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Clinical Study Protocol

INCB 99280-201

A Phase 1/2 Study of INCB099280 in Combination With Axitinib in Adults With Advanced Solid Tumors

Product:	**INCB099280**
EudraCT Number:	**2022-003663-13**
EU CT Number:	**2023-510281-27-00**
IND Number:	[redacted]
Phase of Study:	**1/2**
Sponsor:	**Incyte Corporation** **1801 Augustine Cut-Off** **Wilmington, DE 19803 USA**
Original Protocol:	**01 JUN 2023**
Amendment 1:	**28 MAR 2024**
Amendment 2:	**04 APR 2024**

INVESTIGATOR'S AGREEMENT

I have read the INCB 99280-201 Protocol Amendment 2 (dated 04 APR 2024) 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.

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(Printed Name of Investigator)

_____ _____

(Signature of Investigator) (Date)

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LIST OF ABBREVIATIONS

Abbreviations and Special Terms	Definition
ACC	American College of Cardiology
ACE	angiotensin-converting enzyme
AHA	American Heart Association
ACTH	adrenocorticotropic hormone
AE	adverse event
Ag	antigen
AHA	American Heart Association
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
anti-HBc	hepatitis B core antibody
anti-HBs	hepatitis B surface antibody
anti-HBV	hepatitis B virus antibody
anti-HCV	hepatitis C virus antibody
aPTT	activated partial thromboplastin time
ARB	angiotensin receptor blocker
ART	antiretroviral therapy
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
$AUC_{0\text{-}4h}$	area under the steady-state plasma or serum concentration-time curve from 0 to 4 hours
$AUC_{0\text{-}12h}$	area under the steady-state plasma or serum concentration-time curve from 0 to 12 hours
$AUC_{0\text{-}24h}$	area under the steady-state plasma or serum concentration-time curve from 0 to 24 hours
$AUC_{0\text{-}tau}$	area under the steady-state plasma or serum concentration-time curve over 1 dose interval
BCG	Bacillus Calmette–Guérin
BID	twice daily
BP	blood pressure
C_{avg}	average concentration
C_{trough}	trough concentration
CCB	calcium channel blocker
CFR	Code of Federal Regulations
CHF	congestive heart failure

Abbreviations and Special Terms	Definition
CI	confidence interval
CLIA	Clinical Laboratory Improvement Amendments
CL_{ss}/F	apparent oral dose clearance at steady state
C_{max}	maximum observed concentration
$C_{max,ss}$	maximum observed concentration at steady state
C_{min}	minimum observed concentration
$C_{min,ss}$	minimum observed concentration at steady state
CNS	central nervous system
COVID-19	coronavirus disease 2019
CR	complete response
CrCl	creatinine clearance
CSF	cerebrospinal fluid
CSR	Clinical Study Report
CT	computed tomography
C_{tau}	concentration at the end of a dosing interval
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor deoxyribonucleic acid
CTLA-4	cytotoxic T-lymphocyte–associated protein 4
CXCL9	chemokine ligand 9
CXCL10	chemokine ligand 10
CYP	cytochrome P450
DBP	diastolic blood pressure
DCR	disease control rate
DDI	drug-drug interaction
DILI	drug-induced liver injury
DLCO	diffusing capacity of the lung for carbon monoxide
DLT	dose-limiting toxicity
DMC	Data Monitoring Committee
dMMR	deficiency mismatch repair
DNA	deoxyribonucleic acid
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EMA	European Medicines Agency

Abbreviations and Special Terms	Definition
EMG	electromyography
EOT	end of treatment
ESC	European Society of Cardiology
ESH	European Society of Hypertension
ESMO	European Society for Medical Oncology
FAS	full analysis set
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
FT4	free thyroxine
GCV	geometric coefficient of variation
GDPR	General Data Protection Regulation
GI	gastrointestinal
GITR	glucocorticoid-induced tumor necrosis factor receptor related
HbA_{1c}	hemoglobin A_{1c}
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HPV	human papillomavirus
HRT	hormone replacement therapy
IB	Investigator's Brochure
IC_{50}	concentration that results in 50% inhibition
IC_{90}	concentration that results in 90% inhibition
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICI	immune checkpoint inhibitor
ID	identification
IFNγ	interferon gamma
IL	interleukin
INR	international normalized ratio
irAE	immune-related adverse event
iRECIST	Immune Response Evaluation Criteria in Solid Tumors
IRT	interactive response technology
IV	intravenous
LAG-3	lymphocyte-activation gene 3

Abbreviations and Special Terms	Definition
LAIV	live-attenuated influenza vaccine
LFT	liver function test
LVEF	left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MMR	measles, mumps, and rubella
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
MSI	microsatellite instability
MSI-H	microsatellite instability–high
MTD	maximum tolerated dose
mTPI	modified toxicity probability interval
NA	not applicable
NCA	noncompartmental analysis
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NSCLC	non–small cell lung cancer
NYHA	New York Heart Association
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PD	progressive disease
PD-1	programmed death-1
PD-L1	programmed death-ligand 1
PET	positron emission tomography
PFS	progression-free survival
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
PPI	proton pump inhibitor
PR	partial response
PT	prothrombin time
Q12W	every 12 weeks
QD	once daily
QTc	QT interval corrected
QTcF	QT interval corrected using Fridericia's formula
RCC	renal cell carcinoma
RDE	recommended dose for expansion

Abbreviations and Special Terms	Definition
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SBP	systolic blood pressure
SCC	squamous cell carcinoma
SCCOHT	small cell cancer of the ovary, hypercalcemic type
SD	stable disease
SoA	schedule of activities
SOP	standard operating procedure
$t_{½}$	apparent terminal-phase disposition half-life
T3	triiodothyronine
T4	thyroxine
TEAE	treatment-emergent adverse event
TKI	tyrosine kinase inhibitor
t_{max}	time to maximum concentration
$t_{max,ss}$	time to maximum concentration at steady state
TMB	tumor mutation burden
TMB-H	tumor mutation burden–high
TME	tumor microenvironment
TRAE	treatment-related adverse event
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor
VTE	venous thromboembolism
V_z/F	apparent oral dose volume of distribution
WOCBP	women of childbearing potential

1. PROTOCOL SUMMARY

Protocol Title:

A Phase 1/2 Study of INCB099280 in Combination With Axitinib in Adults With Advanced Solid Tumors

Protocol Number: INCB 99280-201

Objectives and Endpoints:

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

Table 1: Primary and Secondary Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the safety and tolerability of INCB099280 in combination with axitinib (Part 1).	• Occurrence of DLTs. • Incidence of TEAEs, including assessment of physical examinations, changes in vital signs and ECGs, and analysis of clinical laboratory samples. • Incidence of TEAEs leading to a dosing modification (treatment interruption, dose reduction, and permanent discontinuation of either study drug).
To assess the antitumor activity of INCB099280 in combination with axitinib (Part 2).	Objective response, defined as the best overall response of CR or PR by investigator assessment per RECIST v1.1.
Secondary	
To evaluate the safety and tolerability of INCB099280 in combination with axitinib (Part 2).	• Incidence of TEAEs, including assessment of physical examinations, changes in vital signs and ECGs, and analysis of clinical laboratory samples. • Incidence of TEAEs leading to dosing modification (treatment interruption, dose reduction, and permanent discontinuation of either study drug).
To assess the antitumor activity of INCB099280 in combination with axitinib.	• Objective response (Part 1), defined as the best overall response of CR or PR by investigator assessment per RECIST v1.1. • Disease control, defined as the best overall response of CR, PR, or SD by investigator assessment per RECIST v1.1. • DOR, defined as the time from the first CR or PR until disease progression by investigator assessment per RECIST v1.1 or death from any cause, whichever occurs earlier.
To characterize the PK profile of INCB099280 when administered in combination with axitinib.	• INCB099280 and axitinib plasma concentrations. • INCB099280 PK parameters by NCA methods such as C_{max}, t_{max}, $AUC_{0\text{-}4h}$, $C_{max,ss}$, $t_{max,ss}$, $AUC_{0\text{-}12h}$, C_{avg}, C_{tau}, $t_{½}$, CL_{ss}/F, and V_z/F.

Overall Design:

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

Table 2: Key Study Design Elements

Study Phase	Phase 1/2
Clinical Indication	Treatment of adults with advanced select solid tumors who have received at least 1 prior line of systemic chemotherapy and are not candidates for curative surgery or (chemo)radiation.
Population	Adult participants who meet the following criteria: • Advanced disease measurable according to RECIST v1.1 • ECOG performance status score of 0 or 1 • Adequate bone marrow, renal, liver, and cardiac function • Not a candidate for curative surgery or (chemo)radiation • Recurrent, locally advanced, unresectable or metastatic cancer with the following histologies: − Cohort 1: Clear cell ovarian cancer (including primary peritoneal and fallopian tube) with at least 50% clear cell histology − Cohort 2: Other rare histological subtype epithelial cancer of the gynecological tract, including but not limited to carcinosarcoma, neuroendocrine tumors of low and high grade (including small cell carcinoma), ovarian mucinous adenocarcinoma, low-grade ovarian serous carcinoma, SCCOHT, squamous cell cancer (excluding cervical and endometrial), and vulvar or vaginal cancer, regardless of histological subtype − Cohort 3: Endometrial cancer (including clear cell histology) Note: This cohort excludes endometrial carcinosarcoma (malignant mixed Müllerian tumor), endometrial leiomyosarcoma, and endometrial stromal sarcoma. − Cohort 4: Cervical cancer, including squamous, adenosquamous, or adenocarcinoma (including clear cell histology) Key exclusion criteria are prior treatment with small-molecule TKIs targeting the VEGF pathway; autoimmune disease that required systemic treatment within the past 5 years or a history of primary immunodeficiency; evidence of uncontrolled, concurrent illness (including inadequately controlled hypertension despite maximal medical therapy); evidence of inadequate wound healing; and unresolved toxic effects of Grade 2 or higher (according to the CTCAE) from prior therapy, excluding alopecia.
Number of Participants	Up to approximately 132 participants will be enrolled. • Part 1 (dose finding): up to approximately 12 participants • Part 2 (dose expansion): up to approximately 120 participants
Study Design	Phase 1/2, open-label, multicenter study composed of a dose-finding part and a dose-expansion part.

Table 2: Key Study Design Elements (Continued)

Estimated Duration of Study Participation	This study consists of 3 periods: screening, study treatment, and follow-up. The study will include up to 28 days for screening, continuous combination treatment in consecutive 21-day cycles as long as participants are receiving benefit and have not met any criteria for study withdrawal, and safety follow-up at 30 (+ 7) days and 90 (+ 14) days after EOT as well as disease status follow-up Q12W (± 14 days) after EOT for participants who discontinue for reasons other than PD. It is estimated that an individual will participate for approximately 12 months.
DMC	Yes (external)
Coordinating Principal Investigator	To be determined

Treatment Groups and Duration:

INCB099280 and axitinib will be administered orally BID, either with a [redacted] meal or after the participant has [redacted] for at least [redacted] hours, on a continuous daily dose administration schedule. If a participant is unable to tolerate combination treatment, they will have met the criterion for study treatment discontinuation. However, on a case-by-case basis, after discussion between the medical monitor and the investigator, INCB099280 monotherapy may be allowed. The planned treatment duration for INCB099280 is up to 2 years (ie, up to 35 treatment cycles of 21 days), calculated from the first dose of study treatment, or until a criterion for treatment discontinuation is met.

The study design is shown in Figure 1, and the SoA is detailed in Table 3. Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

Figure 1: Study Design Schema

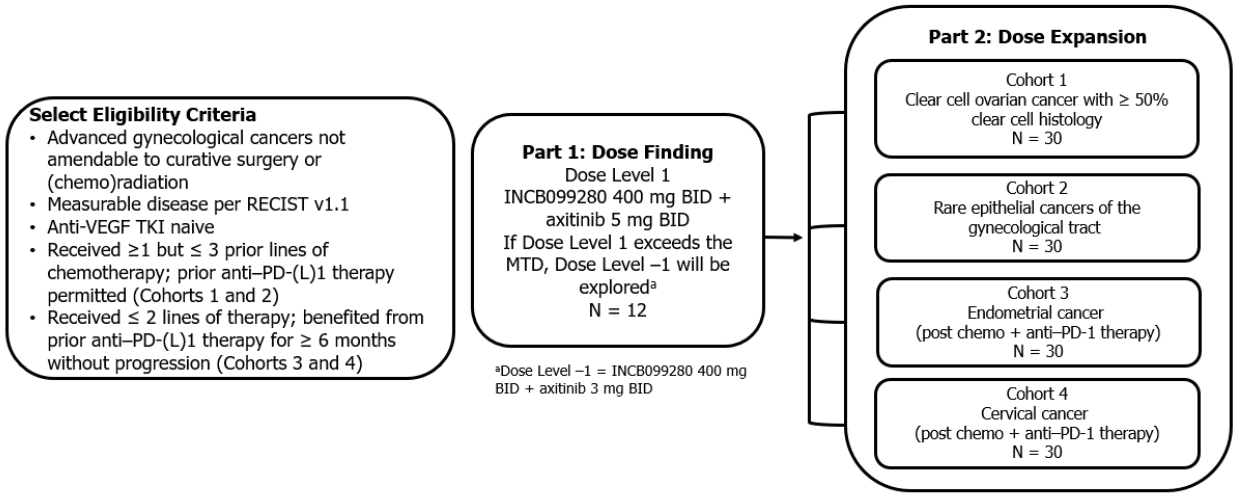


Table 3: Schedule of Activities

Visit Day (Range)	Screening	Treatment				EOT	Follow-Up			Notes
		Cycles 1-2			Cycles 3+		Safety		Disease Status	
	Days −28 to −1	Day 1	Day 8 (± 3 d)	Day 15 (± 3 d)	Day 1 (± 3 d)	(± 7 d)	EOT + 30 d (+ 7 d)	EOT + 90 d (+ 14 d)	Q12W (± 14 d) After EOT	
Administrative procedures										
Informed consent	X									Section 8.1.1.
Contact IRT	X	X			X	X				Section 8.1.3.
Inclusion/exclusion criteria	X	X								Section 5.
Cancer history	X									Section 8.1.5.2.
Demographics and general medical history	X									Section 8.1.5.1.
Prior/concomitant medications	X	X	X	X	X	X	X	X	X*	Section 6.7. *Concomitant medications administered for treatment of SAEs (as defined in Section 9.2) should be recorded even if the SAE is reported beyond 90 days after the last dose of study treatment.
Dispense INCB099280		X			X					Section 6.
Dispense axitinib		X			X					Section 6.
Administer INCB099280 in the clinic		X*			X*					Section 8.4.1. *On days of PK sample collection, administration of INCB099280 should be held until arriving at the clinic.
Administer axitinib in the clinic		X*			X*					Section 8.4.1. *On days of PK sample collection, administration of axitinib should be held until arriving at the clinic.
Distribute participant information card	X									Section 8.1.4.
Distribute reminder cards		X	X	X	X	X	X	X	X	Section 8.1.4.
Record dose administration data in dose diary		X	X	X	X					Section 8.1.4. Dose administration will be recorded via electronic diary platform. Paper diary will be provided as backup.

Table 3: Schedule of Activities (Continued)

Visit Day (Range)	Screening	Treatment				EOT	Follow-Up			Notes
		Cycles 1-2			Cycles 3+		Safety		Disease Status	
	Days −28 to −1	Day 1	Day 8 (± 3 d)	Day 15 (± 3 d)	Day 1 (± 3 d)	(± 7 d)	EOT + 30 d (+ 7 d)	EOT + 90 d (+ 14 d)	Q12W (± 14 d) After EOT	
Administrative procedures (continued)										
Collect study drug and review dosing diary		X*	X	X	X	X				Section 6.4. *Cycle 2 only.
Assess compliance		X*	X	X	X	X				Section 6.4. *Cycle 2 only.
Clinical examination										
ECOG performance status	X	X			X	X	X			Section 8.3.4.
Vital signs	X	X	X	X	X	X	X	X		Section 8.3.2. Obtained prior to blood collection.
Physical examination	X*	X	X	X	X	X*	X	X		Section 8.3.3. *Comprehensive physical examination to be performed at screening and EOT visits only.
12-Lead ECG	X	X*			X†	X	X			Section 8.3.5. In the event that a single QTcF is > 480 ms at screening, the participant may enroll if the average QTc for 3 ECGs is ≤ 480 ms. *Collected predose and 2 and 4 hours postdose of INCB099280 and axitinib. †Collected predose beginning at Cycle 3 and then every third cycle (eg, Cycles 6, 9, 12, etc) until EOT and as clinically indicated.
Echocardiogram	X									Section 8.3.6. Additional assessments should be performed if clinically indicated.

Table 3: Schedule of Activities (Continued)

Visit Day (Range)	Screening	Treatment				EOT	Follow-Up			Notes
		Cycles 1-2			Cycles 3+		Safety		Disease Status	
	Days −28 to −1	Day 1	Day 8 (± 3 d)	Day 15 (± 3 d)	Day 1 (± 3 d)	(± 7 d)	EOT + 30 d (+ 7 d)	EOT + 90 d (+ 14 d)	Q12W (± 14 d) After EOT	
Laboratory-based investigations (analysis performed by local laboratory)										
Hematology panel	X	X	X	X	X	X	X			Section 8.3.7.
Coagulation panel	X	When clinically indicated				X				Section 8.3.7.
Blood chemistry panel	X*	X	X	X	X	X	X			Section 8.3.7. *Albumin measured at screening only and as clinically indicated.
Endocrine function panel	X	X*			X*	X	X			Section 8.3.7. *Cycle 2 and then every other cycle (eg, Cycle 4, 6, 8, etc).
Pregnancy testing	X*	X†			X†	X*	X†	X†	X†,‡	Section 8.3.7.1. *Serum pregnancy test for WOCBP. †Urine pregnancy test for WOCBP. ‡Monthly telephone visits should take place to check pregnancy status (may be home pregnancy tests) during the period when contraception is mandatory (190 days after the last dose of study treatment).
Hepatitis serology	X				X*					Section 8.3.7.2. *For participants with past HBV infection (HBsAg negative and anti-HBc positive with either positive or negative anti-HBs), monitor HBsAg at Cycle 3 and then every third cycle (eg, C6, C9, C12, etc).
HBV/HCV viral load	X				X*	X				Section 8.3.7.2. HBV DNA and HCV RNA for all participants at baseline. *Monitor HBV DNA at Cycle 3 and then every third cycle (Cycle 6, 9, 12, etc) for patients with chronic HBV infection (HBsAg positive).

Table 3: Schedule of Activities (Continued)

Visit Day (Range)	Screening	Treatment				EOT	Follow-Up			Notes
		Cycles 1-2			Cycles 3+		Safety		Disease Status	
	Days −28 to −1	Day 1	Day 8 (± 3 d)	Day 15 (± 3 d)	Day 1 (± 3 d)	(± 7 d)	EOT + 30 d (+ 7 d)	EOT + 90 d (+ 14 d)	Q12W (± 14 d) After EOT	
Laboratory-based investigations (analysis performed by local laboratory) (continued)										
HIV management testing (HIV viral load, CD4+ cell count)	X	X*			X†	X		X	X†	Section 8.3.7. Only participants who are known to be HIV positive. *Cycle 1 only. †Cycle 3 and then every third cycle (ie, Cycles 6, 9, 12, etc) and more frequently if clinically indicated. Frequency may be reduced to every 6 months during the disease status follow-up period.
Urinalysis and urinary protein measurement*	X	X	X	X	X	X	X	X		Section 8.3.7. *Performed for proteinuria ≥ 2+ on dipstick urinalysis; collect 24-hour urine and measure total protein. Microscopic examination only if blood is suspected in urine.
AEs										
AE assessments	X	X	X	X	X	X	X	X		Section 8.3.1
Efficacy assessments										
Tumor imaging (CT/MRI) and disease assessment (RECIST v1.1)	X	X*			X*				X†	Section 8.2.1 and Section 8.9.2. *First 2 tumor assessments 6 and 12 weeks (± 7 days) after initiation of study treatment and Q12W (± 14 days) thereafter. Imaging should be performed relative to the start of treatment; imaging should not be adjusted for delays in cycle starts and should continue until disease progression. †Imaging during follow-up is only required for participants who discontinued study treatment for reasons other than disease progression.

Table 3: Schedule of Activities (Continued)

Visit Day (Range)	Screening	Treatment					Follow-Up			Notes
		Cycles 1-2			Cycles 3+		Safety		Disease Status	
	Days −28 to −1	Day 1	Day 8 (± 3 d)	Day 15 (± 3 d)	Day 1 (± 3 d)	EOT (± 7 d)	EOT + 30 d (+ 7 d)	EOT + 90 d (+ 14 d)	Q12W (± 14 d) After EOT	
PK assessments										
PK plasma (INCB099280)		X*			X†					Section 8.4. *Predose and 1, 2, and 4 hours postdose. †Predose at Cycles 4 and 8 only.
PK plasma (axitinib)		X*			X†	X				Section 8.4. *Predose only. †Predose at Cycles 4 and 8 only.
[redacted]										

Table 3: Schedule of Activities (Continued)

	Screening	Treatment					Follow-Up			
		Cycles 1-2			Cycles 3+		Safety		Disease Status	
Visit Day (Range)	Days −28 to −1	Day 1	Day 8 (± 3 d)	Day 15 (± 3 d)	Day 1 (± 3 d)	EOT (± 7 d)	EOT + 30 d (+ 7 d)	EOT + 90 d (+ 14 d)	Q12W (± 14 d) After EOT	Notes
[redacted]										

Note: Each cycle is 21 days.

2. INTRODUCTION

2.1. Background

Immune evasion is a pivotal mechanism exploited by tumor cells to escape the host immune system and facilitates tumor progression. Tumors achieve this through several mechanisms. One such mechanism, which plays a critical role in tumor evasion, involves the PD-1 receptor-ligand interaction. Many human cancers express PD-L1; PD-1/PD-L1 interaction induces host immunosuppression through the downregulation and exhaustion of cytotoxic T cells, promoting tumor progression. On this basis, blocking the PD-1/PD-L1 pathway has been exploited therapeutically and there is now substantial evidence for the use of these ICIs as an effective cancer therapy. The potential for durable responses, activity in a broad range of cancers that includes the possibility of long-term survival and improved quality of life in patients with metastatic disease, and manageable toxicities has led to PD-(L)1 inhibitors becoming a core pillar of cancer therapy for multiple malignancies (Haslam and Prasad 2019). As a consequence, US and European regulatory authorities have approved various categories of ICIs (PD-1 inhibitors [nivolumab, pembrolizumab, and cemiplimab], PD-(L)1 inhibitors [atezolizumab, durvalumab, and avelumab], a LAG-3 inhibitor [relatlimab-rmbw], and a CTLA-4 inhibitor [ipilimumab]) for the treatment of a variety of cancers.

Despite these promising results, only a subset of patients with cancer respond to PD-(L)1 inhibitor monotherapy and, of those who do, many develop resistance to treatment over time. Consequently, novel therapeutic approaches are needed to enhance clinical outcomes and efforts are being aimed at investigating therapeutic combinations with PD-(L)1 inhibitors (Vilgelm et al 2016). This observation also underscores the need for improved predictive biomarkers to refine the selection of patients who may benefit from treatment with PD-(L)1 inhibitors.

The addition of antiangiogenic agents to immunotherapy has emerged as one of the most successful immunotherapeutic combination strategies in the treatment of cancer, with several ongoing clinical trials across various malignant solid cancers (Song et al 2020). Dysfunctional angiogenesis in the TME caused by proangiogenic factors such as VEGF results in an immunosuppressive TME by multiple mechanisms. Although proangiogenic factors disrupt normal vasculature formation in tumors, the immune composition in the TME is important for normalizing the tumor vasculature (Fukumura et al 2018, Killock 2017, Kut et al 2007, Tian et al 2017, Zheng et al 2018). Immune cells that drive normal tumor vascularization are enhanced in the presence of ICIs, as revealed in anti–PD-1— and anti–CTLA-4—treated mouse models in which type 1 T-helper cells led to vascular reprogramming (Tian et al 2017). Because this reciprocal regulation of immune responses and vascular normalization has been identified, the promise of combined antiangiogenic therapy and ICIs has been established.

Given the extensive preclinical data, multiple ICI and antigenic inhibitor strategies have been approved by regulatory authorities (Bilen et al 2022, Choueiri et al 2020, Motzer et al 2019, Motzer et al 2020, Motzer et al 2022, Powles et al 2020, Rini et al 2019). Most of these ICI combinations, either with multitargeted or selective VEGFR TKIs or anti-VEGF antibodies, have resulted in an OS benefit.

The hypothesis is that axitinib could be safely administered with INCB099280 (an orally administered small-molecule inhibitor of PD-L1) and result in improved clinical outcomes in

adults with previously treated advanced clear cell or rare histological subtype epithelial gynecological cancers who are not candidates for curative surgery or (chemo)radiation.

2.2. INCB099280

INCB099280 is an investigational, orally administered, small-molecule inhibitor of PD-L1. It offers potential advantages over therapeutic antibodies targeting the PD-1/PD-L1 immune checkpoint pathways, including convenience to patients due to its oral bioavailability. It lacks immunogenicity and is therefore not associated with systemic reactions upon administration. Oral administration also enables more convenient dosing both as monotherapy and in combination with other targeted agents.

In vitro, INCB099280 binds selectively and with high affinity to PD-L1 and potently blocks the PD-L1/PD-1 interaction. INCB099280 has been shown to induce IFNγ secretion in a concentration-dependent manner, stimulates cytokine production in primary human immune cells, and dose-dependently reduces available surface PD-L1 on IFNγ-stimulated human monocytes in a whole blood assay with an IC_{50} of 25 nM and IC_{90} of 457.5 nM.

