8.4, [redacted] Immunogenicity Assessments; Section 9, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting**

    Description of change: Added "Blood" before chemistries in schedules of assessments; added "/DSMB" to "DMC"; added pathologic tumor assessments to cystectomy; added Exclusion Criteria 24 regarding participants enrolled in France; added "The status of the participant should be updated to EOT in the IRT." to discontinuation procedures; added "Any changes in the timing or addition of timepoints for any planned study assessments must be documented and approved by the relevant study team member and then archived in the sponsor and site study files but will not constitute a Protocol Amendment. The IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICF."; and updated adverse events definitions and procedures to current template.

    Rationale for change: Changes made based on updated protocol template dated JUL 2020.

17. **Incorporation of administrative changes.** Other minor, administrative changes have been incorporated throughout the Protocol and are noted in the redline version of the amendment. "INCMGA00012" has been updated throughout the document with the generic name "retifanlimab."

Signature Page for VV-CLIN-011890 v9.0

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

Signature Page for VV-CLIN-011890 v9.0