In vivo, INCB099280 reduced tumor growth in $CD34^{+}$ humanized mice bearing MDA-MB-231 tumors and induced T-cell activation gene signatures consistent with PD-L1/PD-1 pathway blockade.

As of 14 JAN 2024, 282 participants have been enrolled across 6 studies evaluating INBC099280; 273 participants received at least 1 dose of INCB099280 (76 healthy participants and 197 participants with advanced solid tumors) and 9 participants received placebo.

Preliminary data from an ongoing Phase 1 study (INCB 99280-112) in participants with advanced solid malignancies indicate that INCB099280 is well tolerated, has a favorable safety profile, and shows promising antitumor activity (Prenen et al 2022). Refer to the INCB099280 IB for a complete summary of nonclinical information.

2.3. Axitinib

Axitinib is a potent and selective TKI of VEGFR-1, VEGFR-2, and VEGFR-3. These receptors are implicated in pathologic angiogenesis, tumor growth, and metastatic progression of cancer. Axitinib has been shown to potently inhibit VEGF-mediated endothelial cell proliferation and survival. Axitinib inhibited the phosphorylation of VEGFR-2 in xenograft tumor vasculature that expressed the target in vivo and produced tumor growth delay, regression, and inhibition of metastases in many experimental models of cancer (Hu-Lowe et al 2008). The plasma half-life of axitinib is 2.5 to 6.1 hours and is expected to reach steady state within 2 to 3 days of dosing. It is metabolized primarily in the liver by CYP3A4/5 and to a lesser extent by CYP1A2, CYP2C19, and UGT1A1.

2.3.1. Clinical Experience With Axitinib Monotherapy

Data from a randomized, multicenter, Phase 3 study directly comparing 2 VEGFR TKIs (axitinib and sorafenib) showed that inhibition of VEGFRs with axitinib translated into clinically meaningful efficacy with manageable toxicities in 361 participants with advanced RCC who had disease progression despite first-line therapy compared to sorafenib (n = 362; Rini et al 2011). The data also supported the hypothesis that biochemically more potent inhibition of the VEGFR

(as achieved with axitinib) produces a more robust clinical effect. On this basis, axitinib has been approved in the United Kingdom and European Economic Area as monotherapy for the treatment of adults with advanced RCC after failure of prior treatment with sunitinib or a cytokine.

The most frequent adverse effects or laboratory abnormalities (any Grade/Grade 3 or 4) associated with axitinib and reported in ≥ 15% of participants were diarrhea (55%/11%), creatinine elevation (55%/0%), hypertension (40%/16%), fatigue (39%/11%), hypocalcemia (39%/1%), anemia (35%/< 1%), decreased appetite (34%/5%), lymphopenia (33%/3%), nausea (32%/3%), dysphonia (31%/0%), palmar-plantar erythrodysesthesia and lipase elevation (27%/5%), weight decreased (25%/2%), vomiting (24%/3%), asthenia (21%/5%), constipation (20%/1%), hypothyroidism (19%/<1%), arthralgia (15%/2%), cough as well as mucosal inflammation and stomatitis (15%/1% each), and thrombocytopenia (15%/1%). There were no treatment-related deaths, but there were 4 reported treatment-related or causality unknown deaths (asthenia, gastrointestinal bleed, sepsis, and disease progression).

One or more dose interruptions (due to missed doses or toxic effects) were reported in 77% of participants given axitinib; however, the median relative dose intensity was 99%. At least 1 dose reduction was reported in 31% of participants.

Although caution should be exercised when comparing across studies, a similar safety profile was observed in a randomized, open-label, Phase 3 study in which 192 participants with previously untreated advanced RCC received axitinib monotherapy compared to sorafenib (n = 96; Hutson et al 2013).

2.3.2. Clinical Experience With Axitinib in Combination With PD-(L)1 Inhibitors

Clinical experience with axitinib in combination with PD-(L)1 inhibitors include data from 2 studies in participants with previously untreated advanced RCC: an open-label Phase 3 study of axitinib in combination with the anti–PD-1 monoclonal antibody pembrolizumab (Rini et al 2019) and a Phase 1b study in which axitinib was administered with the anti–PD-L1 monoclonal antibody avelumab (Motzer et al 2019). On the basis of the results from these 2 studies, the FDA approved axitinib in combination with pembrolizumab and avelumab in APR 2019 and MAY 2019, respectively, for the first-line treatment of participants with advanced RCC. The European Commission granted approval of avelumab plus axitinib for the same therapeutic indication in OCT 2019.

The observed safety profile of axitinib plus pembrolizumab was as expected on the basis of the known profile of these 2 drugs, although the incidence of Grade 3 or 4 elevations in liver enzyme levels was higher than observed when each agent was used as monotherapy; there were no deaths related to hepatic AEs. A further exception was a greater incidence of hyperthyroidism and of hypothyroidism, which was not unexpected given that thyroid abnormalities are also a known side effect of axitinib.

Adverse events of any cause occurred in 98.4% of the 429 participants who received axitinib in combination with pembrolizumab. These events were ≥ Grade 3 in 75.8% of participants and in 62.9% were attributed by the investigators to study treatment. Adverse events ≥ Grade 3 that occurred in ≥ 10% of participants were hypertension and increased ALT levels (Grade 3, Grade 4, and Grade 5 events occurred in 8.4% 1.6%, and 0.7% of participants, respectively). The

most common AEs of any cause and the most common AEs related to treatment were diarrhea and hypertension.

Treatment-emergent AEs (any Grade/Grade 3 or 4) reported in ≥ 15% of participants were diarrhea (54.3%/9.1%), hypertension (44.5%/22.1%), fatigue (38.5%/2.8%), hypothyroidism (35.4%/0.2%), decreased appetite (29.6%/2.8%), palmar-plantar erythrodysesthesia syndrome (28%/5.1%), nausea (27.7%/0.9%), ALT increased (26.8%/13.3%), AST increased (26.1%/7%), dysphonia (25%/0.2%), cough (21.2%/0.2%), constipation (20.7%/0%), arthralgia (18.2%/0.9%), weight decreased (17.7%/3%), proteinuria (17.5%/2.8%), dyspnea (16.1%/1.6%), headache (15.9%/0.9%), stomatitis (15.6%/0.7%), asthenia (15.2%/2.6%), and pruritus and stomatitis (15.%/0.2% each).

Adverse events of any cause led to discontinuation of either drug in 30.5% of participants, discontinuation of both drugs in 10.7%, interruption of either drug in 69.9%, and dose reduction of axitinib in 20.3%. The median time to discontinuation of both pembrolizumab and axitinib because of AEs of any cause was 105.5 days, and the median time to discontinuation of pembrolizumab because of AEs of any cause was 65 days. Of the 11 participants (2.6%) who died from AEs, 4 (0.9%) died from treatment-related AEs (myasthenia gravis, myocarditis, necrotizing fasciitis, and pneumonitis in 1 participant each).

A similar safety profile was observed in 442 participants who received avelumab plus axitinib. Additionally, the frequency and severity of AEs observed with the combination treatment were generally consistent with the known safety profiles of avelumab and axitinib administered as monotherapy.

2.4. Study Rationale

The overall aim of this study is to determine whether INCB099280 administered in combination with axitinib is safe and tolerable and to gain early evidence of the effectiveness of this combination therapy in adults with advanced solid tumors.

The study will also comprise an analysis of PK data and an [redacted]

2.4.1. Rationale for Treatment With INCB099280 and Axitinib in Rare Gynecological Cancers

There is a significant unmet need for effective treatment strategies for rare gynecological cancers because benefit from standard therapeutic approaches is extremely limited, with response rates in recurrent disease generally < 10%. Additionally, these cancers are molecularly distinct from gynecological cancers that do respond well to chemotherapy. Molecular profiles reported to be present in rare gynecological cancer subtypes include high TMB, ARID1A, phosphatidylinositol 3-kinase pathway aberration, RAS/RAF lesions, PD-L1 expression, and dMMR, all of which can promote sensitivity to checkpoint inhibition. Targeting angiogenesis is a standard approach for many gynecological cancers and, where data exist, also has potential benefit for the rare subtypes. This observation supports the idea that using an antiangiogenic TKI in this population could enhance inherent sensitivity to a checkpoint inhibitor.

Rare gynecological histotypes comprise approximately 50% of all gynecological cancers, so advances in treatment would affect a significant number of patients. Rare gynecological cancers can be divided into epithelial and nonepithelial subtypes. The rare epithelial histological subtypes can include clear cell, low-grade ovarian serous carcinoma, ovarian mucinous adenocarcinoma, low- and high-grade neuroendocrine tumors (including small cell carcinoma), carcinosarcoma, squamous cell cancer (excluding cervical and endometrial), SCCOHT, and vulvar or vaginal cancer, regardless of histological subtype.

The largest body of data for the benefit of immunotherapy among these patients exists for clear cell gynecological cancer. The PEACOCC study, evaluating pembrolizumab monotherapy as treatment for advanced gynecological clear cell cancer, demonstrated a 25% response rate and a 1-year duration of response rate of 47.7% (Kristeleit et al 2022). Additionally, preliminary results from the INOVA study (Liu et al 2022) suggest that the addition of bevacizumab, an antibody targeting VEGF, increased the benefit of PD-1–targeting immunotherapy in clear cell cancer with objective response rates of 40% with the combination. Furthermore, low-grade and mucinous histotypes, although clinically very distinct, do share molecular similarities in that disruption of the RAS/RAF pathway occurs at a higher rate than in other gynecological cancers. In addition, although there are very limited data, patients with low-grade and mucinous cancers appear to derive improved benefit from the addition of antiangiogenic treatment to standard chemotherapy (Gore et al 2019, Grisham et al 2014).

An immunotherapeutic approach in low-grade and mucinous cancers, in addition to targeting angiogenesis, may enable enhanced recognition of neoantigens within these tumors based on their distinct molecular profiles, including aberrant RAS/RAF signaling. Finally, vulvar and vaginal cancers have no established evidence-based first-line chemotherapy, although carboplatin/paclitaxel or cisplatin/5-fluorouracil are used often with little objective or clinical benefit. These tumor types can be HPV driven and SCC in histotype, both features associated with sensitivity to immune checkpoint inhibition. The biology of these cancers is also consistent with potential sensitivity to angiogenic targeting therapy. There are a few case reports of durable response to single-agent immunotherapy in vaginal and vulvar cancer, as well as occasional reports of benefit from antiangiogenic therapy. In the absence of other effective therapeutics, there is a clear rationale for investigating a combinatorial immunotherapy and antiangiogenic therapeutic approach in these cancer types.

Based on the current data, this study will focus on epithelial histological subtypes and any histological subtype of vaginal or vulvar cancer.

Overall, the distinct molecular profile of rare histological subtype epithelial gynecological cancer and vulvar and vaginal cancers, in the absence of effective therapeutic options in recurrent disease, and a biological rationale supported by early reports of efficacy with immunotherapy and/or antiangiogenic approaches in many of these subtypes, supports the evaluation of a combinatorial immunotherapy and antiangiogenic strategy in this patient population.

2.4.2. Rationale for Treatment With INCB099280 and Axitinib Following Disease Progression With Prior Immunotherapy

Novel, effective treatment approaches are needed following disease recurrence across gynecological malignancies. This study will focus on advanced cervical and endometrial malignancies in which the clinical benefit of anti–PD-(L)1 monoclonal antibodies has led to their

use in recurrent disease and as first-line regimens in combination with systemic chemotherapy. In cervical cancer, pembrolizumab has received FDA approval in combination with chemoradiation for Stage III to IVA disease, in addition to FDA and European Commission approvals in combination with chemotherapy with or without bevacizumab for patients with PD-L1–positive recurrent or metastatic disease. As seen in cervical cancer, ICIs have also demonstrated significant clinical benefit in endometrial cancer. Significant improvements in PFS with the addition of dostarlimab to chemotherapy led to FDA and European Commission approvals in patients with dMMR/MSI-H primary advanced or recurrent endometrial cancer (Mirza et al 2023). The addition of pembrolizumab to chemotherapy in the Phase 3 NRG-GY018 study in patients with advanced endometrial cancer also led to significant increases in PFS, resulting in its addition to frontline regimens per NCCN guidelines (Eskander et al 2023).

Despite these advances, as demonstrated across tumor types, tumor resistance eventually develops and there are limited effective subsequent treatment options. While there have been a few prospective studies, several studies evaluating ICI rechallenge, primarily in NSCLC and melanoma, suggest a potential clinical benefit and an overall tolerable safety profile with this approach (Plazy et al 2022). As anti–PD-(L)1 agents become standard in front-line regimens in gynecological malignancies, further studies evaluating ICI rechallenge and novel combinations aimed at restoring the immune response following prior immune checkpoint inhibition are needed. With its role not only in suppressing angiogenesis but also in modifying the immunosuppressive TME, a VEGF inhibitor when combined with an anti–PD-(L)1 agent offers an attractive approach to restore the tumor's sensitivity to immunotherapy. In endometrial cancer, the Phase 3 Study 309/KEYNOTE-775 comparing lenvatinib and pembrolizumab versus chemotherapy in patients who failed to respond to platinum-based chemotherapy established that the combination of an anti-VEGF TKI and an anti–PD-1 agent has clinical benefit in recurrent disease leading to significant increases in PFS and OS (NCT03517449; Makker et al 2023). The hypothesis that the combination of VEGF and PD-1 inhibition may benefit patients with recurrent disease following prior immunotherapy is supported by early clinical evidence. The combination of the anti–VEGFR-2 antibody ramucirumab and pembrolizumab in the Phase 2 Lung-MAP S1800A substudy led to a significant increase in median OS versus standard of care chemotherapy in patients with advanced NSCLC previously treated with ICI therapy and platinum-based chemotherapy who had disease progression on ICI therapy (median OS: 14.5 vs 11.6 months; hazard ratio: 0.69, $p = 0.05$; Reckamp et al 2022). In gynecological malignancies, similar approaches with anti-VEGF TKIs in combination with ICI therapy are planned to further investigate this hypothesis, including a Phase 2 study with zimberelimab and lenvatinib in patients with advanced cervical cancer following prior ICI therapy and chemotherapy (NCT05824468).

Overall, the high unmet need for effective treatment options for recurrent disease, especially as immunotherapy is being incorporated across front- and second-line regimens, as well as the biological rationale and preliminary clinical benefits with combination VEGF and PD-(L)1 inhibition support further investigation of this combination in gynecological malignancies.

2.4.3. Justification for INCB099280 Dose Selection

2.4.3.1. Safety/Efficacy

INCB099280 at a dose of 400 mg BID is being evaluated in this study. INCB099280 will be administered orally in 21-day treatment cycles. The dose to be studied was selected based on preclinical data as well as clinical data from the Phase 1 dose-finding study in participants with advanced solid tumors (INCB 99280-112). As of [redacted], INCB099280 has been evaluated in [redacted] participants with advanced cancer in the Phase 1 study. Participants have been treated at 100 mg QD (n = [redacted]), 200 mg QD (n = [redacted]), 200 mg BID (n = [redacted]), 300 mg BID (n = [redacted]), 400 mg BID (n = [redacted]), 600 mg QD (n = [redacted]), 600 mg BID (n = [redacted]), 800 mg QD (n = [redacted]), and 800 mg BID (n = [redacted]). INCB099280 has been generally well tolerated across dose levels, and the MTD has not been reached. The most frequently occurring TRAEs assessed, as related to INCB099280 by the investigator, are asthenia ([redacted]%), nausea ([redacted]%), fatigue ([redacted]%), decreased appetite ([redacted]%), pruritus ([redacted]%), and diarrhea ([redacted]%). Most TEAEs were Grade 1 or 2 in severity. Refer to the INCB099280 IB for more detailed safety information.

As of [redacted], antitumor activity has been noted at dos[redacted]s ≥ 300 mg BID in this previously treated population, with [redacted]% having received ≥ 3 prior lines of therapy. A total of [redacted] participants were treated at dose levels ≥ 300 mg BID. The ORR for the entire population was [redacted]) and was highest ([redacted]]) at a dose of 400 mg BID. The response rate was only [redacted]) at 600 mg BID and [redacted] at 800 mg BID.

Although participants with mixed types of tumors were enrolled in this Phase 1 study, the population was comparable with respect to the tumor types across all dose levels. No dose level preferentially enrolled tumors that were more likely to respond to immunotherapy. The most common tumor was anal cancer ([redacted]]), followed by cervical cancer ([redacted]]). Less than [redacted]% of participants had highly responsive tumor types (eg, melanoma, PD-L1 high NSCLC, or RCC).

Overall, there is a modest trend for increasing response rate with increasing dose of INCB099280 up to a dose level of 400 mg BID. No improvement in response rate is seen beyond a dose of 400 mg BID. There is a suggestion that the incidence of TEAEs may increase with increasing doses. This pattern is similar to what has been observed with monoclonal anti–PD-1 or PD-L1 antibodies. Most anti–PD-1 and anti–PD-L1 antibodies demonstrated a plateaued exposure-response curve at the doses tested in clinical studies (Centanni et al 2019).

2.4.3.2. Pharmacodynamic and Translational Data

Immune activation has been observed in participants who received doses of INCB099280 ≥ 200 mg BID. Increases in immune markers of T-cell activation and IFN-related cytokines have been observed in plasma. Increases in [redacted], and [redacted] were increased with treatment at 200 mg QD, 200 mg BID, 300 mg BID, 400 mg BID, 600 mg QD, and 800 mg QD. In addition, changes in $CD8^+$ T-cell proliferation as measured by Ki67 and activation as measured by HLA-DR were observed. The mean values of these biomarkers are numerically higher at 400 mg BID than with treatment at lower doses; however, the differences are not statistically significant. These biomarker results in combination with the clinical data described above demonstrate that 400 mg BID is a biologically as well as clinically

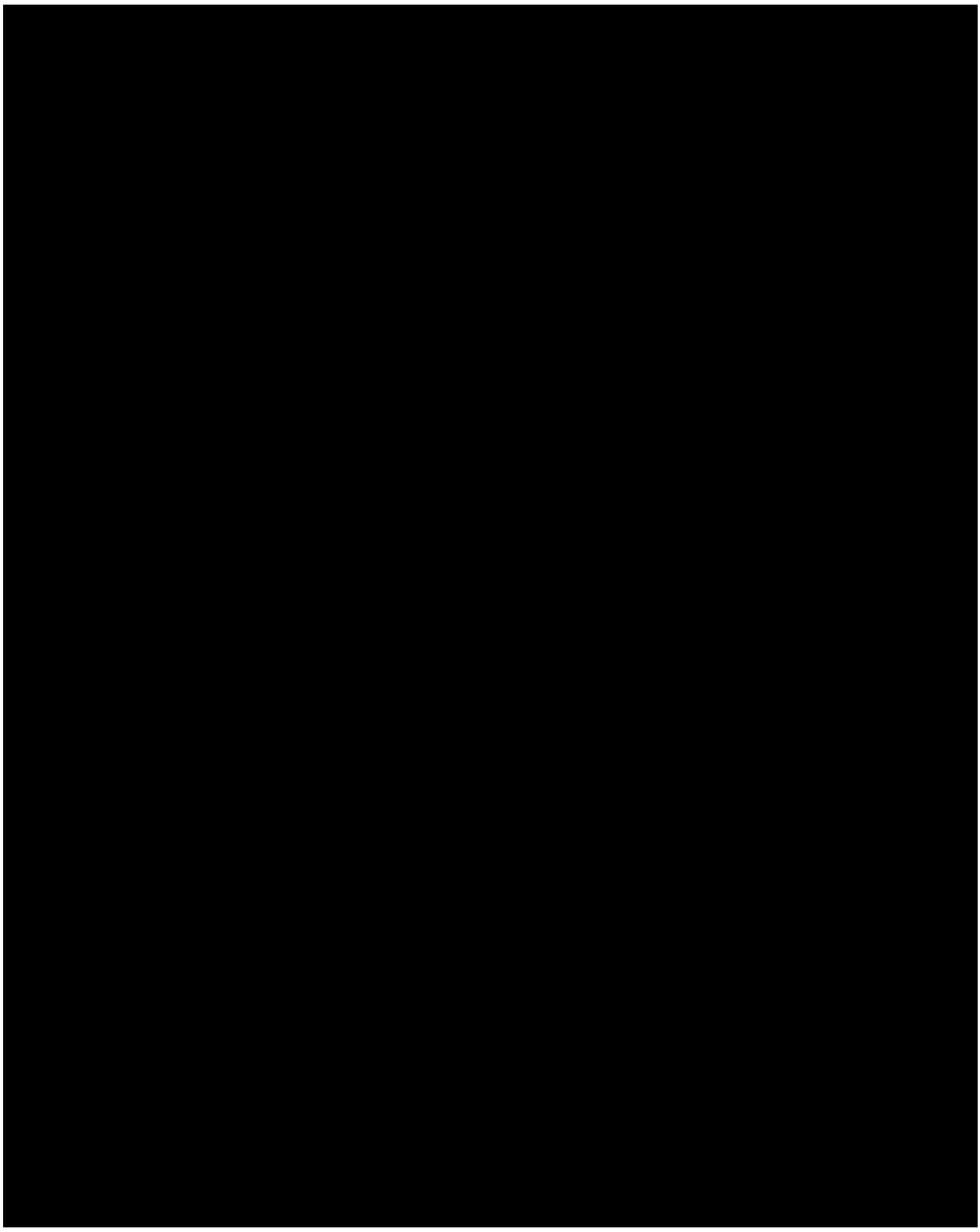
active dose. Demonstration of immune activation with INCB099280 treatment aligns with the effects observed with anti–PD-(L)1 monoclonal antibodies.

2.4.3.3. Pharmacokinetics

Preliminary PK data from participants with advanced solid tumors in Study INCB 99280-112 demonstrate that steady-state PK is achieved by Cycle 1 Day 8 with up to [redacted]-fold accumulation in C_{max} but up to [redacted]-fold in AUC_{0-4h}. The interindividual variability in C_{max} and AUC_{0-4h} is high ([redacted]% GCV) for the largest dose groups of 300 mg BID (n = [redacted]) and 400 mg BID (n = [redacted]; PK-evaluable population as of [redacted]). Such a magnitude of interindividual variability is comparable with that observed in healthy participants ([redacted]% GCV). The PK exposures appeared to increase proportionally as the dose increased up to 800 mg BID. The geometric mean of the observed steady-state trough concentrations consistently exceeded [redacted] for BID dose levels of ≥ 300 mg. Based on the overall experience with INCB099280 to date, the sponsor considers 400 mg BID to be the appropriate dose that should be used to further evaluate the efficacy and safety of INCB099280 in participants with solid tumors. At this dose, more than half (ie, [redacted]% based on population PK simulations) of the participants are expected to have steady-state trough concentrations above the target [redacted]

2.4.3.4. Exposure/Response Data

Preliminary exposure-safety analysis suggested shallow relationships between PK exposures and irAE (see Figure 2). There was no apparent trend for a list of other AEs surveyed (SAEs; Grade 3 or above TEAEs; TEAEs leading to dose interruption, dose reduction, or dose discontinuation; diarrhea (any grade); and TEAEs with [redacted]% incidence rate, such as anemia, arthralgia, asthenia, constipation, cough, decreased appetite, dyspnea, fatigue, nausea, pruritus, pyrexia, and vomiting). Further, preliminary analyses of clinical ECG data suggested that large QTc effects (ie, > 20 milliseconds) can be excluded at dose levels up to 800 mg BID studied in Study INCB 99280-112.



2.4.4. Rationale for INCB099280 Treatment Duration

Despite a large body of evidence with ICIs targeting the PD-1/PD-L1 pathway, the optimal treatment duration with these agents had not been defined to date (Banks and Sullivan 2020, Marron et al 2021). In the majority of studies, participants were treated for up to 2 years in the absence of unacceptable toxicity and disease progression. However, evidence from pembrolizumab trials, real-world evidence, and smaller studies collectively suggest that participants can experience durable responses with low incidence of relapse after significantly shorter treatment times. Further, among complete responders, the risk of relapse after discontinuation is low even after treatment for 6 months.

While the results of well-designed trials to identify the optimal duration of therapy and biomarkers to identify participants that would benefit from shorter courses of immunotherapy are awaited, participants may continue to receive INCB099280 for 2 years.

2.4.5. Clinical Safety Profile of INCB099280

The foreseeable risks associated with the administration of INCB099280 are currently based on the clinical safety information from 6 studies in which INCB099280 has been administered.

For further information, refer to the INCB099280 IB.

2.5. Benefit/Risk Assessment

Immunotherapy with ICIs has come to represent a paradigm shift in the management of cancers, and their indications for use continue to expand. Moreover, while ICIs blocking the PD-1/PD-L1 pathway have revolutionized opportunities for therapeutic intervention in cancer, there is clearly a need for new therapeutic strategies to enhance clinical outcomes with PD-(L)1 inhibition. This unmet medical need is reflected in these agents being effective in a minority of unselected patients and many patients having PD as their best response (Haslam and Prasad 2019), an outcome that was also noted in the PEACOCC study (Kristeleit et al 2022). Continued translational and clinical research, therefore, holds promise to change the landscape of gynecological and other cancers and improve the lives of people impacted by malignant disease.

There is a robust biological rationale, supported by preclinical data, for the addition of an antiangiogenic agent to INCB099280 in adults with advanced gynecological cancers as well as other malignant solid tumors, where it is hoped that, in addition to its antiproliferative and antiangiogenic effects, there will also be a potential for a synergistic/additive effect with PD-(L)1 inhibition. Clinical experience with the combination of axitinib and anti–PD-(L)1 therapies has shown a manageable safety profile, consistent with either agent administered as monotherapy, and with a low rate of TRAEs leading to discontinuation (Motzer et al 2019, Rini et al 2019). For these reasons, this study has been designed to determine whether the concurrent administration of INCB099280 and axitinib is safe and tolerable and enhances antitumor activity in a well-defined population where the benefit/risk profile is considered favorable. Additionally, this combination treatment avoids the toxicities associated with cytotoxic chemotherapy for participants whose disease progressed on or following prior systemic chemotherapy.

The translational component of this study will provide an opportunity to evaluate potential molecular determinants of response in tumor tissue and circulating biomarkers for correlative translational analyses with clinical outcomes with INCB099280 in combination with axitinib.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of axitinib and INCB099280 may be found in the approved label and IB, respectively.

3. OBJECTIVES AND ENDPOINTS

Table 4 presents the objectives and endpoints.

Table 4: Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the safety and tolerability of INCB099280 in combination with axitinib (Part 1).	• Occurrence of DLTs. • Incidence of TEAEs, including assessment of physical examinations, changes in vital signs and ECGs, and analysis of clinical laboratory samples. • Incidence of TEAEs leading to a dosing modification (treatment interruption, dose reduction, and permanent discontinuation of either study drug).
To assess the antitumor activity of INCB099280 in combination with axitinib (Part 2).	Objective response, defined as the best overall response of CR or PR by investigator assessment per RECIST v1.1.
Secondary	
To evaluate the safety and tolerability of INCB099280 in combination with axitinib (Part 2).	• Incidence of TEAEs, including assessment of physical examinations, changes in vital signs and ECGs, and analysis of clinical laboratory samples. • Incidence of TEAEs leading to a dosing modification (treatment interruption, dose reduction, and permanent discontinuation of either study drug).
To assess the antitumor activity of INCB099280 in combination with axitinib.	• Objective response (Part 1), defined as the best overall response of CR or PR by investigator assessment per RECIST v1.1. • Disease control, defined as the best overall response of CR, PR, or SD by investigator assessment per RECIST v1.1. • DOR, defined as the time from the first CR or PR until disease progression by investigator assessment per RECIST v1.1 or death from any cause, whichever occurs earlier.

Table 4: Objectives and Endpoints (Continued)

Objectives	Endpoints
Secondary (continued)	
To characterize the PK profile of INCB099280 when administered in combination with axitinib.	• INCB099280 and axitinib plasma concentrations. • INCB099280 PK parameters by NCA methods such as C_{max}, t_{max}, $AUC_{0\text{-}4h}$, $C_{max,ss}$, $t_{max,ss}$, $AUC_{0\text{-}12h}$, C_{avg}, C_{tau}, $t_{½}$, CL_{ss}/F, and V_z/F.
[redacted]	

4. STUDY DESIGN

4.1. Overall Design

This is an open-label, multicenter study performed to evaluate the safety, tolerability, antitumor activity, and PK and pharmacodynamic effects of INCB099280 in combination with axitinib in adults with previously treated advanced clear cell ovarian cancer, rare histological subtype epithelial cancer of the gynecological tract, endometrial cancer, or cervical cancer who have received at least 1 prior line of systemic chemotherapy and are not candidates for curative surgery or (chemo)radiation. The study will be composed of a dose-finding part and a dose-expansion part. See Table 2 for the key study design elements and Figure 1 for the study design schema.

INCB099280 and axitinib will be administered orally BID, either with a [redacted] meal or after the participant has [redacted] for at least [redacted] hours, on a continuous daily dose administration schedule. If a participant is unable to tolerate combination treatment, they will have met the criterion for study treatment discontinuation. However, on a case-by-case basis, after discussion between the medical monitor and the investigator, a decision may be made to continue INCB099280 monotherapy. The planned treatment duration for INCB099280 is 2 years (ie, up to 35 treatment cycles of 21 days), calculated from the first dose of study treatment.

Participants will be monitored closely for AEs from the time they have given written informed consent until 90 days after the end of treatment or until the initiation of a subsequent systemic

therapy, whichever occurs earlier. Adverse events will be assessed for their severity (graded according to the NCI CTCAE v5.0), seriousness, suspected relatedness to the study medication, action taken with regard to the study treatment and whether they fulfill a DLT criterion, and potential immune-mediated etiology. In the event of toxicity, study treatment may be adjusted by dosing interruptions with or without dose reductions of axitinib on resumption of treatment (see Section 6.6).

Even though INCB099280 and axitinib are metabolized primarily in the liver by [redacted], a clinically significant PK interaction is not anticipated. However, PK assessments will be conducted in this study to identify any effect of the combination on INCB099280.

Antitumor activity will be assessed per RECIST v1.1. Tumor assessments will be performed at baseline, 6 and 12 weeks after the start of treatment, and Q12W thereafter until disease progression or the participant has completed 2 years of treatment.

The study assessments and procedures, including the SoA, are outlined in Table 3.

4.1.1. Part 1: Dose Finding

Participants with diagnoses as defined for all disease-specific cohorts may be enrolled in Part 1. During the dose-finding part of the study, up to 2 doses of axitinib administered in combination with INCB099280 will be evaluated to identify a dose for further evaluation in the dose-expansion phase of the study.

The starting doses (Dose Level 1) are INCB099280 400 mg BID and axitinib 5 mg BID (see Section 2.3 and Section 2.4.2 for further details). Up to approximately 12 participants will be enrolled in this part of the study.

Dose levels, based on Dose Level 1 tolerability, are illustrated in Figure 4.

Dose Level −1 will only be investigated if a dose de-escalation rule is met at Dose Level 1 (see Section 6.5.2).

Decisions on dose will be based on DLTs observed in participants during the first 3 weeks of treatment (see Section 6.5).

No intraparticipant dose escalation of either of the study drugs will be permitted.

Dose finding may conclude after one of the following:

1. At least 9 DLT-evaluable participants have been enrolled in a dose level and with a hybrid design decision rule of "stay" met (see Table 5); then the highest dose with an observed DLT rate no higher than the target toxicity rate of 30% will be treated as the preliminary MTD.
2. At least 3 DLT-evaluable participants have been enrolled in Dose Level 1 and with a hybrid design decision rule of "escalate" met (see Table 5); then Dose Level 1 is considered safe and tolerable, and the MTD has not been reached.
3. At least 3 DLT-evaluable participants have been enrolled in Dose Level −1 and with a hybrid design decision rule of either "de-escalate" or "eliminate" met (see Table 5); then none of the dose levels will be considered safe and tolerable.

Figure 4: Dose Levels in the Dose-Finding Part of the Study

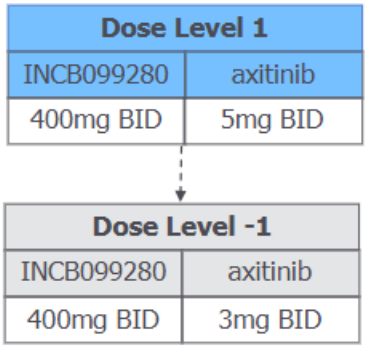


Table 5: Decision Rules of the Hybrid Design With a 30% Target Toxicity Rate

Participants With at Least 1 DLT	Number of Participants Evaluable for DLT												
	3	4	5	6	7	8	9	10	11	12	13	14	15
0	E	E	E	E	E	E	E	E	E	E	E	E	E
1	S	S	S	E	E	E	E	E	E	E	E	E	E
2	D	D	S	S	S	S	S	S	E	E	E	E	E
3	DU	DU	D	D	S	S	S	S	S	S	S	S	S
4		DU	DU	DU	D	D	D	S	S	S	S	S	S
5			DU	DU	DU	DU	DU	D	D	D	S	S	S
6				DU	DU	DU	DU	DU	DU	D	D	D	S
7					DU	DU	DU	DU	DU	DU	DU	D	D
8						DU	DU	DU	DU	DU	DU	DU	DU
9							DU	DU	DU	DU	DU	DU	DU

D = de-escalate to the next lower dose; DU = the current dose is unacceptably toxic; E = escalate to the next higher dose; S = stay at the current dose.

Note: The decision rules are modified from mTPI design of a target DLT rate p_T of 30% and a dose-exclusion cutoff of 0.95 to further control the overdosing toxicity using the posterior probability of the DLT rate in the overdosing interval (0.33, 1) of < 0.75. Flat noninformative prior Beta(1,1) is used as a prior and $\varepsilon_1 = \varepsilon_2 = 0.03$ (Ji et al 2010, Ji et al 2013).

On completion of the dose finding in Part 1, a dose will be selected for further evaluation and optimization in disease-specific expansion cohorts in Part 2 of the study (see Section 4.1.2). The selection of a dose to be evaluated in Part 2 will be based on the collective data available from the dose-finding part of the study, including dose/exposure-response analyses for safety, antitumor activity, and pharmacodynamic activity. The RDE selected for evaluation in Part 2 will not exceed the MTD. These expansion cohorts are intended to further evaluate the safety and tolerability beyond the initial dose-finding part of the study, assess preliminary antitumor activity, accumulate data on exposure and pharmacodynamic activity, and further characterize the dose- and exposure-response relationships of this combination regimen.

4.1.2. Part 2: Dose Expansion

On completion of Part 1, adult participants with recurrent, locally advanced, unresectable or metastatic cancer with the following histologies will be enrolled in 1 of 4 disease-specific cohorts:

- Cohort 1: Clear cell ovarian cancer (including primary peritoneal and fallopian tube) with at least 50% clear cell histology
- Cohort 2: Other rare histological subtype epithelial cancer of the gynecological tract, including but not limited to carcinosarcoma, neuroendocrine tumors of low and high grade (including small cell carcinoma), ovarian mucinous adenocarcinoma, low-grade ovarian serous carcinoma, SCCOHT, squamous cell cancer (excluding cervical and endometrial), and vulvar or vaginal cancer, regardless of histological subtype
- Cohort 3: Endometrial cancer (including clear cell histology)

  Note: This cohort excludes endometrial carcinosarcoma (malignant mixed Müllerian tumor), endometrial leiomyosarcoma, and endometrial stromal sarcoma.
- Cohort 4: Cervical cancer, including squamous, adenosquamous, or adenocarcinoma (inclusive of clear cell histology).

Up to 30 participants will be enrolled in each of the 4 disease-specific cohorts.

Clinical activity and safety will be monitored (see Section 4.1.3 and Section 8) to ensure participant safety and that clinical benefit is seen. Throughout Part 2 of the study, continuous monitoring will occur to ensure that futility is not met. At each interim monitoring of the study, all observed data will be taken into consideration and Bayesian predictive probabilities will guide decisions on future enrollment (see Section 10.5).

4.1.3. Safety Monitoring

During the conduct of Part 1 of the study, the sponsor will convene approximately biweekly telephone conferences with the investigative site staff to provide clinical updates on participants who remain on-study. Investigators who are unable to attend and have participants on-study will be requested to provide written updates prior to the meeting to keep all involved parties informed. An agenda will be provided in advance of these meetings, and minutes (including written summaries of cumulative participant-level safety and tolerability information, antitumor activity, and key discussion points and decisions) will be circulated to all investigative sites.

During Part 2 of the study, the sponsor monitoring of the study will include periodic DMC review. If any issues concerning participant safety arise during the study, this will be discussed at the investigator-sponsor meetings and, if appropriate, will be referred to the DMC.

Enrollment of participants into Part 2 may be suspended if > 40% of participants (when 5 or more participants have been enrolled) have an AE ≥ Grade 3 that is attributable to the investigational agent (INCB099280) and that persists over 7 days despite adequate management.

See Section 5.7 for additional information on the Part 2 DMC.

4.2. Overall Study Duration

The study begins when the first participant signs the study ICF. The end of the study is defined as the date of the last scheduled procedure shown in the SoA (see Table 3) for the last participant in the study globally.

A participant is considered to have completed the study if they have completed all parts of the study, including the last scheduled procedure shown in Table 3. The study is considered completed when the last participant completes the last scheduled procedures shown in the SoA, withdraws from the study, or is lost to follow-up.

In the European Union/European Economic Area, the results of the study will be based on the date of the last scheduled procedure shown in Table 3 of the last participant in the study globally to ensure the results are robust, meaningful, and representative of all multiregions by having complete follow-up data determined by the statistical hypotheses for the objectives established. Not using the global date could potentially jeopardize the integrity of the study and invalidate the study conclusions due to potential bias, thus potentially violating the statistical analysis assumptions.

The study will include a 28-day screening period during which eligibility will be assessed, continuous combination treatment in consecutive 21-day cycles as long as participants are receiving benefit and have not met any criteria for study withdrawal, a safety follow-up period of 30 (+ 7) days and 90 (+ 14) days after EOT, and disease status follow-up Q12W (± 14 days) after EOT for participants who discontinue for reasons other than PD. The planned treatment duration with INCB099280 is up to 2 years.

If there are ≤ 3 participants on study treatment for more than 6 months, a database lock of the study may occur to allow for the analysis of the study data. Any remaining participants may continue to receive study treatment, to be seen by the investigator, and to have study assessments and procedures conducted as per usual standard of care for this population. The investigator will be expected to monitor for and report any AEs leading to study drug discontinuation, SAEs, pregnancies, and deaths as detailed in Section 9. The remaining participants are considered to be on-study until a discontinuation criterion is met and written notification is provided to the sponsor.

4.3. Study Termination

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

The sponsor may terminate the study electively if, for example, required by regulatory decision or upon advice of the DMC. If the study is terminated prematurely, the sponsor will notify the investigators, the IRBs and IECs, and the regulatory bodies of the decision and reason for termination of the study. The DMC will recommend termination of the study if warranted, as described in Section 5.7.

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 this Protocol is essential. Prospective approval of Protocol deviations to recruitment and enrollment criteria, also known as Protocol waivers or exemptions, are not permitted.

5.1. Inclusion Criteria

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

1. Able to understand and willing to sign a written ICF for the study.
2. Age ≥ 18 years at the time of signing of the ICF.
3. Recurrent, locally advanced, unresectable or metastatic cancer with the following histologies:
   a. Cohort 1: Clear cell ovarian cancer (including primary peritoneal and fallopian tube); tumor specimens must be at least 50% clear cell histology as determined by the named specialist gynecological histopathologist(s) reviewing this on behalf of the study site
   b. Cohort 2: Other rare histological subtype epithelial cancer of the gynecological tract, including but not limited to carcinosarcoma, neuroendocrine tumors of low and high grade (including small cell carcinoma), ovarian mucinous adenocarcinoma, low-grade ovarian serous carcinoma, SCCOHT, squamous cell cancer (excluding cervical and endometrial), and vulvar or vaginal cancer, regardless of histological subtype
   c. Cohort 3: Endometrial cancer (including clear cell histology)

      Note: This cohort excludes endometrial carcinosarcoma (malignant mixed Müllerian tumor), endometrial leiomyosarcoma, and endometrial stromal sarcoma.

   d. Cohort 4: Cervical cancer, including squamous, adenosquamous, or adenocarcinoma histologies (including clear cell histology)
4. Disease progression on or after at least 1 prior systemic line of chemotherapy for gynecological cancer:
   - For Cohorts 1 and 2, participants must have received ≥ 1 but ≤ 3 prior lines of systemic chemotherapy for gynecological cancer. Prior anti–PD-(L)1 therapy is permitted.
   - For Cohorts 3 and 4, participants must have received ≤ 2 prior lines of systemic therapy, which may include prior platinum-based chemotherapy. Participants must have received prior anti–PD-(L)1 therapy (≥ 6 months on therapy without progression).

   Note: Endocrine therapy is not counted as a prior line of therapy.
5. Advanced disease not amenable to curative surgery or (chemo)radiation.

6. At least 1 measurable lesion based on radiographic imaging per RECIST v1.1. The measurable lesion should be outside any prior radiation field unless progression occurred at that site.

   Note: If participants have only 1 measurable lesion per RECIST v1.1, the biopsy specimen must be obtained from a nontarget lesion or archival tissue.

7. Willing to provide tumor tissue (fresh or archival). Formalin-fixed, paraffin embedded tissue blocks are preferred to slides.

   - Up to 15 participants in Cohort 1 and up to 15 participants in Cohort 2 must be willing to provide fresh biopsy specimens at screening, 6 to 8 weeks after the start of treatment, and at the time of disease progression/EOT (if technically feasible and safe).

8. ECOG performance status score of 0 or 1.
9. Life expectancy > 3 months, in the opinion of the investigator.
10. Willing and able to comply with all Protocol requirements, including all scheduled visits, Protocol procedures, and the ability to swallow oral medication.
11. Willingness to avoid pregnancy based on the criteria below.

    a. Women of childbearing potential must:

       – Have a negative serum pregnancy test at screening and must agree to take appropriate precautions to avoid pregnancy (with at least 99% certainty) from screening through 190 days after the last dose of study treatment. Permitted methods that are at least 99% effective in preventing pregnancy (see Appendix A) should be communicated to the participants and their understanding confirmed.

       – Refrain from donating oocytes from screening through 190 days after the last dose of study treatment.

    b. Women of nonchildbearing potential (ie, surgically sterile with a hysterectomy and/or bilateral oophorectomy OR ≥ 12 months of amenorrhea and at least 50 years of age) are eligible.

5.2. Exclusion Criteria

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

Cancer History

1. Known additional malignancy that progressed or required treatment during the past 3 years.

   Note: Exceptions include adequately treated basal cell carcinoma, cutaneous SCC, superficial (nonmuscle invasive) bladder cancer, and noninvasive cancers (eg, ductal carcinoma in situ, lobular carcinoma in situ, or in situ cervical cancer).

2. Known leptomeningeal disease.

3. Known CNS metastases as follows:
    a. Participants with untreated CNS metastases.
    b. Participants with treated CNS metastases who have disease progression, are clinically unstable within 2 weeks of the initiation of study treatment, or require increasing doses of steroids and/or a steroid dose of more than 1 mg of dexamethasone daily (or equivalent).

Prior Cancer Therapy

4. Removed during Protocol Amendment 1.
5. Prior therapy with antiangiogenic small-molecule TKIs targeting the VEGF pathway.

    Note: Prior treatment with anti-VEGF therapy (eg, bevacizumab, aflibercept) is allowed.
6. Treatment with anticancer therapies or investigational drugs within the following intervals before the first administration of study treatment:
    a. At least 14 days for chemotherapy or targeted small-molecule therapy
    b. At least 28 days for a prior monoclonal antibody used for anticancer therapy (including anti–PD-1 antibodies)
    c. At least 5 half-lives from receipt of prior anti–PD-L1 therapy

        Note: atezolizumab: ≥ 19 weeks; durvalumab: ≥ 15 weeks; avelumab: ≥ 30 days.
    d. At least 28 days or 5 half-lives (whichever is longer) for investigational study drugs or devices
7. Toxicity from prior therapy that has not recovered to ≤ Grade 1 or baseline.

    Exceptions: Anemia that is not transfusion-dependent and any grade alopecia.
8. Radiation therapy within 2 weeks of the first dose of study treatment.

    Note: Participants must have recovered from all radiation-related toxicities to ≤ Grade 1 and not require corticosteroids.
9. Participation in an interventional clinical study while receiving study treatment.

Medical History

10. History of any of the following cardiovascular conditions within 12 months of the initiation of study treatment:
    a. Symptomatic ischemic heart disease or unstable angina pectoris
    b. Myocardial infarction
    c. Cardiac angioplasty or stenting
    d. Coronary or peripheral artery bypass graft
    e. Class III or IV heart failure per NYHA (see Appendix D)
    f. Cerebrovascular accident or transient ischemic attack
11. Inadequately controlled hypertension (defined as SBP ≥ 150 mm Hg and/or DBP ≥ 90 mm Hg) based on an average of 3 BP readings at least 2 minutes apart.

    Note: Treatment with antihypertensive medication is allowed during screening to achieve BP with SBP/DBP < 150/90 mm Hg.

12. History of hypertensive crisis or hypertensive encephalopathy.
13. Significant vascular disease (eg, aortic aneurysm requiring surgical repair or recent peripheral arterial thrombosis) within 6 months prior to initiation of study treatment.
14. History of deep vein thrombosis or pulmonary embolism within 6 months of screening.
15. History of thromboembolism while on anticoagulation therapy.
16. Active bleeding disorder or other history of clinically significant (non-GI) bleeding episodes within 30 days of enrollment.
17. History of hemoptysis (> 2.5 mL/1 teaspoon of bright red blood per episode) within 6 weeks prior to the initiation of study treatment.
18. Tumor known to invade or encase a major blood vessel.
19. Major surgical procedure within 1 month prior to initiation of study treatment or expected need for a major surgical procedure during the study.
20. Core biopsy or other minor surgical procedure, excluding placement of a vascular access device, within 3 days prior to the initiation of study treatment.
21. Clinically significant nonhealing wound, wound dehiscence, or active ulceration or untreated bone fracture.
22. History of interstitial lung disease, including noninfectious pneumonitis requiring steroids.
23. Clinically significant GI abnormality, including the following:
    - Inability to take oral medication
    - Requirement for enteral or parenteral nutrition
    - Conditions that may affect drug absorption, as well as those that interfere with GI transit, including gastric bypass surgery, gastric sleeve, or gastric band
    - Endoscopically determined active gastroduodenal ulcer(s)
    - GI condition associated with increased risk of perforation (eg, direct tumor invasion of the bowel wall, inflammatory bowel disease, ulcerative colitis) or history of GI perforation
    - Current abdominal/pelvic fistulation or a history of abdominal/pelvic fistulation within the last 12 months
    - Acute or subacute intestinal obstruction
    - GI bleeding (eg, hematemesis, hematochezia, and melena) within 3 months prior to initiation of study treatment
24. Any autoimmune disease requiring systemic treatment in the past 5 years, including corticosteroids of a daily dose exceeding 10 mg of prednisone or equivalent.

    Exceptions: Hypothyroidism stable on hormone replacement or vitiligo.
25. Diagnosis of a primary immunodeficiency.

26. Active HBV or HCV defined as follows (testing must be performed to determine eligibility):
    a. Chronic HBV infection with HBV DNA (viral load) > 500 IU/mL.

       Note: Participants with chronic HBV infection who are on anti-HBV therapy and have HBV DNA < 500 IU/mL may enroll. Anti-HBV therapy must be initiated prior to initiation of study treatment and must continue while on study treatment and for 12 months after the end of study treatment.

    b. Active HCV is defined as a positive HCV antibody result and quantitative HCV RNA (viral load) result greater than the lower limit of detection for the assay.

       Note: Participants previously treated for HCV with undetectable HCV RNA are allowed in the study.
27. HIV infection and any of the following:
    - CD4+ T-cell count < 200 cells/µL
    - Detectable HIV RNA

      OR
    - On an ART regimen containing drugs that are moderate or potent CYP3A4/CYP3A5 inhibitors or inducers.

    Note: Switching to an alternative ART regimen with drugs that are weak or intermediate CYP3A4/5 inhibitors or inducers is allowed but must be taken for at least 28 days before initiating study treatment.
28. Active infection, including tuberculosis, requiring systemic therapy.

    Exceptions: Hepatitis B and C and HIV infections.
29. History of organ transplant (including stem cell transplantation).
30. Known hypersensitivity or severe reaction to any component of study drug or formulation components.

Medications

31. Received systemic antibiotics within 14 days of the initiation of study treatment.
32. Probiotic usage during screening and throughout the study treatment period.
33. Treatment with systemic immunosuppressive medication, including (but not limited to) glucocorticoids with daily doses exceeding an equivalent of 10 mg of prednisone per day, within 14 days prior to the initiation of study treatment.
34. Treatment with vitamin K antagonists.

    Note: Therapeutic use of the following agents is allowed:
    - Low-molecular-weight heparin
    - Direct-acting oral coagulants in alignment with each agent's posology (see Section 6.7.2.2).

35. Received a live-attenuated vaccine within 28 days of the planned start of study treatment or anticipated need to receive such a vaccine during the treatment period and up to 90 days after the last dose of study treatment has been administered.

    - Examples of common live-attenuated vaccines include, but are not limited to, MMR, chickenpox/zoster, yellow fever, rabies, BCG, typhoid, and LAIV.

    Note 1: 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.

    Note 2: COVID-19 vaccines (eg, mRNA) are allowed as long as they are not live vaccines.

36. Treatment with moderate and potent [redacted] inhibitors or inducers or drugs that are known to have proarrhythmic potential (see Appendix C).

    Note: A washout period ≥ 10 days before the first dose of INCB099280 is required for prior treatment with moderate or potent [redacted] inhibitors or inducers.

37. Unable to discontinue medication that is prohibited by this study (see Section 6.7.3) before the initiation of study treatment.

Organ Function

38. Laboratory values at screening as defined in Table 6.

Table 6: Exclusionary Laboratory Values

Laboratory Parameter		Exclusion Criterion
Hematology		
a	Platelets	$< 100 \times 10^9$/L
b	Hemoglobin	< 9 g/dL or < 5.6 mmol/L (transfusion is acceptable to meet this criterion)
c	ANC	$< 1.5 \times 10^9$/L
Hepatic		
d	ALT	> 2.5 × institutional ULN
e	AST	> 2.5 × institutional ULN
f	Total bilirubin	> 1.5 × institutional 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.
g	Albumin	< 3 g/dL
Renal		
h	Calculated CrCl[a]	CrCl < 50 mL/min

Table 6: Exclusionary Laboratory Values (Continued)

Laboratory Parameter		Exclusion Criterion
i	Urine protein	≥ 2+ by dipstick urinalysis and ≥ 2 g urinary protein per 24 hours on a 24-hour urine collection or urine protein-to-creatinine ratio ≥ 2
Coagulation		
j	INR	> 1.5 × institutional ULN (if not receiving therapeutic anticoagulation) > 2 × institutional ULN (if receiving therapeutic anticoagulation)
k	PT	> 1.5 × institutional ULN (if not receiving therapeutic anticoagulation) > 2 × institutional ULN (if receiving therapeutic anticoagulation)
l	aPTT	> 1.5 × institutional ULN
Bone profile		
m	Corrected serum calcium	> 2.9 mmol/L (> Grade 1) despite maximal antihypercalcemic therapy

[a] Cockcroft and Gault (1976): CrCl = {([140–age] × weight [kg]) / (72 × serum creatinine)} × 0.85 (if female).

Diagnostic Assessments

39. Clinically significant and uncontrolled arrhythmia.
40. An average QTcF interval > 480 milliseconds on a triplicate ECG.
41. Left ventricular systolic dysfunction with an LVEF < 50%.

Other Exclusions

42. Pregnant, expecting to conceive, or breastfeeding from consent until 190 days after the last dose of study treatment.
43. History or current evidence of a medical condition, therapy, or laboratory abnormality that, in the opinion of the investigator, might interfere with full participation in the study, increase the risk associated with study participation or the administration of the study medication, confound the results of the study, or make it inappropriate for the participant to take part in this study.
44. The following participants are excluded in France: 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, not affiliated to a social security per article L.1121-8-1 of the French Public Health Code.

5.3. Lifestyle Considerations

5.3.1. Meals and Dietary Restrictions

During each administration period (morning/evening), INCB099280 should be administered on an [redacted]. Meals that exceed [redacted] calories with

[redacted]% calories from fat should be consumed at least [redacted] hours before or after INCB099280 administration. Site staff should discuss light meals or snacks with the participant and provide examples of food consumption that should be avoided within the ± [redacted]-hour [redacted] window. An example of a [redacted] meal in the United States is to be provided as a guide and would include 8 oz of skim [1% fat] milk, 1 boiled egg, and 1 packet of flavored instant oatmeal made with water.

On days of PK sampling, participants should not consume a [redacted] or [redacted], [redacted] within at least [redacted] hours before or after INCB099280 dose administration.

5.3.1.1. [redacted]

Participants will refrain from consuming [redacted] containing these restricted [redacted] from 72 hours before the first dose of study treatment and throughout the study.

5.3.1.2. Probiotics

Probiotic dietary supplements are prohibited.

5.4. Screen Failures

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

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened 1 time.

Tests with results that fail eligibility requirements may be repeated once during screening if the investigator believes the result to be in error. Additionally, a participant who fails screening may repeat the screening process 1 time if the investigator believes that there has been a change in eligibility status. Participants who rescreen must reconsent and be assigned a new participant number.

5.5. Recruitment Strategy and Retention of Participants

Specific strategies may be used to recruit and retain under-represented populations in order to improve diversity enrollment. In this clinical study targeting advanced and metastatic gynecological cancers, it is expected that participants may be identified from the local site's database, as well as through referrals. To raise awareness about the clinical study, doctor-to-doctor letters and local flyers may be used, as permitted by each study site and regulatory bodies. Relevant patient advocacy groups may also be contacted.

To enhance participant retention, the sponsor or its designee may use sponsor- and ethics committee–approved visit reminder cards, where permitted by applicable laws. Information regarding study recruitment and retention materials (as allowed by national regulatory requirements in participating countries) will be discussed in the Study Reference Manual.

If appropriate, participants may be reimbursed for eligible out-of-pocket expenses associated with participation in the study. The amount, form, and timing of the reimbursement will be in accordance with applicable laws and the ICF.

5.6. Replacement of Participants

In Part 1, participants may be replaced for any of the following reasons:

- Does not meet the eligibility requirements of the study (see Section 7.1.1).
- Withdraws from treatment before the completion of the DLT observation period for any reason other than a DLT (eg, not evaluable for DLT) to ensure a minimum number of evaluable participants.
- Participants who were unable to receive at least ≥ 75% (ie, 32 doses) of the planned doses of INCB099280 and axitinib during the 21-day DLT observation period and who did not have a DLT will be replaced.

In Part 2, no participants will be replaced.

5.7. Data Monitoring Committee

This study will use a DMC to monitor safety and preliminary efficacy once Part 2 has begun. The DMC will make recommendations to the sponsor's clinical team regarding steps to ensure both participant safety and the continued ethical integrity of the study. Also, the DMC may review interim study data, consider the overall risk and benefit to study participants, and recommend if the study should continue in accordance with the Protocol. Specific details regarding composition, responsibilities, and governance of the DMC, including the roles and responsibilities of the various members and the sponsor, executive committee, and protocol team, will be described in the DMC charter. Requirements for and proper documentation of DMC reports, minutes, and recommendations will also be described in the DMC charter, which is reviewed and approved by all DMC members.

6. STUDY TREATMENT

Combination treatment with INCB099280 and axitinib will be administered orally BID on a continuous daily dosing schedule (ie, without a break in dosing in the absence of drug-related toxicity). Study treatment will be administered in consecutive 21-day cycles as long as participants are receiving benefit and have not met any criteria for study withdrawal. INCB099280 may be administered for up to 2 years (up to 35 cycles).

If a participant is unable to tolerate combination treatment, they will have met the criterion for study treatment discontinuation. However, on a case-by-case basis, after discussion between the medical monitor and the investigator, a decision may be made to continue INCB099280 monotherapy.

6.1. Study Treatments Administered

Study treatment will be dispensed at the visits noted in Table 3. Each participant will be given a dosing diary to record all administered doses, whether the dose was missed or vomited, and any comments regarding missed doses. Compliance with the study treatment will be reviewed at each visit, and the eCRF will then be completed based on the diary.

Details of the study treatment administration are provided in Table 7.

Table 7: Study Treatment Information

	Study Treatment 1	Study Treatment 1
Study treatment name	INCB099280	Axitinib
Mechanism of action	PD-L1 inhibitor	VEGFR-1, VEGFR-2, VEGFR-3 inhibitor
Dose formulation	Tablet	
Unit dose strengths/dose levels	[redacted] mg, [redacted] mg/400 mg BID	1 mg, 3 mg, 5 mg/2 mg BID, 3 mg BID, or 5 mg BID
Route of administration	Oral	
Administration instructions	Administered as tablets BID every day with a glass of water. INCB099280 may be administered either on an [redacted] or with a [redacted].[a] Note: A [redacted] (a meal that exceeds [redacted] calories with [redacted]% calories from fat) is acceptable if consumed at least [redacted] hours before or after dose administration. Participants must swallow the tablets whole without chewing before swallowing. Tablets must not be crushed, split, or dissolved. INCB099280 and axitinib should be taken in the morning and evening, approximately 12 hours apart. If the administration of either the morning or evening a dose is delayed by more than 4 hours compared with the usual time taken, the dose should be skipped. Participants must be informed that if they miss a dose or vomit after taking the tablets, an additional dose should not be taken. The next dose should be taken at the usual time.	
Packaging and labeling	INCB099280 will be provided in a bottle. Each bottle will be labeled as required per country requirement.	Axitinib will be provided in a bottle or as a blister pack. Axitinib will be a commercial supply. When applicable, each bottle or blister pack will be labeled as required per country requirement.
Storage	[redacted]-mg tablets: Must be refrigerated. Store at [redacted] [redacted]-mg tablets: Store at [redacted]	Axitinib does not require any special storage conditions.
Status of treatment in participating countries	Investigational	Approved

[a] An example of a [redacted] meal in the United States typically contains 11-14 g of fat and a total caloric value of 400-500 kcal (eg, 8 oz of skim [1% fat] milk, 1 boiled egg, and 1 packet flavored instant oatmeal made with water).

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 the following:

- Delivery of study drugs to the study site.
- Inventory of study drugs at the site.
- Participant use of the study drugs, including tablet counts from each supply dispensed.
- Return of study drugs to the investigator or designee by participants.

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 the destruction of any remaining study drug according to institutional SOPs. If, however, local procedures do not allow on-site destruction, shipment of the study drug back to the sponsor is allowed. In this case, the site should (where local procedures allow) maintain the investigational supply until the study monitor inspects the accountability records in order to evaluate compliance and accuracy of accountability by the investigative site. At sites where 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.

See Appendix B for instructions for participant handling of INCB099280. Axitinib should be stored, prepared, and handled according to the nationally approved label.

6.3. Measures to Minimize Bias: Randomization and Blinding

Not applicable.

6.4. Study Treatment Compliance

Compliance with all study-related treatments should be emphasized to the participant by the site personnel, and appropriate steps should be taken to optimize compliance during the study. Compliance with INCB099280 and axitinib will be calculated by the sponsor based on the drug accountability (ie, tablet counts) documented by the site staff and monitored by the sponsor/designee. Participants 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. Returned study drug should not be redispensed to the participants.

Qualified clinical study staff will review the participants' diary entries (see Section 8.1.4) for participant compliance with dose administration instructions. Participants who are noncompliant with their study drug schedule (defined as any missed dose) will have their administration instructions reinforced by the investigator or a qualified designee, and the sponsor should be consulted by the investigator for instruction on the proper handling of participants who are not compliant.

6.5. Dose-Limiting Toxicity and Determination of a Recommended Dose for Expansion

Any AE that is at least possibly related to study treatment and listed in Table 8 will be classified as a DLT. For the purpose of dose finding, decisions on dose will be based on DLTs observed during the first 21 days of treatment.

All DLTs will be assessed for severity by the investigator using CTCAE v5.0. Toxicities with a clear alternative explanation (eg, due to disease progression) or transient (≤ 72 hours) abnormal laboratory values without associated clinically significant signs or symptoms, based on investigator determination, can be deemed a non-DLT. All potential DLTs must be reported to the medical monitor within 24 hours of diagnosis. Participants who receive ≥ 75% of the doses of INCB099280 and axitinib (ie, 32 doses) at the level assigned or have a DLT will be considered evaluable for determining tolerability of the dose.

Individual participant dose interruptions or axitinib dose reductions may be made based on events observed at any time during treatment; however, for the purposes of dose escalation/de-escalation, expanding a dose level, and determining the MTD for the combination of INCB099280 with axitinib, decisions will be made based on treatment-related events that are observed from the first day of study drug administration through and including the final day of the DLT observation period (Day 21). Although the DLT observation period will be the first 21 days of treatment, DLTs observed beyond this period will be considered in all participants before an RDE is determined. As such, a lower RDE may be selected for further evaluation in Part 2.

6.5.1. Definition of a Dose-Limiting Toxicity

Treatment-emergent AEs listed in Table 8 will be classified as a DLTs.

Table 8: Definition of Dose-Limiting Toxicity

Nonhematologic toxicity
• Any liver function abnormalities that meet the definition of DILI (see Section 9.5). • Encephalopathy of any grade. • Grade 4 (life-threatening) vomiting or diarrhea. • Any Grade ≥ 3 nonhematologic toxicity EXCEPT the following: – Transient (≤ 72 hours) abnormal laboratory values without associated clinically significant signs or symptoms. – Nausea, vomiting, and diarrhea adequately controlled with supportive care within 48 hours. – An event clearly associated with the underlying disease, disease progression, a concomitant medication, or comorbidity. – Asymptomatic changes to lipid profiles. – Asymptomatic changes in amylase and lipase (in France only, with abdominal imaging to allow assessment of DLT criteria). – Singular or nonfasting elevations in blood glucose (ie, blood glucose excursions will be considered toxicities if fasting blood glucose is elevated on 2 separate occasions).
Hematologic toxicity
• Grade 3 thrombocytopenia with clinically significant bleeding (ie, requires hospitalization, transfusion of blood products, or other urgent medical intervention). • Grade 4 thrombocytopenia. • ≥ Grade 3 febrile neutropenia (ANC < 1.0×10^9/L and single temperature > 101°F/38.3°C or sustained temperature ≥ 100.4°F/38.0°C for more than 1 hour). • Grade 4 neutropenia that does not recover to ≤ Grade 2 in ≤ 7 days. • Grade 4 anemia not explained by the underlying disease or some other concomitant disorder.
Immune-related toxicity
• ≥ 2 Grade ocular irAEs. • Grade 3 irAEs that do not improve to at least Grade 1 in < 5 days with appropriate care or with corticosteroid therapy. *Exception:* Grade 3 or 4 endocrinopathy that is adequately controlled with hormone supplementation. • Grade 4 irAEs, regardless of duration. • Grade ≥ 2 myocarditis and/or pericarditis • Grade ≥ 2 myasthenia gravis, Guillain-Barré syndrome • Any grade encephalitis and/or demyelinating disease
General
Participant being unable to receive at least 75% (ie, 32 doses) of INCB099280 or axitinib doses during the DLT observation period because of treatment-related toxicity, even if the toxicity does not meet DLT criteria defined above. Note: Exceptions include the DLT exclusions mentioned above.
MTD
• In Part 1, the MTD will be defined as described in Section 4.1.1 and according to Table 5. • In Part 2, participants will be continually evaluated for safety, including AEs ≥ Grade 3 that are attributable to the study treatment. If warranted, enrollment of participants may be suspended until the sponsor, investigators, and DMC have determined the appropriate course of action.

6.5.2. Procedures for Cohort Review and Dose Finding

Decisions on dose will be guided by the hybrid design for dose escalation (Liao et al 2022; see Section 4.1.1) and will be consensus based, involving the investigators and the sponsor. Decision rules, based on the hybrid design after the totality of safety information has been considered, will determine if additional cohorts should involve dose escalation, no change in dose, or dose de-escalation or if a dose level should be eliminated.

Decisions on dose using the hybrid design include the following:

- Decisions will be based on DLTs observed in participants during the first 3 weeks of treatment.
- Enrollment in Dose Level 1 will start with a cohort of at least 3 participants.

Dose de-escalation will proceed if the decision rule to de-escalate to the lower dose level in the dosing algorithm is met, based on the condition that the current dose level was deemed overly toxic. Re-escalation may be considered after at least 3 evaluable participants treated at Dose Level −1 are followed for at least 3 weeks and escalation is warranted.

- Should the decision rule determine "stay," the DLT rate at the current dose level will be used to guide further enrollment.
  - For example, if 2 of 6 participants have a DLT, up to 3 additional DLT-evaluable participants will be enrolled. After the DLT period, if no DLTs occur in the 3 additional participants, an additional cohort of up to 6 DLT-evaluable participants may be enrolled. However, enrollment into that dose level may be stopped if ≤ 2 of 11 participants have a DLT because per the decision rule, dose-escalation criteria will have been met.
- If a participant withdraws from study treatment before receiving at least 75% of the planned doses of INCB099280 and axitinib during the 3-week DLT observation period (ie, 32 of the 42 planned doses) for reasons other than study treatment–related toxicity, another participant will be enrolled.

6.6. Dose Modifications

The management of some AEs may require dose modifications; these include treatment interruptions (see Section 6.6.1), dose reductions of axitinib (see Section 6.6.2), or the permanent discontinuation of study treatment (see Section 6.6.7).

General guidance on the management of AEs is as follows:

- Every effort should be made to exclude other etiologies in the differential diagnosis (such as neoplastic, infectious, nonspecific inflammatory, metabolic causes) to enable optimal medical management. A specialist referral is strongly encouraged when appropriate.
- When attributing an AE to either INCB099280 or axitinib proves challenging, the most conservative management recommendation should be followed.
  - The investigator's final assessment of causality/attribution and the rationale for this assessment must be documented in the participant's medical records.

- In the event that > 1 AE occurs, dose modifications should be based on the organ system with the greatest degree of toxicity.
- Toxicity management guidelines are provided in Table 11, Table 12, Table 13, and Table 14. If the guidance on the recommended management of a specific toxicity is not covered in this Protocol, participants should be managed according to best clinical practice.
- Supportive care should be provided as clinically indicated and in accordance with local, national, or international guidelines, as appropriate. When prescribing supportive medication, the potential DDIs and known risk QT interval prolongation should be considered (see Appendix C for further details).
  - The medical management of AEs must be documented in the participant's medical records.
- All dose modifications, including the justification, must be documented in the participant's medical records.

General guidance on the evaluation and management of AEs potentially associated with either INCB099280 or axitinib or both study drugs is as follows:

- Based on the known safety profiles of INCB099280 and axitinib, certain treatment-related AEs are uniquely associated with 1 drug versus the other.
  - For example, hypertension, arterial thrombotic events, proteinuria, and hemorrhagic events are known risks associated with axitinib treatment; irAEs are risks known to be associated with ICI treatment, including INCB099280.
- However, in some circumstances, attributing certain AEs, such as diarrhea, hypothyroidism, and liver enzyme elevation, to INCB099280 may be challenging when overlapping toxicities are expected with axitinib, anticipated for the population under study, or due to effects not related to the study treatment or another condition (eg, infection). In some circumstances, individual case assessment might be clarified with consideration to the following:
  - Time to onset
  - Diagnostic workup: after excluding alternative causes, an irAE should be considered until proven otherwise; events for which irAE-directed therapy was initiated but later stopped in favor of an alternative cause for the event should be captured in the participant's medical records
  - Follow-up response to immunosuppressive therapy
  - Positive dechallenge (eg, if an AE improves/resolves following interruption of axitinib, the event is most likely attributable to axitinib)
  - Rechallenge (if appropriate)

Regardless of the above, if the AE is severe/life-threatening at the time of onset or rapidly worsens, interrupt both drugs and initiate supportive care.

6.6.1. Dose Interruptions

The doses of INCB099280 and axitinib may be adjusted by dose interruptions with or without dose reductions of axitinib. Treatment interruptions for AEs associated with INCB099280 and axitinib are provided in Table 11, Table 12, Table 13, and Table 14. The criteria for dose interruptions are based on the severity of an AE. Treatment interruptions may occur independently for the 2 study drugs. Study treatment may also be interrupted for reasons other than treatment-related AEs (such as medical/surgical events or logistical reasons not related to study therapy).

In general, treatment may resume once the AE has improved to ≤ Grade 1 unless there are other comorbidities or other circumstances present that would contraindicate the resumption of study treatment.

Treatment may be interrupted for up to 3 weeks (21 days), after which it should be discontinued. However, if further clinical benefit is anticipated with resumption of treatment, interruptions between 4 and 8 weeks may be considered in consultation/agreement with the sponsor.

6.6.2. Dose Reductions

Dose reductions of INCB099280 below 400 mg BID are not permitted.

Axitinib dose reductions (see Table 9) may be indicated based on individual safety and tolerability. If axitinib dose reduction from 5 mg BID is required, the next recommended dose level is 3 mg BID. If a further dose reduction is required, the next dose level will be 2 mg BID. Axitinib should be permanently discontinued if the participant cannot tolerate 2 mg BID.

Table 9: Axitinib Dose-Reduction Scheme

Initially Assigned Axitinib Dose	First Dose Reduction	Second Dose Reduction
5 mg BID	3 mg BID	2 mg BID
3 mg BID	2 mg BID	NA

Intraparticipant dose escalation is not permitted.

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

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

Treatment with INCB099280 and axitinib may be delayed up to 3 weeks (21 days) to allow for resolution of toxicity. Participants may resume treatment if no medical condition or other circumstance exists that, in the opinion of the investigator, would make the participant unsuitable for participation in the study. The treating investigator should contact the sponsor to discuss the case of a participant whose treatment has been delayed for more than 21 days before restarting treatment with INCB099280 or axitinib.

Management guidelines for AEs requiring dose modifications for INCB099280 and axitinib are described for general toxicities (see Section 6.6.4) and for irAEs (see Section 6.6.5). Participants requiring dose reduction of INCB099280 will be discontinued from INCB099280 treatment. Dose reductions of axitinib should be made following the dose-modification guidelines and

according to the clinical judgment of the investigator. Participants may resume treatment once the AE resolves to ≤ Grade 1 or baseline if no medical condition or other circumstance exists that, in the opinion of the investigator, would make the participant unsuitable for further treatment and participation in the study.

6.6.4. Management of Non–Immune-Related Adverse Events

The guidance presented in Table 10 should be followed as best practice for decisions regarding management of non-irAEs.

Table 10: Non–Immune-Related Adverse Event Management Guidelines for INCB099280

CTCAE Grade	Suggested Modification for INCB099280
Grade 1 or Grade 2	Continue treatment at the discretion of the investigator.
Grade 3	Withhold treatment until resolution to ≤ Grade 1 or baseline. Restart INCB099280 at the same dose at the discretion of the investigator. Permanently discontinue study drug at the third occurrence unless approved by the medical monitor to continue.
Grade 4	Permanently discontinue study treatment or discuss with the medical monitor if a treatment algorithm for CTCAE Grade 3 events (above) is appropriate.

6.6.5. Management of Immune-Related Adverse Events

An AE of a potential immunologic etiology or an irAE may be defined as an AE consistent with an immune phenomenon associated with drug exposure after all other etiologies have been eliminated. Immune-related AEs are expected based on the mechanism of action of INCB099280 and reported experience with other anti–PD-(L)1 agents. If an irAE is suspected, efforts should be made to rule out neoplastic, infectious, metabolic, autoimmune, toxic, or other etiologic causes before categorizing an AE as an irAE. Participants who develop a ≥ Grade 2 irAE should be discussed immediately with the sponsor.

Continuation, withholding, or discontinuation of INCB099280 will depend on the severity of the irAE and affected organ/organ system and should be discussed with the medical monitor. Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested measures for the management of irAEs for INCB099280 are outlined in Table 11. For each AE, attempts should be made to rule out other causes, including but not limited to metastatic disease, bacterial infection, or viral infection that might require specific supportive care.

For additional management guidance for irAEs not detailed in the Protocol, or for details on diagnostic algorithms for an irAE if needed, refer to the ASCO, ESMO, or NCCN Clinical Practice Guidelines (Haanen et al 2022, NCCN 2021, Schneider et al 2021).

Table 11: Management Guidelines for Immune-Related Adverse Events

Severity (CTCAE v5 Grade)	INCB099280	Evaluation and Management
Pneumonitis		
Grade 1	• Withhold INCB099280 or continue with close monitoring. • Withhold INCB099280 for radiographic evidence of pneumonitis progression. • May resume with radiographic evidence of improvement or resolution if held.	• Monitor as appropriate (CT, spirometry/DLCO, history and physical examination, pulse oximetry, chest x-ray). • If no improvement, treat as Grade 2.
Grade 2	Withhold INCB099280 until improvement to ≤ Grade 1.	• Administer systemic corticosteroid (prednisone 1-2 mg/kg or equivalent) with taper over 4-6 weeks. • Consider empirical antibiotics. • Consider bronchoscopy with bronchoalveolar lavage. • Monitor at least once per week (history and physical examination, pulse oximetry, consider radiologic imaging). • If no improvement within 2-3 days of treatment with prednisone, treat as Grade 3. • Consultation with pulmonary and infectious disease specialists as necessary.
Grade 3, Grade 4, or recurrent Grade 2	Permanently discontinue INCB099280.	• Administer IV methylprednisolone 1-2 mg/kg or equivalent with taper. • Consider empirical antibiotics. • If no improvement after 2 days, may add infliximab 5 mg/kg, IV mycophenolate mofetil 1 g twice daily, IV immune globulin for 5 days, or cyclophosphamide. • Consultation with pulmonary and infectious disease specialists if necessary. • Bronchoscopy with bronchoalveolar lavage and/or transbronchial biopsy. Note: If clinical presentation is consistent with pneumonitis, transbronchial biopsy is not needed.
Diarrhea/colitis		
Grade 1	• Continue INCB099280 or hold INCB099280 temporarily. • Resume INCB099280 if toxicity does not exceed Grade 1 or resolves.	• Closely monitor by telephone or electronic medical system for symptom changes every 3 days or more frequently if needed until stabilized. • Provide supportive care (hydration, electrolyte replacement, dietary changes). • May obtain consultation with a gastroenterology specialist for prolonged event and consider endoscopy with biopsies.

Table 11: Management Guidelines for Immune-Related Adverse Events (Continued)

Severity (CTCAE v5 Grade)	INCB099280	Evaluation and Management
Diarrhea/colitis (continued)		
Grade 2 or Grade 3	Withhold INCB099280 until improvement to ≤ Grade 1.	Grade 2: • Consider consultation with a gastroenterology specialist. • Consider symptomatic treatment with an antidiarrheal agent if infection has been ruled out. • Administer systemic corticosteroids (prednisone 1 mg/kg or equivalent) until symptoms improve to Grade 1 and then taper over 4-6 weeks. • Consider infliximab or vedolizumab for steroid-refractory colitis (no decrease by 1 grade in 72 hours) or steroid-dependent colitis or colitis with high-risk features on initial endoscopy examination. Grade 3: • Administer systemic corticosteroids (prednisone 1-2 mg/kg or equivalent) until symptoms improve to Grade 1 and then taper over 4-6 weeks. • Consider IV methylprednisolone. • Consider early introduction of infliximab or vedolizumab in addition to steroids in participants with high-risk endoscopic features or inadequate response to steroids. • Consider hospitalization for participants with dehydration or electrolyte imbalance. • Consultation with a gastroenterology specialist for additional workup as appropriate.
Grade 4 or recurrent Grade 3	Permanently discontinue INCB099280.	• Administer IV methylprednisolone 1-2 mg/kg or equivalent until symptoms resolve to Grade 1 and then taper over 4-6 weeks. • If no improvement after 3 days, consider infliximab or vedolizumab. • Consultation with a gastroenterology specialist for additional workup as appropriate.
Hepatitis (AST/ALT increased and/or total bilirubin increased)		
Grade 1	Continue INCB099280.	• Repeat laboratory measurements 1-2 times/week. • Consider alternate etiologies. • Provide supportive care for symptoms.

Table 11: Management Guidelines for Immune-Related Adverse Events (Continued)

Severity (CTCAE v5 Grade)	INCB099280	Evaluation and Management
Hepatitis (AST/ALT increased and/or total bilirubin increased) (continued)		
Grade 2	Withhold INCB099280 until improvement to ≤ Grade 1.	• Repeat laboratory measurements every 3 days until return to baseline. • If elevations persist after 3 days or symptomatic, administer systemic corticosteroids (prednisone 0.5-1 mg/kg or equivalent) with taper over at least 1 month when symptoms improve to ≤ Grade 1. • If inadequate improvement over 3 days, consider adding mycophenolate mofetil if an infectious cause is ruled out. • Infliximab should NOT be used.
Grade 3	Permanently discontinue INCB099280.	• Repeat laboratory measurements every 1-2 days until return to baseline. • Administer IV methylprednisolone 1-2 mg/kg or equivalent with taper around 4-6 weeks when ≤ Grade 1 with re-escalation as needed. • If corticosteroid refractory, consider liver biopsy and addition of azathioprine or mycophenolate mofetil. • Infliximab should NOT be used. • Consultation with a hepatology specialist for additional workup as appropriate.
Grade 4	Permanently discontinue INCB099280.	• Recommendations as above for Grade 3. • 2 mg/kg/d methylprednisolone or equivalent.
Dermatitis		
Grade 1	Continue INCB099280.	Treat with topical emollients and/or mild- to moderate-potency topical steroids.
Grade 2	Consider holding INCB099280.	• Monitor weekly for improvement. If no improvement after 4 weeks, regrade toxicity as Grade 3. • Supportive care with topical emollients, oral antihistamines, and medium- to high-potency topical steroids. • Consider initiating prednisone 0.5-1 mg/kg or equivalent followed by tapering over 4 weeks. For participants with pruritus without rash, consider topical anti-itch remedies.
Grade 3	Withhold INCB099280 until improvement to ≤ Grade 1.	• Consultation with a dermatology specialist advised. • Administer IV methylprednisolone 1-2 mg/kg or equivalent with slow taper upon resolution. • Monitor for progression to severe cutaneous adverse reaction (eg, Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms/drug-induced hypersensitivity syndrome).
Grade 4 or recurrent Grade 3	Permanently discontinue INCB099280.	

Table 11: Management Guidelines for Immune-Related Adverse Events (Continued)

Severity (CTCAE v5 Grade)	INCB099280	Evaluation and Management
Nephritis or renal dysfunction (creatinine increased)		
Grade 1 (> ULN to 1.5 × ULN)	Consider temporarily holding INCB099280. If creatinine was within normal range at baseline and increased to Grade 1, recheck laboratory values in 48-72 hours.	Evaluate for alternative etiologies (eg, IV contrast, fluid status).
Grade 2 (> 1.5 to 3.0 × baseline; > 1.5 to 3.0 × ULN)	• If creatinine was within the normal range at baseline, withhold INCB099280 until improvement to ≤ Grade 1. • If creatinine was Grade 1 at baseline, INCB099280 may be continued and laboratory values checked in 48-72 hours. If creatinine is stable, INCB099280 may be continued and laboratory values rechecked in 48-72 hours. Additional consultation with the medical monitor is recommended. If creatinine increases, withhold INCB099280 and recheck chemistry laboratory values in 48 hours. INCB099280 treatment may resume when creatinine returns to Grade 1 or baseline.	• Consultation with nephrology specialist advised. • Evaluate for alternative etiologies (eg, IV contrast, fluid status). • If other etiologies are ruled out, administer prednisone 0.5-1 mg/kg or equivalent with taper over at least 4 weeks once improved to ≤ Grade 1.
Grade 3 (> 3.0 × baseline; > 3.0 to 6.0 × ULN), Grade 4 (> 6.0 × ULN), or persistent Grade 2	Permanently discontinue if INCB099280 is directly implicated in the renal toxicity.	• Consultation with a nephrology specialist advised. • Evaluate for alternative etiologies (eg, IV contrast, fluid status). • Administer prednisone 1-2 mg/kg or equivalent with taper over at least 4 weeks. • If elevations persist for > 3 days, consider additional immunosuppressive agents.
Diabetes mellitus		
Grade 1	Continue INCB099280 with close follow-up.	May initiate oral therapy for those with new-onset type 2 diabetes mellitus; intensify medical therapy for those with worsening type 2 diabetes mellitus.

Table 11: Management Guidelines for Immune-Related Adverse Events (Continued)

Severity (CTCAE v5 Grade)	INCB099280	Evaluation and Management
Diabetes mellitus (continued)		
Grade 2	May hold INCB099280 until glucose control is obtained.	• Urgent consultation with an endocrine specialist and consultation for new-onset checkpoint inhibitor–associated diabetes mellitus. • Insulin for checkpoint inhibitor–associated diabetes mellitus. • Titrate therapy to achieve glucose control.
Grade 3 or Grade 4	Withhold INCB099280 until glucose control is achieved and ≤ Grade 1.	• Admit for inpatient management of diabetic ketoacidosis, volume and electrolyte resuscitation, and insulin initiation. • Consultation with an endocrine specialist for all participants. • Insulin therapy for all participants.
Hypothyroidism		
Grade 1	Continue INCB099280.	Monitor TSH and FT4 as appropriate.
Grade 2	May continue or withhold until improved to ≤ Grade 1.	• Consider consultation with an endocrinology specialist. • Thyroid hormone replacement for symptomatic participants with any TSH elevation or participants with asymptomatic TSH levels persistently > 10 mIU/L (measured 4 weeks apart). • Monitor TSH and FT4 while titrating hormone replacement and once adequately resolved.
Grade 3 or Grade 4	Withhold INCB099280 until improvement to ≤ Grade 1 with appropriate thyroid hormone supplementation.	• Consultation with an endocrinology specialist advised. • Hospital admission for developing myxedema. • Thyroid hormone replacement as in Grade 2.
Hyperthyroidism		
Grade 1	Continue INCB099280.	• Monitor TSH and FT4 every 2-3 weeks. • Beta-blocker for symptomatic relief. • Consider consultation with an endocrine specialist for persistent hyperthyroidism.
Grade 2	Consider withholding until improvement to ≤ Grade 1.	• Consider consultation with an endocrinology specialist. • Beta-blocker for symptomatic relief. • Hydration and supportive care. • Consider consultation with an endocrine specialist for persistent hyperthyroidism.
Grade 3 or Grade 4	Withhold INCB099280 until improvement to ≤ Grade 1 with appropriate therapy.	• Consultation with an endocrinology specialist advised. • Prednisone 1-2 mg/kg or equivalent with taper. • Beta-blocker for symptomatic relief. • Consider thionamide.

Table 11: Management Guidelines for Immune-Related Adverse Events (Continued)

Severity (CTCAE v5 Grade)	INCB099280	Evaluation and Management
Hypophysitis or adrenal insufficiency		
Grade 1 or Grade 2	Consider withholding until improvement to ≤ Grade 1.	Grade 1: • Consultation with an endocrinology specialist advised. • Systemic corticosteroid replacement with preference for hydrocortisone. Hormone replacement as clinically indicated. Grade 2: • Clinic evaluation to assess need for steroids and volume repletion. • Hypophysitis: Consider oral pulse-dose therapy in participants with MRI findings of swelling or impending optic chiasm compression. • Hormone supplementation as in Grade 1.
Grade 3 or Grade 4	Withhold INCB099280 until improvement to ≤ Grade 1.	• Consultation with an endocrinology specialist advised. • Inpatient management of fluids and stress-dose corticosteroids. • Maintenance therapy as in Grade 1.
Myocarditis or pericarditis		
All grades		• The prompt diagnosis of immune-mediated myocarditis is important, particularly in participants with baseline cardiopulmonary disease and reduced cardiac function. • Immediately consult a cardiologist. • Initial diagnostic workup should include a clinical evaluation, ECG, and telemetry monitoring as well as cardiac imaging, that is, echocardiogram and cardiac MRI (strongly recommended). • Recommended laboratory testing includes cardiac biomarkers (creatine kinase, brain natriuretic peptide, and troponin) and inflammatory biomarkers (erythrocyte sedimentation rate, C-reactive protein, and white blood cell count). • Participants should be thoroughly evaluated to rule out any alternative etiologies (eg, disease progression, other medications, or infections via viral titers). • Consider discussing with the study physician, as needed. • Monitor symptoms daily. As some symptoms can overlap with lung toxicity, simultaneously evaluate for, and rule out, pulmonary toxicity as well as other causes (eg, pulmonary embolism, CHF, malignant pericardial effusions).
Elevated troponin Grade 1	Withhold treatment	• Hold INCB099280. Recheck troponin 6 hours later. May consider resuming once normalized or if believed not to be related to INCB099280.

Table 11: Management Guidelines for Immune-Related Adverse Events (Continued)

Severity (CTCAE v5 Grade)	INCB099280	Evaluation and Management
Myocarditis or pericarditis (continued)		
Grade 2, Grade 3, and Grade 4 as well as biopsy-proven immune-mediated myocarditis, pericarditis (all grades)	Permanently discontinue INCB099280.	• Intensive care monitoring is strongly recommended. • Promptly start IV methylprednisolone (consider methylprednisolone pulse dosing [1 g/day for 3-5 days]); treat until cardiac function returns to baseline and then dose taper over 4-6 weeks. • If no improvement is noted within 24 hours on steroids, consider adding immunosuppressive agents (such as infliximab, antithymocyte globulin, and mycophenolate mofetil). • It is important to rule out sepsis and refer to the infliximab label for general guidance before using infliximab; infliximab is contraindicated in participants who have heart failure.
Nervous system disorders		
Grade 1	Continue INCB099280, or may withhold and monitor. Note: The following conditions require a hold of INCB099280: • Aseptic meningitis • Encephalitis	• Consultation with a neurology specialist is advised. • Monitor closely for any symptom progression. • Exclude alternative etiologies, empiric treatment as indicated.
Grade 2	Withhold INCB099280 until improvement to ≤ Grade 1. Note: Demyelinating diseases require INCB099280 to be stopped; may resume in consultation with neurology.	• Consultation with a neurology specialist advised and workup including MRI. Consider EMG, lumbar puncture, and CSF analysis. • Administer supportive care and corticosteroids. • Monitor closely for any symptom progression. • Workup for alternative etiologies, empiric treatment as indicated.
Grade 3	Withhold INCB099280 until improvement to ≤ Grade 1 OR Permanently discontinue INCB099280.	• Consultation with a neurology specialist advised and workup including MRI. Consider EMG, lumbar puncture, and CSF analysis. • Administer supportive care and corticosteroids. • Workup for alternative etiologies, empiric treatment as indicated. • Continuation, withholding, or discontinuation of INCB099280 will depend on the severity of the irAE and affected organ/organ system. Restarting participants after Grade 3 nervous system AEs requires medical monitor approval.

Table 11: Management Guidelines for Immune-Related Adverse Events (Continued)

Severity (CTCAE v5 Grade)	INCB099280	Evaluation and Management
Nervous system disorders (continued)		
Grade 4	Permanently discontinue INCB099280.	• Consultation with a neurology specialist advised and workup including MRI. Consider EMG, lumbar puncture, and CSF analysis. • Administer supportive care and/or corticosteroids. • Workup for alternative etiologies, empiric treatment as indicated.
Other irAEs		
Grade 1	Continue INCB099280	• Administer supportive care, which may include corticosteroids. • Consider relevant specialist consultations, as appropriate.
Grade 2	Continue INCB099280 OR Withhold INCB099280 until improvement to ≤ Grade 1 OR Permanently discontinue INCB099280.	
Grade 3 or intolerable/ persistent Grade 2	Withhold INCB099280 until improvement to ≤ Grade 1 OR Permanently discontinue INCB099280.	
Grade 4 or recurrent Grade 3	Permanently discontinue INCB099280.	

6.6.6. Dose-Modification Guidelines for Adverse Events Potentially Associated With Axitinib Treatment

Participants should be monitored throughout the study for the development of safety events known to be associated with axitinib treatment.

General guidance on specific safety events described with the use of axitinib is as follows:

- BP should be well controlled prior to initiating study treatment.
  - The median time to onset of hypertension (SBP > 150 mm Hg or DBP > 100 mm Hg) is within the first month of the start of treatment, but BP increases have been observed as early as 4 days after starting axitinib. See Section 6.6.6.1 for further details.
- Participants should be monitored for signs or symptoms of heart failure.
  - Underlying cardiac contractile dysfunction can either be left ventricular systolic dysfunction or left ventricular diastolic dysfunction (impaired relaxation, as is frequently seen in participants with arterial hypertension). See Section 6.6.6.2 for further details.

- Axitinib should be used with caution in participants who are at risk for or who have a history of arterial and venous embolic and thrombotic events.
  - Increases in hemoglobin or hematocrit (polycythemia) may occur during treatment with axitinib; an increase in red blood cell mass may increase the risk of embolic and thrombotic events.
- Palmar-plantar erythrodysesthesia syndrome (hand-foot syndrome) is a common skin reaction that should be anticipated (see Section 2.3).
  - Awareness and early recognition are important to ensure timely treatment and avoidance of dose reductions or treatment discontinuation.
  - It may have a serious impact on a participant's quality of life and, as a result, their ability to continue or complete study treatment.
  - Effective measures for the prevention and treatment (including systemic and topical treatments, axitinib dose reductions) exist; these approaches may allow participants to continue study treatment while reducing negative impacts on their quality of life.
  - A referral to a dermatologist is recommended.
- Liver-related adverse reactions:
  - The most commonly reported liver-related adverse reactions include increases in ALT, AST, and blood bilirubin.
  - Differentiating whether elevations in transaminase levels are attributable to INCB099280 or axitinib, or both, may be challenging, as no specific clinical picture or laboratory markers are available.
  - A referral to a hepatologist is recommended.
  - See Section 6.6.6.3 for further details.
- GI perforation and fistula formation:
  - Prior radiation therapy has been identified as a possible predisposing risk factor for fistula formation in participants undergoing treatment with axitinib.
  - Monitor participants for signs and symptoms of perforation and fistula.
- Reversible posterior leukoencephalopathy syndrome, also known as posterior reversible encephalopathy syndrome:
  - Should be considered in any participant presenting with headache, seizure, lethargy, confusion, blindness, and other visual and neurological disturbances.
  - It has been observed in association with mild to severe hypertension.
  - MRI is necessary to confirm the diagnosis.

Guidance on the management of specific safety events potentially associated with axitinib treatment is provided in Table 12, Table 13, and Table 14.

6.6.6.1. Blood Pressure Measurement and Hypertension

Blood pressure will be monitored for the development or worsening of pre-existing hypertension at the timepoints indicated in Table 3. Additionally, participants may be encouraged to monitor their BP at home as needed. Participants should be instructed to contact the site for guidance if BP measurements are > 150 mm Hg systolic and/or 100 mm Hg diastolic or if they develop signs or symptoms thought to be related to increased BP (eg, headache, visual disturbance).

The ESC/ESH and ACC/AHA place strong emphasis on accurate measurement of BP by using validated devices and multiple readings for the diagnosis and management of hypertension (Whelton et al 2018, Williams et al 2018). Additionally, standardized clinical settings for a valid measurement include the following:

- Conditions:
  - Avoid smoking, caffeine, and exercise for 30 minutes; empty bladder; seated comfortably in a quiet environment for 5 minutes before beginning BP measurements.
  - Neither participant nor staff should talk before, during, and between measurements.
- Position:
  - Arm resting on table with midarm at heart level; back supported on chair, legs uncrossed and feet flat on floor.
- Cuff:
  - The cuff should be positioned at the level of the heart, with the back of the arm supported to avoid muscle contraction and isometric exercise–dependent increase in BP.
- Protocol:
  - Measure BP in both arms at first visit to detect possible between-arm differences. Use the arm with the higher value as the reference.
  - The ESC/ESH recommends repeated readings (3 BP measurements should be recorded 1-2 minutes apart, with additional measurements only if the first 2 readings differ by > 10 mm Hg or BP is unstable because of an arrhythmia).
  - BP is recorded as the average of the last 2 BP readings.

Hypertension should be managed in accordance with the ESC/ESH or ACC/AHA guidelines. Both guidelines have similar core strategies and recommend the use of agents from 4 drug classes (diuretics, CCBs, ACE inhibitors, or ARBs) where there is no compelling indication for selection of a specific BP-lowering medication. Additionally, both guidelines also advise combination therapy (usually an initial combination of ACE inhibitors or an ARB, a diuretic, and/or a CCB followed by a 3-drug combination if necessary) if there is no compelling indication for drug choice. However, treatment intensity and the choice of drugs should be based on clinical judgment (especially in participants with a high burden of comorbidity), participant preference, and team-based approach to assessing risk/benefit.

- General guidance:
  - The target SBP is ≤ 140 mm Hg and DBP ≤ 90 mm Hg, provided that the treatment is well tolerated.
  - Initiate antihypertensive drug therapy when SBP ≥ 140 mm Hg or DBP ≥ 90 mm Hg.
  - A referral to a cardiologist is recommended for participants who develop hypertension during the study, and management of hypertension should ideally be supervised by a cardiologist.
  - The plasma half-life of axitinib is 2 to 6 hours, and BP usually decreases within 1 to 2 days following dose interruption. Therefore, if axitinib is interrupted in participants receiving antihypertensive medication, monitor them closely for orthostatic hypotension (a reduction in SBP ≥ 20 mm Hg or in DBP ≥ 10 mm Hg within 3 minutes of standing).
- Guidance on the management of hypertension, based on severity, is provided in Table 12.

6.6.6.2. Left Ventricular Function and Heart Failure

Left ventricular systolic and diastolic function will be monitored at the timepoints indicated in Table 3. Since numerous echocardiographic techniques are used in the assessment of left ventricular function, sites should use their preferred method of assessment and supplement it by any other technique deemed essential to guide management. Every effort should be made to schedule serial monitoring at the same cardiac imaging facility.

Management of cardiovascular risk factors should be optimized prior to initiation of treatment with axitinib. Signs and symptoms of cardiac failure should be monitored throughout the study. Participants must be permanently discontinue from study drug for clinically manifested CHF. See Table 12 for guidance on the management of cardiac failure and Appendix D for NYHA functional classifications of heart failure.

6.6.6.3. ALT and AST Elevation

General considerations when evaluating elevated transaminase levels are as follows:

- The determination of immune-related hepatitis mostly relies on the exclusion of other causes, including treatment with axitinib; however, the attribution of AST/ALT elevation to treatment with either INCB099280 or axitinib may be challenging. Potential alternative causes that should also be evaluated and excluded before more definitively concluding the attribution to study treatment include the following:
  - Exposure to other drugs, including over-the-counter and herbal medications that are potentially associated with DILI (eg, statins, acetaminophen)
  - History of alcohol use and recent alcohol use
  - Viral hepatitis A, B, C, and E; cytomegalovirus, Epstein-Barr virus, and other systemic infections

  - Autoimmune screening tests
  - Liver metastasis and obstructive hepatic disease
  - Cardiac or vascular etiology (eg, any cause of severe hypoperfusion of the liver, severe cardiac failure)
  - Other causes as appropriate
- Time to onset:
  - Early onset (compared to ICI-related elevations in transaminase levels that occur predominately with the first 6-12 weeks after treatment initiation) suggests the event is likely associated with axitinib after excluding other alternative explanations.
- Response to drug dechallenge:
  - A prompt recovery from elevation in transaminase levels in response to axitinib interruption without confounding by corticosteroid treatment suggests the event is likely associated with axitinib (after excluding other alternative explanations).
  - If the initial elevation in transaminase levels does not respond rapidly to axitinib interruption but responds to subsequent corticosteroid treatment, it suggests a potential for immune-mediated hepatitis by INCB099280. It should be kept in mind that not all cases of immune-mediated hepatitis will respond to corticosteroid treatment.
- A positive rechallenge (see notes below and further details in Table 14; ie, recurrence of elevation in transaminase levels following resumption with study treatment) will provide further support for its attribution.
- Guidelines on causality elevation and management of AST/ALT elevations during axitinib/INCB099280 treatment are described (see Table 14) for action taken with study medication:
  - Promptly interrupt (or permanently discontinue) both study drugs and any other suspected concomitant medications, including over-the-counter and herbal medications and supplements.
  - Adequately monitor liver enzymes and LFTs. This should include AST, ALT, alkaline phosphatase, total bilirubin, direct bilirubin, and PT/INR. Repeat LFTs within 24 to 72 hours to confirm the initial laboratory value. Continue to monitor LFTs at least twice weekly, while evaluating other causes, until AST/ALT values are trending downward.

While corticosteroid therapy is essential for managing immune-mediated hepatitis, administering immunosuppressants prior to identifying the most likely causes of transaminase elevation will confound the causality assessment and impact proper management of the event. Initiating corticosteroids should be considered if transaminase elevation:

- Is associated with clinical significant hepatic dysfunction (eg, AST/ALT > 3 × ULN with concurrent total bilirubin ≥ 2 × ULN (excluding biliary obstruction) and/or PT/INR ≥ 1.5 × ULN

  OR

- Has been persistent or further increased (without an alternative cause identified); consider observing liver biochemistry for approximately 3 to 7 days prior to making the decision if the participant is stable.

Rechallenge after AST/ALT elevation:

- Rechallenge should occur at the discretion of the investigator in consultation with the medical monitor. The guidelines in Table 14 are suggestions; clinical judgment should always be used when deciding whether or not to restart each study drug.

Recommended axitinib dose modifications in case of drug-related toxicity are shown in Table 12, Table 13, and Table 14.

Table 12: Axitinib Toxicity Management Guidelines

Event/Severity (CTCAE v5 Grade)	Management Guideline
Hypertension	
SBP > 150 mm Hg OR DBP > 100 mm Hg	• SBP < 150 mm Hg − Continue axitinib at the current dose level. − Initiate/optimize antihypertensive therapy to achieve target SBP ≤ 140 mm Hg. • SBP > 150 mm Hg or DBP > 100 mm Hg − Initiate/optimize antihypertensive therapy. − Reduce axitinib dose by 1 dose level (see Table 9).
SBP > 160 mm Hg OR DBP > 105 mm Hg	• Interrupt axitinib until BP < 150/100 mm Hg. • Initiate/optimize antihypertensive therapy (unless already on maximal antihypertensive therapy). • Resume axitinib with a dose reduction of 1 level (see Table 9).
Grade 4 Life-threatening consequences (eg, malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis)	Discontinue axitinib.

Table 12: Axitinib Toxicity Management Guidelines (Continued)

Event/Severity (CTCAE v5 Grade)	Management Guideline
Cardiac failure	
Asymptomatic cardiomyopathy (LVEF > 20% but < 50% below baseline or below the lower limit of normal of baseline was not obtained)	• Interrupt axitinib until resolution to Grade 0 or 1 or baseline. • Resume axitinib with a dose reduction of 1 level (see Table 9).
Clinically manifested CHF	Discontinue axitinib.
Fistula	
Trachea-esophageal fistula Any grade	Discontinue axitinib.
Fistula other than trachea-esophageal Grade 1 or Grade 2	• Interrupt axitinib. • Either resume axitinib at a dose reduction (see Table 9) or discontinue depending on the severity and persistence of the adverse reaction.
Fistula other than trachea-esophageal fistula Grade 3 or Grade 4	Discontinue axitinib.
Impaired wound healing	
Any grade	• The safety of resumption of axitinib after resolution of wound healing has not been established. • Either resume axitinib at a reduced dose (see Table 9) or discontinue, depending on the severity and persistence of the adverse reaction.
GI perforation	
Any grade	Discontinue axitinib.
Arterial thromboembolic events	
Any grade	Discontinue axitinib.
Venous thromboembolic events	
Any grade	• Interrupt axitinib. • Either resume axitinib at the same dose level or discontinue, depending on the severity of the VTE. • Permanently discontinue for severe VTE.
Hemorrhage	
Grade 1	• For hemoptysis, interrupt axitinib and evaluate underlying causes. • Resume axitinib at the discretion of the investigator. • For other Grade 1 hemorrhage/bleeding events, continue axitinib at the current dose level and monitor as clinically indicated.

Table 12: Axitinib Toxicity Management Guidelines (Continued)

Event/Severity (CTCAE v5 Grade)	Management Guideline
Hemorrhage (continued)	
Grade 2	• For pulmonary or GI bleed (other than hemorrhoidal bleeding): − Discontinue axitinib. • Other bleeding events: − Interrupt axitinib until the severity of the event improves to Grade ≤ 1. − Resume axitinib with a dose reduction of 1 level (if permitted by Table 9).
Grade 3 and Grade 4	Discontinue axitinib.
Hypothyroidism	
All grades	Continue axitinib while thyroid replacement therapy is initiated. See Table 11 for further details on event management.
Hyperthyroidism	
Grade 1 and Grade 2	Continue axitinib at the current dose level. See Table 11 for further details on event management.
Grade 3	If symptoms can be controlled with symptomatic medications, or if asymptomatic: may continue axitinib at the same dose level or dose reduced by 1 dose level (see Table 9) per investigator judgment. See Table 11 for further details on event management.
Grade 4	• Hold axitinib until recovery to Grade ≤ 1 or baseline. • Resume axitinib at 1 dose level reduced (see Table 9). See Table 11 for further details on event management.
Reversible posterior leukoencephalopathy syndrome/posterior reversible encephalopathy syndrome	
Any grade	Discontinue axitinib.
Proteinuria	
Grade 1 1+ proteinuria OR Urinary protein ≥ ULN to < 1 g/24 h AND Without nephrotic syndrome	Continue axitinib at the current dose level.
Grade 2 and Grade 3 ≥ 2+ proteinuria OR Urinary protein 1 to < 3.5 g/24 h AND Without nephrotic syndrome	Proteinuria ≥ 2+ on dipstick urinalysis • Perform 24-hour urine collection and measure total protein. • May continue with axitinib while awaiting results: <u>≤ 2 g protein/24 hour</u> − Continue axitinib at the current dose level. <u>≥ 2 g protein/24 hour</u> − Interrupt axitinib until proteinuria < 2 g/24 h. − Repeat 24-hour urine collection and protein measurement (frequency at discretion of the investigator) until proteinuria < 2 g/24 h. − Resume axitinib at a reduced dose (see Table 9).

Table 12: Axitinib Toxicity Management Guidelines (Continued)

Event/Severity (CTCAE v5 Grade)	Management Guideline
Proteinuria (continued)	
Nephrotic syndrome	Discontinue axitinib.
Creatinine increased	
Grade 1 or Grade 2	Continue axitinib at the current dose level. See Table 11 for further details on event management.
Grade 3 or Grade 4	• Interrupt axitinib until recovery to Grade < 2 • Resume axitinib with a dose reduction of 1 level (see Table 9) Note: Caution should be used in participants with end-stage renal disease (CrCl < 15 mL/min). See Table 11 for further details on event management.
Other adverse reactions	
Grade 1, Grade 2	Continue axitinib at the current dose level.
Grade 3	Reduce axitinib by 1 dose level (see Table 9).
Grade 4	• Interrupt axitinib until resolution to Grade < 2. • Resume axitinib when severity has improved to Grade ≤ 2 with a dose reduction of 1 level (see Table 9).

Table 13: Management Guidelines for Specific Adverse Events Common to Both INCB099280 and Axitinib

Event/Severity (CTCAE v5 Grade)	Evaluation and Management
Liver enzyme elevation[a]	
ALT/AST ≥ 3 × ULN but < 10 × ULN without concurrent total bilirubin ≥ 2 × ULN	• Interrupt both INCB099280 and axitinib until resolution to Grade 0-1. • Consider rechallenge with INCB099280 and axitinib. See Table 14 for further details on event management.
ALT/AST ≥ 3 × ULN with concurrent total bilirubin ≥ 2 × ULN or ALT/AST ≥ 10 × ULN	Permanently discontinue both INCB099280 and axitinib.
Diarrhea	
Grade 1 or Grade 2	Initiate symptomatic medications. See Table 11 for further details on event management.
Grade 3	• Interrupt axitinib and initiate symptomatic medications. • If diarrhea is controlled, axitinib may be resumed at either the same dose level or reduced by 1 dose level (see Table 9). See Table 11 for further details on event management.
Grade 4	Interrupt axitinib until resolution to Grade < 2, then restart axitinib dose reduced by 1 dose level (see Table 9). See Table 11 for further details on event management.
Major adverse cardiovascular events	
Grade 3 and Grade 4	Permanently discontinue both INCB099280 and axitinib.

[a] Consider corticosteroid therapy.

Table 14: Algorithms of Decision on INCB099280/Axitinib Rechallenge After Recovery From Drug-Related ALT/AST Elevation

Initial ALT/AST Elevation Scenario	Rechallenge Decision
Scenario 1: ALT/AST > 3 × ULN concurrent with total bilirubin ≥ 2 × ULN (excluding biliary obstruction) and/or PT/INR > 1.5 × ULN (ie, ALT/AST elevation with clinically significant signs of hepatic dysfunction)	No rechallenge with either INCB099280 or axitinib is allowed.
Scenario 2: ALT/AST > 3-5 × ULN without clinically significant signs of hepatic dysfunction (ie, total bilirubin < 2 × ULN and PT/INR < 1.5 × ULN)	Unacceptable toxicity or the inability to tolerate study treatment with both INCB099280 and axitinib will require discontinuation from both study drugs. Combination treatment with INCB099280 and axitinib can be resumed sequentially with axitinib (at the previous dose) resumed first for 2-3 weeks with weekly liver test monitoring: • If no recurrence, rechallenge with INCB099280. • If ALT/AST recurrence is > 5 × ULN (ie, Grade 3 or 4), discontinue axitinib. A rechallenge with INCB099280 monotherapy may be considered on a case-by-case basis after discussion between the medical monitor and investigator. See Section 6.6.7 for further details. • If ALT/AST recurrence is > 3-5 × ULN (ie, Grade 2), reduce the dose of axitinib and then rechallenge or discontinue axitinib and rechallenge with INCB099280. If axitinib needs to be discontinued, on a case-by-case basis, after discussion between the medical monitor and investigator, INCB099280 monotherapy may be considered. Permanently discontinue INCB099280 if ALT/AST recurrence is > 5 × ULN or interrupt INCB099280 if ALT/AST recurrence is > 3 to 5 × ULN after rechallenge.
Scenario 3: ALT/AST > 5 to 10 × ULN without clinically significant signs of hepatic dysfunction (ie, total bilirubin < 2 × ULN and PT/INR < 1.5 × ULN).	No rechallenge with either INCB099280 or axitinib is allowed.
Scenario 4: ALT/AST > 10 × ULN without clinically significant signs of hepatic dysfunction	No rechallenge with either INCB099280 or axitinib is allowed.

Note 1: Participants should have weekly monitoring with liver tests (ie, liver enzyme and function tests) for 2-3 weeks after each drug rechallenge.
Note 2: If both study drugs are discontinued due to a hepatic event, participants should be monitored until AE resolution as per Protocol and continue imaging as per Protocol.
Note 3: Liver tests include liver enzyme (ALT, AST, and ALP) and liver function (bilirubin and PT/INR) tests.

6.6.7. Criteria for Permanent Discontinuation of Study Drugs Due to Unacceptable Toxicity

Unacceptable toxicity or the inability to tolerate study treatment with both INCB099280 and axitinib will require discontinuation of study treatment.

On a case-by-case basis, following discussion between the medical monitor and investigator, participants who are required to discontinue treatment with axitinib may continue treatment with INCB099280 until such time that an INCB099280 discontinuation criterion is met.

Study treatment must be permanently discontinued for the following:

- Any AE meeting a criterion for treatment discontinuation of INCB099280 and axitinib as detailed in Table 11, Table 12, Table 13, and Table 14.
- AEs requiring more than the allowed dose reductions of axitinib as detailed in Table 9.
- A persistent AE requiring an interruption of study treatment for more than 3 weeks (21 days) unless a greater delay has been approved by the sponsor.
- The occurrence of an AE that is related to study drug that, in the judgment of the investigator or the sponsor's medical monitor, compromises the participant's ability to continue study-specific procedures or is considered to not be in the participant's best interest.

See Section 7 for discontinuation procedures.

6.6.8. Treatment After Initial Evidence of Radiologic Evidence of Disease Progression

An immunotherapeutic agent such as INCB099280 may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents and can manifest as a clinical response after an initial increase in tumor burden or even the appearance of new lesions. Principles of iRECIST (Seymour et al 2017) may be used by the investigator to guide treatment decisions once an initial RECIST v1.1 progression is noted.

If radiologic imaging shows PD, tumor assessment should be repeated after ≥ 4 weeks but no later than 8 weeks to confirm PD with the option of continuing treatment per Table 15 while awaiting radiologic confirmation of progression. When feasible, participants should not be discontinued from study treatment until PD is confirmed; however, the decision to continue study treatment after the first evidence of PD is at the investigator's discretion based on the clinical status of the participant. Participants must have the opportunity to be reconsented if treatment beyond initial RECIST v1.1 progression is planned.

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

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

Table 15: Imaging and Treatment After First Radiologic Evidence of Progressive Disease

	Clinically Stable		Clinically Unstable	
	Imaging	**Treatment**	**Imaging**	**Treatment**
First radiologic evidence of PD	Repeat imaging at ≥ 4 weeks but no later than 8 weeks to confirm PD	May continue study treatment at the investigator's discretion while awaiting confirmatory scan	Repeat imaging at ≥ 4 weeks but no later than 8 weeks to confirm PD if possible	Discontinue treatment
Repeat scan confirms PD	No additional imaging required	Discontinue treatment	No additional imaging required	Not applicable
Repeat scan shows SD, PR, or CR	Continue regularly scheduled imaging assessments according to Table 3	Continue study treatment at the investigator's discretion	Continue regularly scheduled imaging assessments according to Table 3	May restart study treatment if condition has improved and/or clinically stable per investigator's discretion

If repeat imaging confirms PD, participants should discontinue study drug except in cases where a participant is believed to derive clinical benefit, has no other suitable treatment options, and is not experiencing any treatment-related AEs that are CTCAE Grade 2 or higher, with sponsor approval.

6.7. Concomitant Medications and Procedures

All prescription and over-the-counter medicines (including vitamins, vaccines, and/or herbal supplements) and concomitant procedures must be recorded in the eCRF from consent to 90 days after the last dose of study treatment or until the participant begins a new anticancer therapy, whichever occurs first. Any subsequent changes of these medications must also be recorded. Concomitant medications administered for treatment of SAEs (as defined in Section 9.2) should be recorded even if the SAE is reported beyond 90 days after the last dose of study treatment. Concomitant treatments/procedures that are required to manage a participant's medical condition during the study will also be recorded in the eCRF. The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.7.1. Permitted Medications and Procedures

With the exception of those treatments specifically prohibited in this Protocol as outlined in Section 6.7.3, any treatment that the investigator considers clinically indicated may be provided in accordance with local, national, or international guidelines (eg, ASCO guidelines for the use of WBC growth factors [Smith et al 2015]).

In particular, the following are allowed:

- Administration of COVID-19 vaccines (eg, messenger RNA) provided they do not meet criteria for exclusion as outlined in Section 5.2

- Premedication with glucocorticoids as prophylaxis for an established contrast allergy during imaging
- Inhaled or topical corticosteroids

6.7.2. Restricted Medications and Procedures

6.7.2.1. Systemic Corticosteroids

Systemic glucocorticoids with daily doses of less than or equal to an equivalent of 10 mg of prednisone may be used.

6.7.2.2. [redacted]

INCB099280 is an [redacted] of [redacted]. The concomitant use of medications that are [redacted] substrates with a narrow therapeutic index (eg, apixaban, colchicine, cyclosporine, dabigatran, digoxin, edoxaban, rivaroxaban, and tacrolimus) should be administered with caution. INCB099280 administration should be separated by at least [redacted] hours before or after the administration of a [redacted] substrate.

6.7.2.3. [redacted]

A clinical DDI study in which INCB09980 was coadministered with a [redacted] demonstrated lower plasma exposures than without a concomitant [redacted] however, no changes in INCB099280 PK were detected when INCB099280 was coadministered with an [redacted].

For participants who are using a [redacted] if there is a need for the continued use of acid-reducing medication, switching from a [redacted] to a [redacted] is recommended as [redacted] are a prohibited medication.

6.7.2.4. Agents With Antiplatelet Properties

The use of agents with antiplatelet properties, such as nonsteroidal anti-inflammatory drugs should be minimized whenever possible. If concomitant therapy cannot be avoided, addition of an H_2-receptor antagonist to mitigate GI bleeding should be considered.

6.7.3. Prohibited Medications and Procedures

Medications and vaccines that are exclusionary on this Protocol (see Section 5.2) are also not allowed after the initiation of study treatment. If there is a clinical indication for the use of one of these treatments or administration of any of these vaccines during the study, study treatment must be interrupted or discontinued. The following treatments are prohibited on this Protocol:

- Any systemic anticancer medications other than study treatment
- Investigational agents other than study treatment

- [redacted]
  - A clinical DDI study in which INCB099280 was coadministered with a [redacted] demonstrated lower plasma exposures with a concomitant [redacted] however, no changes in INCB099280 PK were detected when INCB099280 was coadministered with an[redacted]
- Vitamin K antagonists
- Antiplatelet therapy (aspirin > 325 mg/day, $P2Y_{12}$ inhibitors)
- Medications known to result in QT-interval prolongation and pose a risk of torsades de pointes (see Appendix C)
- Potent and moderate [redacted] inducers and inhibitors (see Appendix C)

  Note: A washout period of ≥ 10 days is required before the first dose of study treatment.
- Any immunological-based treatment for any reason from screening through EOT

  Note: Completed adjuvant therapy (eg, vaccines), inhaled or topical corticosteroids, systemic corticosteroids (eg, prednisone or equivalent) at doses ≤ 10 mg/day, and immunosuppressants are allowed for the treatment of irAEs as described in Section 6.6.5 or as prophylaxis for contrast allergy for imaging procedures.

  Note: Allergen immunotherapy or sublingual immunotherapy (allergy shots) may be permitted.
- Concomitant radiation therapy
- Vaccination with a live-attenuated virus vaccine from 28 days before the initiation of study treatment and up to 90 days after the last dose of study medication has been administered

- Examples of live vaccines include but are not limited to the following: MMR, chickenpox/zoster, yellow fever, rabies, BCG, typhoid, and LAIV

Note: 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. COVID-19 vaccines (eg, mRNA) are allowed as long as they are not live vaccines.

- Administration of systemic antibiotics within 14 days before the initiation of study treatment.
- Probiotic dietary supplements (from consent until the end of the treatment period)
- Invasive procedures:
  - Treatment with both INCB099280 and axitinib should be stopped prior to surgery. Withhold axitinib for at least 2 days prior to elective surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing. Follow guidelines for impaired wound healing if noted.

- The decision to resume treatment with INCB099280 and axitinib after surgery should be based on clinical judgment of adequate wound healing.
- Treatment may resume after 3 days following a minor surgical procedure.

6.8. Supportive Care Guidelines

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator, including but not limited to the items outlined below.

- Diarrhea: All participants who experience diarrhea should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
- Nausea/vomiting: Nausea and vomiting should be treated aggressively, and consideration should be given in subsequent cycles to the administration of prophylactic antiemetic therapy according to standard institutional practice. Participants should be strongly encouraged to maintain liberal oral fluid intake.
- Anti-infectives: Participants with a documented infectious complication should receive oral or IV antibiotics or other anti-infective agents as considered appropriate by the treating investigator for a given infectious condition, according to standard institutional practice.
- Anti-inflammatory or narcotic analgesics may be offered as needed. Acetaminophen/paracetamol to a maximum total daily dose of 2 g is permitted. Daily intake > 2 g is prohibited.
- Participants who need to be on anticoagulant therapy during treatment should be treated with low-molecular-weight heparin. If low-dose heparin cannot be administered, the administration of Coumadin® (warfarin) or other coumarin derivatives or other anticoagulants may be allowed; however, appropriate monitoring of PT/INR should be performed.

6.9. Treatment After the End of the Study

Following treatment discontinuation, participants will not be eligible to receive further study treatment as part of this study. Participants should remain on the study and continue in follow-up accordingly, as outlined in Sections 8.8 and 8.9.

7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT WITHDRAWAL

7.1. Discontinuation of Study Treatment

7.1.1. Reasons for Discontinuation

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

- Radiographically confirmed disease progression.

  Note: In select instances, participants may continue on treatment past confirmed disease progression. See Section 6.6.8 for details.

- 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 the public domain, may be solicited from or collected on the participant. Consent may also be partial. Participants may choose to discontinue study treatment and remain in the study to be followed for disease status follow-up.

- Further participation would be injurious to the participant's health or well-being, in the investigator's medical judgment.
- Unacceptable toxicity as noted in Section 6.6.7.
- The study is terminated by the sponsor or the DMC.
- The study is terminated by the local health authority, IRB, or IEC.
- The participant has completed 2 years of study treatment with INCB099280 from the date of first dose, including dose interruptions.

  Note: If a participant is unable to tolerate combination treatment, they will have met the criterion for study treatment discontinuation. However, on a case-by-case basis, after discussion between the medical monitor and the investigator, a decision may be made to continue INCB099280 monotherapy for a maximum of 2 years.

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

- The participant is found not to have met eligibility criteria.
- If a participant is noncompliant with study procedures or study drug administration in the investigator's opinion, the sponsor should be consulted for instruction on handling the participant.

7.1.2. Discontinuation Procedures

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

If a participant is discontinued from study treatment:

- The study monitor or sponsor must be notified.
- The reason(s) for discontinuation must be documented in the participant's medical record and the primary reason for discontinuation must be included in the eCRF.
- The EOT visit should be performed and date 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 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 their own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.

If a participant withdraws from the study, they may request destruction of any samples taken and not tested, and the investigator must document this in the site study records. 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 for data to be collected at the time of study withdrawal and follow-up and for any further evaluations that need to be completed.

7.3. Lost to Follow-Up

A participant will be considered lost to follow-up if they repeatedly fail to return for scheduled visits and are 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, they will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Administrative and General Procedures

8.1.1. Informed Consent Process

- The investigator or their representative will explain the nature of the study to the participant 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 most current IRB/IEC-approved version in a language that is native and understandable to the participant. An ICF 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, and all site-specific changes must be approved by the IRB/IEC and the sponsor or its designee. 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 including optional samples/procedures (eg, optional biopsy) 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 will be required to sign a statement of informed consent that meets the applicable requirements and regulations for the countries in which the study is being conducted as well as the IRB/IEC or study center.
- The participant must be informed that their personal data collected for the study will be used by the sponsor and/or their designee(s) in accordance with local data protection laws. The level of disclosure must also be explained to the participant.
- The participant must be informed that their 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 during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.
- Participants who are rescreened are required to sign a new ICF.
- Participants who are treated beyond disease progression are required to sign a new ICF.

8.1.2. Screening Procedures

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

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

Results from the screening visit evaluations will be reviewed to confirm eligibility before randomization/enrollment or the administration of study treatment. Tests with results that fail eligibility requirements may be repeated once during screening if the investigator believes the results to be in error. For screening assessments that are repeated, the most recent available result before enrollment will be used to determine eligibility. Treatment should start as soon as possible but within 3 days after the date of enrollment.

See Sections 5.4 and 5.6 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 the participant number. Site staff should contact the IRT to obtain the participant ID number during screening.

Upon determining that the participant is eligible for study entry (enrollment), the IRT will be contacted to obtain the treatment assignment. Additionally, the IRT will be contacted at the study visits indicated in Table 3 to update the study drug supply. Additional details will be provided in the IRT Reference Manual.

8.1.4. Distribution of Participant Information Cards, Reminder Cards, and Diaries

Participants will be provided with a participant information card at the completion of screening identifying them as participants in a research study. The card will contain study site contact information (including direct telephone numbers) to be utilized in the event of an emergency.

Reminder cards will be provided at each visit through the end of study. The reminder card will indicate the date and time of the next visit and will also remind the participant that they should not take their morning doses of INCB099280 and axitinib on visit days, as they will take it after blood draws for safety evaluation or PK have been completed. The reminder cards will have an area on which the date, time, and contents of their last meal before the visit should be recorded.

Starting at the Day 1 visit and each treatment period visit thereafter, an INCB099280 and axitinib–specific diary (electronic or paper) will be given to each participant in order to record use of the study drug. The completed diary will be reviewed during each of the participant's study visits, and data entered in the paper diary or electronic diary (ie, provisioned device, downloaded app, or paper diary available as a backup) will be confirmed by the study staff. Participants will be trained on all software applications and devices necessary for the conduct of the study by site personnel.

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 (see additional guidance below), medical and surgical history, and current illnesses. Medical history will include relevant medical and surgical treatments within the last 10 years that are considered to be clinically significant by the investigator. Race and ethnicity data may be collected where permitted to evaluate racial differences in participants' efficacy outcomes.

As race and/or ethnicity data are not to be analyzed from a scientific or medical perspective, but rather are to be reported in a descriptive format only in the CSR, data on race and/or ethnicity from France must not be collected as per GDPR and local data protection law and requirements.

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, relevant disease characteristics, and prior treatments, including systemic treatments, radiation, and surgical procedures, will be recorded.

8.1.5.3. Baseline Biomarker Documentation

Information regarding tumor markers (eg, TMB, MSI and/or DNA MMR deficiency, PD-L1, BRAF, HPV status) should be recorded in the eCRF at screening, if available.

8.2. Efficacy Assessments

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

Efficacy baseline assessments will be performed at screening, and further efficacy assessments will be performed throughout the study at the intervals defined in the SoA (see Table 3). Cycle delays should not interrupt the 6-week (or 12-week when applicable) scan interval; thus, tumor assessments and cycles may become out of sync. A central imaging vendor will not be used in this study.

8.2.1. Tumor Imaging and Disease Assessment per RECIST v1.1

The same imaging technique should be used for a participant throughout the study. The baseline scan must be a contrast-enhanced CT or MRI, except in circumstances where there is a contrast allergy or with medical monitor approval. When the CT component of a PET/CT scan uses higher energy and thinner slices, it may be acceptable with medical monitor approval.

Imaging must capture all known sites of disease, including the anatomical region of any externally visible disease, and must include images of the chest, abdomen, and pelvis. Additional imaging of anatomical sites (eg, head, neck, brain) should be performed as applicable.

8.2.1.1. Baseline Assessment During Screening

Initial tumor imaging must be performed within 28 days before the first dose of study treatment. The site study team must review prestudy reports and images to confirm that the participant has measurable disease per RECIST v1.1. Tumor lesions that are located in a previously irradiated area or in an area subjected to other locoregional therapy should not be selected as target lesions. Participants with a single target lesion that has been previously irradiated or subjected to other locoregional therapy may be enrolled if the target lesion is considered measurable per RECIST v1.1 and has demonstrated at least a 10-mm increase in the shortest diameter of the lesion. Additionally, it is recommended that tumor lesions selected for biopsy not be selected as target lesions.

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

8.2.1.2. Assessment of Disease Response During Treatment

The first 2 disease assessments should be performed 6 and 12 weeks (± 7 days) after the first dose of INCB099280 and axitinib and then Q12W (± 14 days) thereafter (see Table 3). Imaging assessments may be performed more frequently if clinically indicated.

Imaging should follow calendar days and should not be delayed for delays in cycle starts.

Disease progression should be confirmed at least 4 weeks but less than 8 weeks after the first scan indicating disease progression in clinically stable participants as per guidelines in Section 6.6.8. A PET scan may be incorporated into the disease assessment to confirm progression per RECIST guidance. Participants who have unconfirmed disease progression may

continue on treatment until progression is confirmed, provided that they have met the conditions detailed in Section 6.6.8.

8.2.1.3. Assessment of Disease Response After Treatment

Participants who discontinue study treatment for a reason other than disease progression should continue to have efficacy assessments performed according to the original schedule following their final on-study treatment assessment until disease progression as determined by RECIST v1.1, new anticancer therapy is started, withdrawal of consent, lost to follow-up, death, or the end of the study, whichever occurs first.

8.2.2. Medical Resource Utilization and Health Economics

Medical resource utilization and health economics parameters are not evaluated in this study.

8.3. Safety Assessments

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

8.3.1. Adverse Events

Adverse events will be monitored from the time the participant signs the ICF until at least 90 days after the last dose of study treatment or until the start of new anticancer therapy. Adverse events for enrolled participants that begin or worsen after informed consent should be recorded on the Adverse Events Form in the eCRF regardless of the assumption of a causal relationship with the study treatment. Conditions that were already present at the time of informed consent should be recorded on the Medical History Form in the eCRF. Adverse events (including laboratory abnormalities that constitute AEs) should be described using a diagnosis whenever possible rather than by individual underlying signs and symptoms.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver or surrogate). 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, that are considered related to the study treatment/procedures, or that caused the participant to discontinue the study treatment or withdraw from the study. 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 reported to the sponsor or designee by the investigator immediately without undue delay and not later than 24 hours of obtaining knowledge of the events. The investigator will also submit any updated SAE data to the sponsor immediately without undue delay and not later than 24 hours of obtaining knowledge of the update. 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. Vital Signs

Vital sign measurements (to be taken before blood collection for laboratory tests at the timepoints indicated in the SoA [see Table 3]) include BP, pulse, respiratory rate, and body temperature. If vital signs cannot be taken before blood collection for laboratory tests, there must be a minimum of 30 minutes from the completion of the blood collection procedures to the beginning of the vital signs collection. Blood pressure and pulse will be taken with the participant in a recumbent, semirecumbent, or sitting position after 5 minutes of rest (see Section 6.6.6.1).

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.

8.3.3. Physical Examinations

Physical examinations must be performed by a medically qualified individual, such as a licensed physician, a physician assistant, or an advanced registered nurse practitioner, as local law permits. Abnormalities identified after the first dose of study treatment constitute an AE if they are considered clinically meaningful, induce clinical signs or symptoms, require concomitant therapy, or require changes in study treatment. Investigators should pay special attention to clinical signs related to previous serious illnesses. Physical examinations will be performed at the timepoints indicated in the SoA (see Table 3).

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

8.3.4. Eastern Cooperative Oncology Group Status

The ECOG performance status score will be assessed as outlined in Table 3 and according to the criteria in Table 16.

Table 16: Eastern Cooperative Oncology Group Performance Status Scoring

Grade	ECOG 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.

8.3.5. Electrocardiograms

Single 12-lead ECGs will be obtained as outlined in Table 3 and Table 17 using a local ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF intervals. All 12-lead ECGs will be performed with the participant in a recumbent or semirecumbent position after 5 minutes of rest.

The 12-lead ECGs will be interpreted by the investigator at the site to be used for immediate participant management. Additional 12-lead ECGs may be performed as clinically indicated to manage participant safety. The decision to include or exclude a participant or discontinue study 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. The Fridericia correction method for calculating QTc will be used and recorded in the eCRF.

In the event that a single QTcF is > 480 milliseconds at screening, the participant may enroll if the average QTc for 3 ECGs is ≤ 480 milliseconds.

Table 17: Timing of Electrocardiograms

Study Visit	Timing of Collection			
	Any Time	Before the Morning Dose of INCB099280 and Axitinib[a]	2 Hours After the Morning Dose of INCB099280 and Axitinib[b]	4 Hours After the Morning Dose of INCB099280 and Axitinib[b]
Screening	X			
Cycle 1 Day 1		X	X	X
Cycle 2 Day 1		X	X	X
Cycle 3 Day 1 and Day 1 of every third cycle (eg, Cycles 6, 9, 12, etc) thereafter		X		
EOT	X			
Safety follow-up	X			

[a] INCB099280 and axitinib are administered in the clinic on days of timed ECGs.

[b] To be collected within 15 minutes before blood draws. Electrocardiogram measurements should be aligned with timing of PK blood draws.

8.3.6. Echocardiograms

Left ventricular systolic function as measured by LVEF will be assessed by echocardiography at screening and as clinically indicated. Every effort should be made to schedule serial monitoring at the same cardiac imaging facility.

Participants should be assessed and monitored for the development of symptoms and signs of CHF. Participants who develop CHF should permanently discontinue study treatment.

8.3.7. Laboratory Assessments

See Table 18 for the list of clinical laboratory tests to be performed and Table 3 for the timing and frequency. A CLIA-certified or local equivalent laboratory local to the investigative site will perform all clinical laboratory assessments for safety (ie, blood chemistry, hematology, coagulation, endocrine function, pregnancy testing, hepatitis serology and viral load, 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. All Protocol-required laboratory assessments must be conducted in accordance with the Study Laboratory Manual and Table 3. Information regarding collection, processing, and shipping of samples for laboratory assessment is provided in the Study Laboratory Manual.

Clinically significant abnormal laboratory findings are those that are clinically meaningful, induce clinical signs or symptoms, require concomitant therapy, require changes in study drug, and are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 90 days after the last dose of study treatment 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 28 days before Cycle 1 Day 1. If performed more than 7 days before Cycle 1 Day 1, then the tests must be repeated and eligibility confirmed before study treatment administration on Cycle 1 Day 1.

Laboratory sample collection on Cycle 1 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.

See Section 9.1 for information regarding laboratory abnormalities that should be recorded as an AE in the eCRF. Additionally, if laboratory values from laboratory assessments performed at the institution's local laboratory require a change in participant management (eg, require treatment) or are considered clinically significant by the investigator (eg, SAE, AE, dose modification; see Section 9.3), then the result(s) of the specific laboratory assessment(s) must be recorded in the eCRF.

Table 18: Required Laboratory Analytes

<table>
<tr><th>Hematology</th><th>Blood Chemistry</th><th>Endocrine Function</th><th>Urinalysis[a]</th><th>Coagulation</th></tr>
<tr><td rowspan="3">Complete blood count, including the following:
• Red blood cell count
• Hemoglobin
• Hematocrit
• Platelet count

Total white blood cell count including a differential count with absolute values:
• Basophils
• Eosinophils
• Lymphocytes
• Monocytes
• Neutrophils

For participants with HIV:
CD4+ cell count[b]</td><td rowspan="3">Albumin[c]
Total protein
ALP
ALT
AST
Lactate dehydrogenase
Total bilirubin
Direct bilirubin (if total bilirubin is elevated above ULN)
Amylase
Lipase
Glucose
Creatinine
Urea or blood urea nitrogen
Sodium
Potassium
Chloride
Bicarbonate or CO_2
Calcium
Magnesium
Phosphate
Uric acid
C-reactive protein (low-sensitivity assay)</td><td>TSH
FT4

Only when clinically indicated:
• Total T4
• Total T3
• Free T3</td><td>Color and appearance
pH and specific gravity
Bilirubin
Glucose
Ketones
Leukocytes
Nitrite
Occult blood
Protein</td><td>INR
PT
aPTT</td></tr>
<tr><th>Pregnancy Testing</th><th colspan="2">Hepatitis Serology and Viral Load</th></tr>
<tr><td>Beta-human chorionic gonadotropin</td><td colspan="2">Hepatitis B surface antigen
Hepatitis B surface antigen antibody
Hepatitis B core antibody
HBV DNA
HCV antibody
HCV RNA

Participants with HIV:
HIV RNA to confirm eligibility; thereafter, when clinically indicated</td></tr>
</table>

Note 1: Additional tests (eg, interstitial lung disease, tuberculosis) may be performed at any time during the study as determined necessary by the investigator or required by local regulations, or required by regions, or based on emerging safety data. Amylase, lipase, and endocrine tests and other specific laboratory tests may be performed more frequently for management of irAE toxicities.

Note 2: Additional tests may be required, as agreed upon by the investigator and sponsor, based on emerging safety data or to rule out a diagnosis.

[a] Microscopic examination is required only if blood is suspected in urine.

[b] At screening, Cycle 1 Day 1, Cycle 3 Day 1, and then every third cycle (ie, Cycles 6, 9, 12, etc) and more frequently if clinically indicated. Frequency may be reduced to every 6 months during the disease status follow-up period.

[c] At screening only and as clinically indicated.

8.3.7.1. Pregnancy Testing

A serum pregnancy test will be required for all WOCBP during screening and at the EOT visit. Urine pregnancy tests may be performed locally for all other visits as outlined in the SoA (see Table 3), as medically indicated (eg, in case of loss of menstrual cycle, when pregnancy is suspected), or per country-specific requirement (note that country-required urine pregnancy testing will be outlined and communicated to investigational sites under separate cover). If a urine pregnancy test is positive, the result should be confirmed with a serum pregnancy test.

If the serum pregnancy test result is negative after a urine test result 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 result, see Section 9.8 for reporting requirements.

For WOCBP, monthly telephone visits should take place after the safety follow-up period to check pregnancy status (via testing, including home pregnancy tests) during the period when contraception is mandatory (ie, through 190 days after the last dose of study treatment).

8.3.7.2. Serology

Hepatitis screening assessments will be performed at the screening visit to rule out hepatitis infection; required analytes are shown in Table 18. Generally, hepatitis tests should be performed early in the screening process due to the length of time needed to obtain the results. Additional tests may be performed if clinically indicated.

Participants with past HBV infection (HBsAg negative and anti-HBc positive with either positive or negative anti-HBs) should have HBsAg monitored approximately every 3 months and ALT monitored periodically as indicated in Table 3, and antiviral treatment should be started if HBsAg becomes positive or HBV DNA > 1000 IU/mL in the setting of a hepatitis flare.

8.4. Pharmacokinetic Assessments

Blood samples will be collected from all participants to perform PK analyses as specified in Table 3 and Section 8.4.1. Samples collected for analyses of study drug concentrations may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study. The actual date and time (24-hour clock time) of each sample and administration of study treatment at the clinic will be recorded. In addition, the actual date and time of the last dose administered prior to trough PK blood draws will be recorded. Instructions for the collection and handling of biological samples will be provided in the Study Reference Manual.

8.4.1. Blood Sample Collection

INCB099280 and axitinib PK samples will be obtained before the first dose on Cycle 1 Day 1, Cycle 2 Day 1, Cycle 4 Day 1, and Cycle 8 Day 1. Postdose PK samples will be obtained for INCB099280 on Cycle 1 Day 1 and Cycle 2 Day 1 at 1, 2, and 4 hours. An axitinib PK sample will be obtained at the EOT visit (see Table 19).

On days of PK sampling, study treatment will be administered in the clinic (see Table 3) and participants should not consume a [redacted] meal (a

meal that exceed [redacted] calories with [redacted]% calories from fat) within at least [redacted] hours before or after INCB099280 dose administration. A trough (predose) PK sample will be collected early in the study visit, followed by administration of the study treatment and subsequent timed blood samples. Study drug will be administered with water.

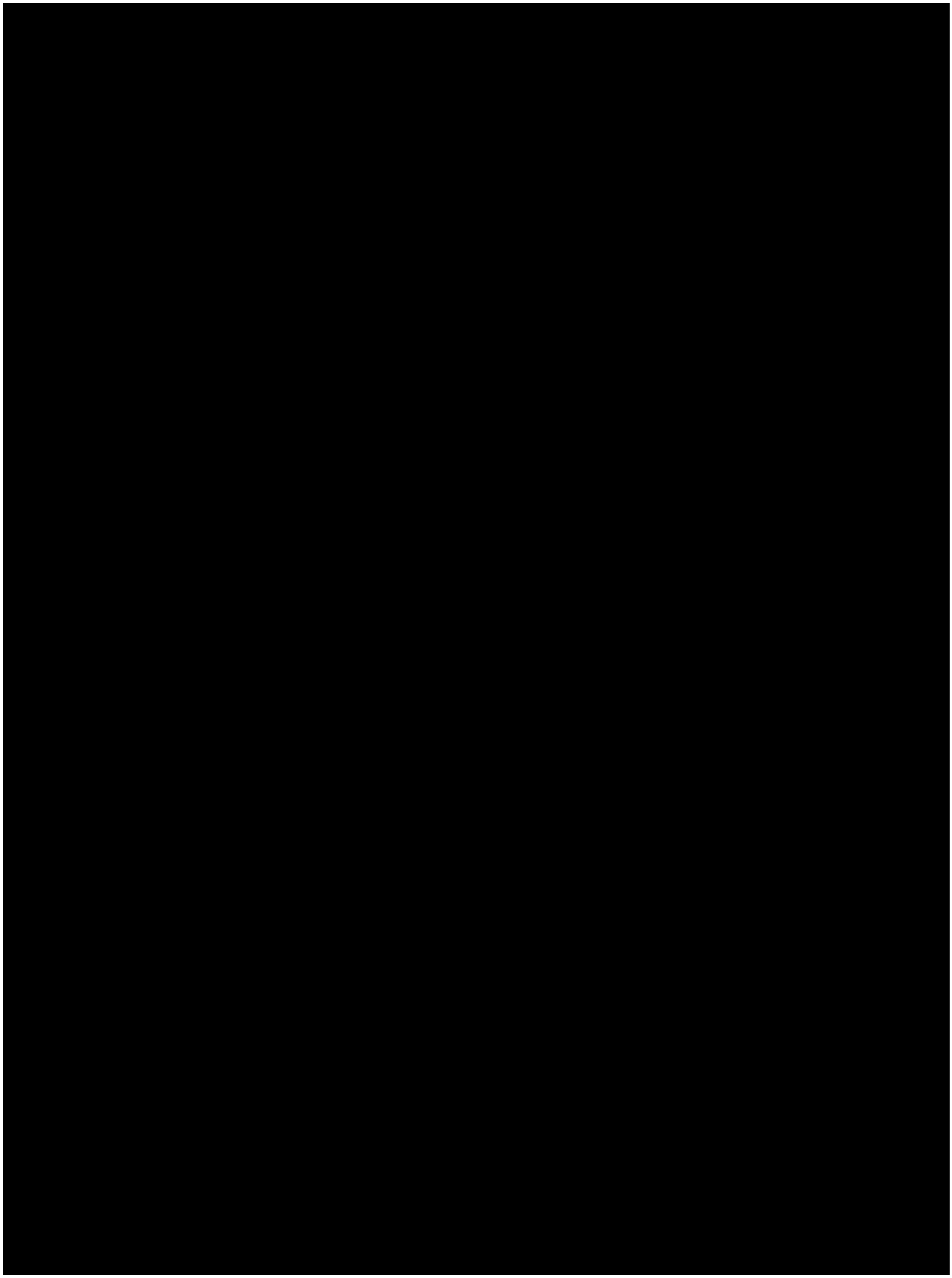
Predose is defined as within 3 hours before administration of study drug.

[redacted]

8.4.2. Bioanalytical Methodology and Sample Analysis

Pharmacokinetic samples for INCB099280 will be analyzed for analytes by the sponsor or their designee using a validated assay. Pharmacokinetic samples for axitinib will only be analyzed if there is a concern that axitinib is not as active as expected. Additionally, residual samples may be used for [redacted] residual pharmacodynamic and translational samples may be utilized for PK testing.

[redacted]



8.6. Storage and Future Use of Biological Samples

Biological samples (eg, biomarkers, pharmacodynamics, PK) will be stored to perform study-related research. Additional research outside of study-related research will not be performed. Pseudonymized participant samples will be transported to the sponsor or designated vendor for analysis as detailed in the laboratory-specific study manual(s). Pharmacokinetic samples will be destroyed after the final bioanalysis report or CSR. Biomarker and pharmacodynamic samples may be stored for up to 10 years from the publication of the first CSR for study-related research unless national regulatory requirements in participating countries or local health authorities require alternate retention timelines. These requirements will be captured in a separate study document (eg, ICF).

8.7. 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.

8.8. End of Treatment

When the participant permanently discontinues study treatment, whether the participant is withdrawing from the study early or the participant has completed the study, the EOT visit should be conducted. If the EOT visit coincides with a regular study visit, the EOT evaluations will supersede those of that scheduled visit, and the data should be entered in the EOT visit in the eCRF. The participant should be encouraged to return for the follow-up visits.

8.9. Follow-Up

Participants who discontinue study treatment are to continue in the follow-up period for up to 90 days (+ 14 days) for collection of post-treatment evaluations. The assessment schedule following treatment discontinuation is shown in Table 3.

8.9.1. Safety Follow-Up

The safety follow-up period is the interval between the EOT visit and the scheduled follow-up visit, which should occur 30 (+ 7) and 90 (+ 14) days after the EOT visit (or after the last dose of study treatment if the EOT visit was not performed). Adverse events and SAEs must be reported up until 1) at least 90 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 or other methods of communication for assessment of any AEs; this contact should be documented in the source.

For WOCBP, monthly telephone visits should take place after the safety follow-up period to check pregnancy status (via testing, including home pregnancy tests) during the period when contraception is mandatory (ie, through 190 days after the last dose of study treatment).

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

8.9.2. Post-Treatment Disease Follow-Up

Participants who discontinue study treatment for a reason other than disease progression will move into the disease status follow-up period and should be assessed by radiologic imaging Q12W (84 ± 14 days).

Every effort should be made to collect this information regarding disease status until the following:

- The start of new anticancer therapy
- Disease progression
- Withdrawal of consent
- Lost to follow-up
- Death
- The end of the study

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 treatment. Whenever possible, a diagnosis (eg, anemia, thrombocytopenia) should be recorded in the eCRF rather than the abnormal laboratory test result (eg, low hemoglobin, platelet count decreased). • Exacerbation of a chronic or intermittent pre-existing condition/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 are to be reported as an AE. • New signs and/or symptoms due to the study disease that develop after the first dose of study treatment are to be reported as an AE. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction are to be reported as an AE. • Signs and/or symptoms from dose administration errors of a study 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. • A condition that leads to a medical or surgical procedure (eg, endoscopy, appendectomy) will be reported as an AE if it occurs after obtaining informed consent. If the condition is present before entering the study, then it should be captured as medical history. • Pre-existing diseases, pre-existing conditions, or new 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 or 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 department 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) is not considered an SAE.
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; development of drug dependency or drug abuse; or suspected transmission of an infectious agent via a medicinal product. Secondary malignancies should always be considered SAEs.

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

Adverse Event and Serious Adverse Event Recording

- An AE/SAE that begins or worsens after informed consent is signed should be recorded on the Adverse Events Form in the eCRF. All AEs/SAEs should be reported for enrolled participants, but only SAEs need to be reported for screen failure participants. For enrolled participants, conditions that were present at the time informed consent was given should be recorded on the Medical History Form in the eCRF. For detailed information, refer to the eCRF guidelines.
- 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 designee) 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 Events 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.
- 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: 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 treatment as a result of the AE/SAE(s).
- The event outcome (eg, not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown).
- The seriousness, as per the SAE definition provided in Section 9.2.
- The action taken with regard to the event. Note: If an AE is treated with a concomitant medication or nondrug therapy, this action should be recorded on the Adverse Events 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. For INCB099280 and axitinib, the relationship to each study treatment must be assessed.
- 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, or marketed products, respectively, in making their 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 they have reviewed the AE/SAE and have 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 their 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 Adverse Events Form in the eCRF until it has resolved or until it is judged to be permanent; assessment should be made at each visit (or more frequently if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat the event, and the outcome. • When the severity of an AE changes over time for a reporting period (eg, between visits), each change in severity will be reported as a separate AE. • Updated SAE information will be recorded in the originally completed eCRF and reported to Incyte Pharmacovigilance (in the SAE EDC CRF) until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up. • Any updated SAE data (including SAEs being downgraded to nonserious) will be submitted to the sponsor (or designee) within 24 hours of receipt of the information.

9.4. Reporting of Serious Adverse Events

Regardless of suspected causality (eg, relationship to study treatment or study procedure[s]), all SAEs occurring after the participant has signed the main study ICF (ie, SAEs that occur during prescreening do not need to be reported) through at least 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) immediately, without undue delay but not later than within **24 hours** of obtaining knowledge of its occurrence unless otherwise specified by the Protocol. The investigator will submit any updated SAE data to the sponsor (or designee) immediately, without undue delay but not later than within 24 hours of it being available.

Investigators are not obligated to actively seek SAE information after the safety follow-up visit or more than 90 days after the last dose of study treatment. If the investigator learns of any SAE, including death, at any time during this period (disease status follow-up period), and they consider 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 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 for the safety of participants and the safety of a study treatment under clinical investigation are met.

If the SAE is not documented in the RSI of the INCB099280 IB or axitinib package insert (Inlyta 2021) for the study treatment (new occurrence) and is thought to be related to the study treatment, 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 including EudraVigilance, as applicable, and relevant ethics committees following the sponsor's (or approved designee) SOPs in accordance with EU CTR No. 536/2014 and/or FDA CFR Part 312 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 Events 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 Study Reference Manual or 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 or Study Reference Manual 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 treatment because of the SAE (eg, dose reduced, interrupted, or discontinued), or participant disposition (eg, continued or withdrew from study participation). Each recurrence, complication, or progression of the original event should be reported as follow-up to that event, regardless of when it occurs.

9.5. Potential Drug-Induced Liver Injury

In the event a participant has 1) an increase in ALT or AST elevation $\geq 3 \times$ ULN, 2) a total bilirubin $\geq 2 \times$ ULN, and 3) an ALP $< 2 \times$ ULN, clinical tests (eg, blood and imaging tests) must be performed frequently as per standard of care until resolution and/or stabilization. In addition, a diagnostic workup must be performed to exclude alternative causes such as viral hepatitis, pre-existing chronic or acute liver disease or abnormalities, the administration of other drug(s) known to be hepatotoxic, or confirmed Hy's law.

Follow the SAE and follow-up reporting requirements per Section 9.2 as potential DILI AEs may be potential SAEs classified in the category of important medical event.

9.6. Events of Clinical Interest

Not applicable.

9.6.1. Adverse Events of Special Interest

Not applicable.

9.7. Emergency Unblinding of Treatment Assignment

Not applicable.

9.8. Pregnancy

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

- The study treatment must be interrupted immediately.
  - If the female participant is no longer pregnant and meets the treatment continuation criteria within 28 days of the scheduled start of a cycle, study treatment may be resumed after approval has been received from the sponsor's 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 evaluations. 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. This form 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 for further details.

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

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, or ectopic pregnancy) are considered SAEs (if occurring in the study participant) and must be reported as described in Section 9.4. If an abnormal pregnancy outcome is reported in a

study participant's partner, the event should be reported to the sponsor on the Clinical Trial Pregnancy Form.

9.9. Warnings and Precautions

Special warnings or precautions for the study drug, derived from safety information collected by the sponsor or its designee, are presented in the INCB099280 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.

9.10. 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 their 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, they will return a copy of the product complaint communication with the product.

9.11. Treatment of Overdose

Overdose is not an SAE unless it meets the criteria of an SAE (see Section 9.2).

For this study, any dose of INCB099280 or axitinib greater than the dose prescribed within a 24-hour time period will be considered an overdose and recorded in the eCRFs.

In the event of an overdose, the investigator/treating physician should do the following:

- Contact the medical monitor immediately.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities until study treatment can no longer be detected systemically (at least 90 days).
- Obtain a plasma sample for PK analysis within 2 days from the date of the last dose of study treatment if requested by the medical monitor (determined on a case-by-case basis).
- Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.

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

There has been no clinical experience with overdose of INCB099280. Treatment of overdose should consist of general supportive measures.

There is no specific treatment for axitinib overdose. In a controlled clinical study with axitinib for the treatment of patients with RCC, 1 participant inadvertently received a dose of 20 mg BID for 4 days and experienced dizziness (Grade 1; Inlyta 2021). In clinical studies, participants who received up to 10 mg BID or 20 mg BID experienced adverse reactions that included hypertension, seizures associated with hypertension, and fatal hemoptysis (Inlyta 2021). In cases of suspected overdose, axitinib should be withheld and supportive care instituted.

10. STATISTICS

This section outlines the statistical analysis strategy and procedures for this study. If changes are made to primary efficacy and safety and/or secondary efficacy hypotheses or the statistical methods related to those hypotheses after the study has begun but before the final database lock, the Protocol will be amended, consistent with ICH E9 (1998) and ICH E9(R1) (2021). The detailed statistical analyses will be documented in the Statistical Analysis Plan.

10.1. Sample Size Determination

The study will be conducted in 2 parts: dose finding in Part 1 and dose expansion in Part 2. In Part 1 of the study, approximately 12 participants with previously treated advanced clear cell ovarian cancer, rare histological subtype epithelial cancers of the gynecological tract, endometrial cancer, or cervical cancer who have received at least 1 prior line of systemic chemotherapy and are not candidates for curative surgery or (chemo)radiation will be enrolled in dose finding of INCB099280 administered at 400 mg BID in combination with axitinib to determine the safety and tolerability of the combination therapy and identify the RDE. A hybrid of a modified mTPI design and a dose-toxicity model will be used to make dose decisions.

In Part 2, up to 30 participants will be enrolled in each of the 4 disease cohorts to further evaluate the safety and tolerability of the combination therapy as well as to continue characterizing the PK and antitumor activity.

With 30 participants in a cohort-specific dose group, the probabilities of observing different numbers of events with true rates of 0.05, 0.1, 0.2, 0.25, 0.3, 0.35, 0.4, and 0.5 are listed in Table 20. This calculation is applicable to detecting events of DLTs, objective responses, Grade 3 or higher TEAEs, etc.

Table 20: Distributions of Observed Events Under Different Event Rates

Number of Events	Rate With a Sample Size of 30							
	0.05	**0.1**	**0.2**	**0.25**	**0.3**	**0.35**	**0.4**	**0.5**
> 1 event	78.5%	95.8%	99.9%	> 99.9%	> 99.9%	> 99.9%	> 99.9%	> 99.9%
> 2 events	44.6%	81.6%	98.9%	99.8%	> 99.9%	> 99.9%	> 99.9%	> 99.9%
> 5 events	1.6%	17.5%	74.5%	90.2%	97.0%	99.2%	99.8%	> 99.9%
> 10 events	< 0.1%	< 0.1%	6.1%	19.7%	41.1%	64.2%	82.4%	97.9%
> 15 events	< 0.1%	< 0.1%	< 0.1%	0.3%	1.7%	6.5%	17.5%	57.2%

With 30 participants within each cohort, precisions of 95% Wald CI (1.96 times standard error) for true event rate given different numbers of observed events are shown in Table 21.

Table 21: Precisions of 95% Wald Confidence Intervals for Event Rate

	Number of Events for a Sample Size of 30							
Type	**4**	**6**	**7**	**9**	**10**	**12**	**13**	**15**
Estimate	0.13	0.20	0.23	0.30	0.33	0.40	0.43	0.50
Precision	0.12	0.14	0.15	0.16	0.17	0.18	0.18	0.18

10.2. Populations for Analysis

The populations for analysis are provided in Table 22, and the associated endpoints are provided in Table 23.

Table 22: Populations for Analysis

Population	Description
FAS	The FAS includes all study participants who received at least 1 dose of either study treatment. The FAS will be used for the summary of demographics, baseline characteristics, participant disposition, and overall efficacy analyses. Participants will be analyzed according to the dose to which they have been assigned.
Safety-evaluable	The safety-evaluable population includes all participants who received at least 1 dose of either study treatment. All safety analyses will be conducted using the safety-evaluable population. Treatment groups for this population will be determined according to the actual dose the participant received regardless of assigned dose.
DLT-evaluable	The DLT-evaluable population includes participants enrolled into Part 1 who received at least 75% of the planned doses of INCB099280 and axitinib (ie, 32 doses of INCB099280 and axitinib) at the level assigned during the DLT observation period or have had a DLT during the 3-week DLT observation period. DLT-evaluable participants will be summarized independently.
PK-evaluable	The PK-evaluable population includes all participants who received at least 1 dose of either study treatment and have provided at least 1 postbaseline sample for PK analysis.
Pharmacodynamic-evaluable	The pharmacodynamic-evaluable population includes all participants who received at least 1 dose of either study treatment and have provided a baseline sample and at least 1 postbaseline plasma sample for pharmacodynamic analysis.
PK/pharmacodynamic-evaluable	The PK/pharmacodynamic-evaluable population includes all participants who are both PK-evaluable and pharmacodynamic-evaluable.

Table 23: Primary and Secondary Endpoints and Analysis Populations

Endpoint	Population	Hypothesis	Population-level Summary Metric
DLT	DLT-evaluable	NA	DLT incidence rate
Incidence of TEAEs	Safety-evaluable	NA	TEAE incidence rate
PK	PK-evaluable	NA	Concentration of INCB099280 in plasma; estimates of PK parameters for INCB099280
Objective response	FAS	NA	ORR
Disease control	FAS	NA	DCR
DOR	Subset of FAS	NA	Median DOR

10.3. Level of Significance

This is an exploratory study, and no formal statistical tests will be performed. Unless otherwise specified, all confidence intervals will be 95% without multiplicity adjustment.

10.4. Statistical Analyses

10.4.1. Primary, Secondary, and Exploratory Efficacy Analyses

All efficacy analyses will be performed independently for each disease cohort and dose level. Analyses for Part 1 and Part 2 participants with the same tumor type and treated at the same dose level may be combined.

10.4.1.1. Objective Response

Objective response rate is defined as the percentage of participants with best overall response of unconfirmed CR or PR, as determined by investigator assessment per RECIST v1.1 (Eisenhauer et al 2009). The ORR and its exact 95% CI will be calculated separately for each cohort and dose for Part 1 and Part 2.

10.4.1.2. Disease Control

Disease control rate is defined as the percentage of participants with best overall response of CR, PR, or SD, as determined by investigator assessment per RECIST v1.1. The DCR and its exact 95% CI will be summarized separately for each cohort and dose for Part 1 and Part 2.

10.4.1.3. Duration of Response

Duration of response is defined as the time from the earliest date of CR or PR to the earliest date of disease progression, as determined by investigator assessment per RECIST v1.1, or death due to any cause if occurring sooner than progression. For participants who have not had disease progression and are still alive at the time of the analysis, DOR will be censored on the day of the last evaluable disease assessment. For participants who have withdrawn from the study or have started other anticancer treatment, DOR will be censored on the day of the last evaluable disease assessment documenting absence of PD before study withdrawal or the start of the new anticancer treatment. The total number of objective responders, number of participants who had disease progression or died, number of participants censored, and the Kaplan-Meier estimate of median DOR and its 95% CI using the Brookmeyer and Crowley's method (Brookmeyer and

Crowley 1982) will be provided separately for each cohort and dose for Part 1 and Part 2 (if the number of responses is > 5).

10.4.2. Safety Analyses

The clinical safety data (eg, vital signs, ECGs, routine laboratory tests, AEs) will be summarized using descriptive statistics (eg, mean, frequency) for the safety-evaluable population. Safety analyses will be provided for each dose for Part 1 and Part 2. An analysis of the combined doses will also be provided for Part 1 and Part 2.

The DLT incidence rate along with a 90% CI based on exact binomial distribution will be provided for each dose level using the DLT-evaluable population. The participants with DLTs and the type of DLT will be listed by dose level.

The tolerability of study drug will be assessed by summarizing the number of participants with a TEAE leading to dose interruptions, dose reductions, and treatment discontinuations for either study drug.

10.4.2.1. Adverse Events

A TEAE is any AE either reported for the first time or worsening of a pre-existing event after the first dose of study treatment up to 90 days after the last dose of study treatment or until the start of new anticancer therapy, whichever occurs first. Analysis of AEs will be limited to TEAEs, but data listings will include all AEs regardless of their timing to study treatment administration. Adverse events will be coded by the MedDRA dictionary, and severity of AEs will be based on the NCI CTCAE v5.0 using Grades 1 through 5.

The subset of AEs considered by the investigator to have a relationship to study treatment will be considered to be treatment-related AEs. If the investigator does not specify the relationship of the AE to study treatment, the AE will be considered treatment related.

The number (%) of participants reporting any TEAEs, any SAEs, any Grade 3 or higher TEAEs, irAEs, any treatment-related TEAEs, any treatment-related serious TEAEs, any treatment-related Grade 3 or higher TEAEs, any fatal TEAEs, and any TEAEs leading to treatment

interruption/reduction/discontinuation will be tabulated by MedDRA system organ class and preferred term.

10.4.2.2. Clinical Laboratory Tests

Laboratory data will be classified into Grades 1 through 4 using CTCAE v5.0 when applicable. The following summaries will be produced for the laboratory data:

Descriptive statistics of the value and change from baseline at each assessment time.

For laboratory parameters that have CTCAE grading, shift tables showing change in CTCAE grade from baseline to the worst postbaseline grade.

For laboratory parameters that do not have defined CTCAE grades, shift tables showing change from baseline to the worst postbaseline value using the low/normal/high classifications based on laboratory reference ranges.

Categorical laboratory data will be tabulated by visit at baseline and postbaseline visits when necessary. Potential DILIs will be listed. The criteria for determining potential DILIs will be provided in the Statistical Analysis Plan.

10.4.2.3. Vital Signs

Descriptive statistics for the value at each assessment and change from baseline will be provided for vital signs (ie, BP, pulse, respiratory rate, and body temperature). Vital sign results will be reviewed for clinically notable abnormalities, and the abnormal values for participants exhibiting clinically notable vital sign abnormalities will be listed. Alert vital sign values are defined as an absolute value outside the defined range and an absolute percentage change of > 25% from baseline. The abnormal values for participants exhibiting alert vital sign abnormalities will be listed.

10.4.2.4. Electrocardiograms

Descriptive statistics for the value at each assessment and change from baseline will be provided for each ECG parameter. Baseline will be determined as the average of all nonmissing values from ECGs before the first administration of study treatment.

Electrocardiogram values outside of predefined ranges will be considered abnormal. Participants exhibiting ECG values outside the normal ranges will be listed. Participants with alert ECG values, defined as both the absolute value and the percentage change from baseline being outside normal ranges, will be identified and listed.

10.4.3. Pharmacokinetic Analysis

Descriptive summary statistics will be generated for plasma INCB099280 and axitinib concentration data by study part, dose levels, visit, and nominal time for the PK-evaluable population. For Part 2, the summaries will be additionally grouped by disease-specific cohorts.

For each participant with evaluable PK data, NCA PK parameters on Cycle 1 Day 1 (ie, C_{max}, t_{max}, $AUC_{0\text{-}4h}$) and on Cycle 2 Day 1 (ie, $C_{max,ss}$, $t_{max,ss}$, $AUC_{0\text{-}12h}$, C_{avg}, C_{tau}, $t_{½}$, CL_{ss}/F, and V_z/F) will be calculated from the observed plasma concentration-time profiles of INCB099280. Descriptive summary statistics will be generated for the NCA PK parameters by study part, dose

levels, and visit. For dose-independent parameters only, such as CL_{ss}/F, $t_{½}$, and V_z/F, additional summaries across dose levels will also be generated.

The INCB099280 PK concentration data obtained in this study may be combined with data from other studies in the clinical development program to develop or refine a population PK model. This model will be used to evaluate the effects of intrinsic and extrinsic covariates on the PK of INCB099280, whichever is applicable.

In addition, model-predicted post hoc exposures of INCB099280 may be used for exposure-response analyses on clinical efficacy (such as RECIST response) and/or safety endpoints as deemed appropriate. Planning and the results of population PK and exposure-response analyses will be reported separately.

For each participant with evaluable PK data, post hoc NCA PK parameters after first dose (ie, C_{max}, t_{max}, $AUC_{0\text{-}24h}$, C_{24h}) and at steady state (ie, $C_{max,ss}$, $t_{max,ss}$, $AUC_{0\text{-}12h}$, C_{avg}, C_{tau}, $t_{½}$, CL/F, and V_z/F) may be calculated from the population PK model–predicted post hoc plasma concentration-time profiles of INCB099280.

Descriptive statistics will be performed for post hoc estimates of plasma INCB099280 population PK model parameters as well as the post hoc NCA PK parameters by dose levels and/or across dose levels (for dose-independent parameters only, such as CL/F, $t_{½}$, and V_z/F) for the PK-evaluable population.

[redacted]

10.5. Interim Analysis

In Part 1, dose decisions from the hybrid design will be based on the current available data. After a DLT observation period for each dose-level cohort in the dose-finding period, the next dose level will be chosen depending on the observed accumulated data.

In Part 2, for each disease-specific cohort, nonbinding efficacy monitoring will be conducted after the first 20 enrolled participants either complete the Week 12 efficacy assessment or have disease progression or discontinue study treatment without halting the enrollment. Based on the observed numbers of participants with objective response (best overall response of CR or PR), cohorts with low number of responders that surpass the futility threshold may be closed.

For each cohort, at least 2 objective responders are required at the time of the first 20 participants either completing the Week 12 efficacy assessment or having disease progression or discontinuing the study. This futility stopping rule is to minimize the risk of participants being exposed to a potentially ineffective treatment.

Preplanned analyses of safety and preliminary efficacy will be provided to the DMC as specified in the DMC charter. The process by which the DMC will review data and make recommendations and decisions will be documented in the DMC charter.

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. All documents must be reviewed and approved by the IRB/IEC and health authorities before the study is initiated. In accordance with EU CTR No. 536/2014, the sponsor will be responsible for submitting all documents in participating countries.
- The investigator is responsible for ensuring that the safety reports provided by the sponsor are reviewed and processed in accordance with regulatory requirements, the policies and procedures established by the IRB/IEC, and institutional requirements.
- Any amendments to the Protocol will require approval from both health authorities and the IRB/IEC before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Recording and documenting AEs or laboratory abnormalities identified in the Protocol as critical to the safety evaluation and reporting them to the sponsor according to the reporting requirements specified in the Protocol.
  - Recording and documenting all AEs, unless the Protocol provides different guidance in Section 9.
  - Reporting to the sponsor all SAEs occurring to participants treated by them in the clinical study unless the Protocol provides different guidance in Section 9.
  - Reporting an SAE to the sponsor per Section 9 procedures and timelines if they become aware of an SAE with a suspected causal relationship to the study treatment that occurs after the end of the study.
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
  - Ensuring (along with the sponsor) that the clinical study is conducted in accordance with the Protocol and with the principles of GCP.
  - Providing oversight of the conduct of the study at the site and adherence to GCP, IRB/IEC requirements, institutional requirements, and applicable laws and country-specific regulations.

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

- The investigator will adhere to the Protocol as described in this document and agree that changes to the Protocol procedures, with the exception of medical emergencies, must be discussed and approved, first, by the sponsor or its designee and, second, by the IRB/IEC. Each investigator is responsible for enrolling participants who have met the specified eligibility criteria.
  - The investigator will retain the content of the clinical trial master file, essential documents, AE documentation, and medical and other study records in accordance with all local, national, and regulatory laws but for a minimum period of at least 30 years after completion or discontinuation of the study or as described in the final executed copy of the individual site agreement, or at least 2 years after the last marketing application approval in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or if not approved, 2 years after formal discontinuation of clinical development of the test article and the regulatory authority is notified, whichever is longer, to ensure the availability of study documentation should it become necessary for the sponsor or a regulatory authority to review.
  - The investigator must not destroy any records associated with the study during the retention period without receiving approval from the sponsor. The investigator must notify the sponsor or its designee in the event of accidental loss or destruction of any study records. If the investigator leaves the institution where the study was conducted, the sponsor or its designee must be contacted to arrange alternative record storage options.
  - All eCRF data entered by the site (including audit trail), as well as computer hardware and software (for accessing the data), will be maintained or made available at the site in compliance with applicable record retention regulations. The sponsor will retain the original eCRF data and audit trail.

11.1.1. Identification of the Coordinating Principal Investigator

An international coordinating investigator has been appointed by the sponsor. As part of their responsibilities, the coordinating principal investigator will review the final CSR. Agreement with the final CSR will be documented by the dated signature of the coordinating principal investigator.

11.2. Data Management

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

The site will be provided with eCRF completion guidelines for instructions on data entry in the eCRF. The study monitor will reference the Monitoring Plan in order to ensure that each issue

identified is appropriately documented, reported, and resolved in a timely manner in accordance with the plan's requirements. Other data outside the EDC system required in the study conduct of the Protocol, such as documents or results transmitted to the sponsor via a central laboratory or specialized technical vendors and as designated by the sponsor, will have their own data flow management plans, study charters, or biomarker plans, as applicable.

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

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

The investigator will be responsible for the following:

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

  - Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed and available at the investigator's site. Examples of source documents are original documents, data, and records (eg, hospital records; electronic hospital records; clinical and office charts; laboratory notes; memoranda; participants' diaries or evaluation checklists; pharmacy dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiches; photographic negatives; microfilm or magnetic media; x-rays; participants' files; and e-records/records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical study).
  - Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Current applicable medical records must be available.

- Sending participants' data, either as unique samples, copies, or photographs, to be evaluated centrally or analyzed centrally, or both, by a qualified vendor designated by the sponsor.
  - As required by privacy and data protection regulations and Incyte's privacy policies, if any photographs of participants are to be used in the study, even if occasionally, or are to be taken, the photographs must be limited to the area of the face or the body that is strictly necessary and the photographs should be masked (ie, identifying features such as eyes, mouth, scars, tattoos, or unique markings or features should be either obscured with a black bar or digitally pixelated so as to not permit the reidentification of the participants and preserve their confidentiality) prior to sending the photographs to Incyte or any other third-party vendors for analysis or further processing.
  - In accordance with French regulations, sites in France must perform the masking before the photographs are transferred, including to any specially designated photography vendor, Incyte, or any other third-party vendors for analysis or further processing. In addition, the participant's specific consent for photographs shall be collected.
- Permitting study-related monitoring, sponsor audits, IRB/IEC review, and regulatory inspections by providing direct access to source data and other relevant clinical study documents.
  - Monitoring: Qualified representatives of the sponsor or its designee, study monitors, will monitor the study according to a predetermined plan. The investigator must allow the study monitors to review any study materials and participant records at each monitoring visit.

- Auditing: Qualified representatives of the sponsor or its designee may audit the clinical study site and study data to evaluate compliance with the Protocol, applicable local clinical study regulations, and overall study conduct. The investigator must allow the auditors to review original source records and study documentation for all participants.
- Regulatory inspection: Regulatory authorities may conduct an inspection of the study and the site at any time during the development of an investigational product. The investigator and staff are expected to cooperate with the inspectors and allow access to all source documents supporting the eCRFs and other study-related documents. The investigator must immediately notify the sponsor when contacted by any regulatory authority for the purposes of conducting an inspection.

11.3. Data Quality Assurance

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

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

11.4. Data Privacy and Confidentiality of Study Records

The investigator and the sponsor or its designee must adhere to applicable data protection laws and regulations. The investigator and the sponsor or its designee are responsible for ensuring that personal information is handled in accordance with local data protection laws (including but not limited to HIPAA and GDPR) as applicable, and the sponsor operates comprehensive data privacy and data security programs that are applicable to this study. Appropriate notice, or notice and consent (as may be required by each applicable jurisdiction), for collection, use, disclosure, and/or transfer (if applicable) of personal information must be obtained in accordance with local data protection laws. Appropriate data protection terms that comply with applicable laws will be included in relevant study agreements.

To ensure confidentiality of records and protect personal data, participant names will not be supplied to the sponsor or its designee. Only the participant number will be recorded in the eCRF; if the participant's name appears on any other document (eg, laboratory report), it must be obliterated on the copy of the document to be supplied to the sponsor or its designee. Study

findings stored on a computer will be stored in accordance with appropriate technical and organizational measures as required by local data protection laws.

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

11.5. Financial Disclosure

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

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

11.6. Publication Policy

By signing the study Protocol, the investigator and their institution agree that the results of the study may be used by the sponsor, Incyte 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.

11.7. Study and Site Closure

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

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

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

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

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APPENDIX A. INFORMATION REGARDING EFFECTIVENESS OF CONTRACEPTIVE METHODS

Definitions

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

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal with 1 of the following:[a]
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy
- Postmenopausal
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with 2 FSH measurements in the postmenopausal range is required.
  - Female participants on HRT and whose menopausal status is in doubt will be required to use 1 of the nonhormonal, highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

For female participants who are WOCBP

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

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

[a] Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

[b] Hormonal contraception may be susceptible to interaction with the investigational medicinal product, which may reduce the efficacy of the contraception method. In this case, 2 methods of contraception should be used.

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

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

[e] 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 treatment. 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. INSTRUCTIONS TO PARTICIPANTS FOR HANDLING STUDY DRUG (INCB099280)

The participant must be instructed in the handling of study drug as follows:

- INCB099280 [redacted]-mg tablets must be [redacted] Store the study drug in a [redacted] at [redacted]
- INCB099280 [redacted]-mg tablets are to be stored at [redacted]
- Only remove the number of tablets needed at the time of administration.
- Do not remove doses in advance of the next scheduled administration.
- Make every effort to take doses on schedule.
- Report any missed doses/lost tablets.
- Take study drug with approximately 240 mL (approximately 8 oz) of water.
  - Participants must swallow the tablets whole without chewing before swallowing. Tablets must not be crushed, split, or dissolved.
- Report compliance with study drug daily.
- On days of PK sampling, participants should not consume a [redacted] meal within at least [redacted] hours before or after INCB099280 dose administration.
- INCB099280 should be taken on an [redacted] or with a [redacted] meal.
  - An example of a [redacted] meal in the United States typically contains 11 to 14 g of fat and a total caloric value of 400 to 500 kcal (eg, 8 oz of skim [1% fat] milk, 1 boiled egg, and 1 packet of flavored instant oatmeal made with water).
  - Meals that exceed [redacted] calories with [redacted]% calories from fat should be consumed at least [redacted] hours before or after INCB099280 administration. Site staff should discuss light meals or snacks with the participant and provide examples of food consumption that should be avoided within the ± [redacted]-hour fasting window.
- Doses should be taken in the morning and evening, approximately 12 hours apart.
  - If a dose of INCB099280 is missed by more than 4 hours, that dose should be skipped, and the next scheduled dose should be taken at the usual time.
- If vomiting occurs after taking study drug, do not take another dose.
- Keep study drug in a safe place and out of sight and reach of children.
- Bring all used and unused study drug bottles/kits to the site at each visit.

APPENDIX C. MEDICATIONS OR SUBSTANCES THAT ARE CONTRAINDICATED DURING STUDY TREATMENT

Examples of contraindicated medications are provided below.

For a comprehensive list, check with pharmacy personnel.

Additional references include the following:

- FDA. Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers.
- EMA (2013) Guideline on the Investigation of Drug Interactions.
- NPS Australia.

Medications that prolong the QT/QTcF interval
Amiodarone, anagrelide, azithromycin, chloroquine, chlorpromazine, ciprofloxacin, citalopram, clarithromycin, cocaine, disopyramide, domperidone, donepezil, erythromycin, escitalopram, fluconazole, gatifloxacin, haloperidol, hydroxychloroquine, levofloxacin, methadone, moxifloxacin, pentamidine, propofol, quinidine, sotalol, terfenadine, thioridazine, vandetanib
Moderate and potent/strong inhibitors of [redacted]
Aprepitant, atazanavir, boceprevir, cannabidiol (CBD), casopitant, clarithromycin, cobicistat, danoprevir, diltiazem, erythromycin, fluconazole, grapefruit, grapefruit juice, indinavir, itraconazole, ketoconazole[a], lopinavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, troleandomycin, voriconazole
Moderate and potent/strong inducers of [redacted]
Apalutamide, bosentan, carbamazepine, efavirenz, enzalutamide, etravirine, mitotane, phenobarbital, phenytoin, primidone, rifampin, St John's wort

[a] Topical use of 2% ketoconazole cream is allowed.

APPENDIX D. NEW YORK HEART ASSOCIATION CLASSIFICATION

The NYHA classification provides a simple way of classifying the extent of heart failure. It classifies patients into 1 of 4 categories based on their limitations during physical activity; the limitations/symptoms are in regard to normal breathing and varying degrees in shortness of breath and/or angina pain.

NYHA Classification – The Stages of Heart Failure

NYHA Class	Symptoms
Class I	No symptoms and no limitation in ordinary physical activity, eg, shortness of breath when walking, climbing stairs, etc.
Class II	Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
Class III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity, eg, walking short distances (20-100 meters). Comfortable only at rest.
Class IV	Severe limitations. Experiences symptoms even while at rest. Mostly bedbound patients.

APPENDIX E. PROTOCOL AMENDMENT SUMMARY OF CHANGES

Document	Date
Amendment 1	28 MAR 2024
Amendment 2	04 APR 2024

Amendment 2 (04 APR 2024)

Overall Rationale for the Amendment:

The primary purpose of this amendment is to provide specific storage conditions for study drug.

1. **Section 6.1, Study Treatments Administered (Table 7: Study Treatment Information); Appendix B, Instructions to Participants for Handling Study Drug (INCB099280)**

   Description of change: Added specific storage conditions for study drug.

   Rationale for change: Clarification.

Amendment 1 (28 MAR 2024)

Overall Rationale for the Amendment:

The primary purpose of this amendment is to update the dose of INCB099280 being evaluated and to update the clinical study design, including the clinical indications being enrolled and the statistical design. Additional changes are summarized below.

1. **Section 1, Protocol Summary (Table 1: Primary and Secondary Objectives and Endpoints); Section 3, Objectives and Endpoints (Table 4: Objectives and Endpoints); Section 10.4.1.2, Disease Control**

   Description of change: Removed the time requirement for SD.

   Rationale for change: Clarification.

2. **Section 1, Protocol Summary (Table 2: Key Study Design Elements; Figure 1: Study Design Schema); Section 2.4.1, Rationale for Treatment with INCB099280 and Axitinib in Rare Gynecological Cancers; Section 4.1.2, Dose Expansion; Section 5.1, Inclusion Criteria**

   Description of change: Clarified the rare indications to be included in the study.

   Rationale for change: Clarification.

3. **Section 1, Protocol Summary (Table 2: Key Study Design Elements; Figure 1: Study Design Schema); Section 2.4.2, Rationale for Treatment with INCB099280 and Axitinib Following Disease Progression with Prior Immunotherapy; Section 4.1, Overall Design; Section 4.1.1, Dose Finding; Section 4.1.2, Dose Expansion; Section 5.1, Inclusion Criteria; Section 10.1, Sample Size Determination**

   Description of change: Added 2 new indications/cohorts to the study.

   Rationale for change: To include participants with recurrent endometrial cancer and cervical cancer post treatment with chemotherapy and immunotherapy.

4. **Section 1, Protocol Summary (Table 2: Key Study Design Elements); Section 5.2, Exclusion Criteria (Criterion 4)**

   Description of change: Removed language prohibiting prior treatment with an immune modulator.

   Rationale for change: Updated study design.

5. **Section 1, Protocol Summary (Table 2: Key Study Design Elements; Figure 1: Study Design Schema); Section 4.1.1, Dose Finding; Section 10.1, Sample Size Determination**

   Description of change: Reduced the total number of participants to be enrolled in the study.

   Rationale for change: Updated study design.

6. **Section 1, Protocol Summary (Table 2: Key Study Design Elements; Table 3: Schedule of Activities); Section 3, Objectives and Endpoints (Table 4: Objectives and Endpoints); Section 4.2, Overall Study Duration; Section 7.1.1, Reasons for Discontinuation; Section 7.1.2, Discontinuation Procedures; Section 8.3.7, Laboratory Assessments (Table 18: Required Laboratory Analytes); Section 8.8.3, Survival Follow-Up; Section 9.4, Reporting of Serious Adverse Events; Section 10.4.1.5, Overall Survival**

   Description of change: Removed assessment of OS.

   Rationale for change: Without a comparator, OS data will not be meaningful.

7. **Section 1, Protocol Summary (Table 2: Key Study Design Elements; Figure 1: Study Design Schema); Section 2.4, Study Rationale; Section 2.4.3, Justification for INCB099280 Dose Selection; Section 4.1, Overall Design; Section 4.1.1, Dose Finding (Figure 4: Dose Levels in the Dose-Finding Part of the Study); Section 4.1.2, Dose Expansion; Section 5.2, Exclusion Criteria; Section 5.4, Screen Failures; Section 6.1, Study Treatments Administered (Table 7: Study Treatment Information); Section 6.3, Measures to Minimize Bias: Randomization and Blinding; Section 6.5, Dose-Limiting Toxicity and Determination of a Recommended Dose for Expansion; Section 6.5.2, Procedures for Cohort Review and Dose Finding; Section 6.6.7, Criteria for Permanent Discontinuation of Study Drugs Due to Unacceptable Toxicity; Section 8.1.2, Screening Procedures; Section 8.1.3, Interactive Response Technology Procedure; Section 8.3.1, Adverse Events; Section 9.3, Recording and Follow-Up of Adverse Events and/or Serious Adverse Events; Section 10.1, Sample Size Determination; Section 10.5, Interim Analysis**

   Description of change: Changed the dose of INCB099280 to 400 mg BID only, removed randomization to different dose levels, and reduced the number of doses administered in Part 1.

   Rationale for change: To reduce the total number of doses explored in the study. A dose of 400 mg BID has been selected for use in Phase 2 monotherapy studies of INCB099280.

8. **Section 1, Protocol Summary; Section 4.1, Overall Design; Section 6, Study Treatment; Section 6.6.7, Criteria for Permanent Discontinuation of Study Drugs Due to Unacceptable Toxicity; Section 7.1.1, Reasons for Discontinuation**

   Description of change: Clarified that if combination treatment is not tolerated, participants have met the criterion for study treatment discontinuation. INCB099280 monotherapy may be allowed on a case-by-case basis.

   Rationale for change: The rationale for this study is the potential for a synergistic/additive effect with the combination of an antiangiogenic agent and PD-(L)1 inhibition. Therefore, if combination treatment is not tolerated, participants will meet the criterion for study treatment discontinuation. If axitinib must be discontinued, INCB099280 monotherapy may be allowed on a case-by-case basis after discussion between the medical monitor and site investigator. There are early clinical data suggesting an improved response rate and PFS with pembrolizumab in clear cell gynecological malignancies (PEACOCC study). In addition, monotherapy with PD-(L)1 monoclonal antibodies is a subsequent treatment option for patients with recurrent/metastatic cervical cancer and for some patients with recurrent endometrial cancer based on biomarker status. Given that participants in this early-phase study may have exhausted other therapeutic options, if the benefit/risk profile is favorable, INCB099280 monotherapy may be an option.

9. **Section 1, Protocol Summary (Table 3: Schedule of Assessments); Section 2.5, Benefit/Risk Assessment; Section 5.1, Inclusion Criteria; Section 8.2.1.3, Assessment of Tumor Markers During Treatment;** [redacted]

   Description of change: Updated the tissue and blood-based biomarker sample collection for the study.

   Rationale for change: To limit participant burden of high sample collection and streamline the analysis plan.

10. **Section 1, Protocol Summary (Table 3: Schedule of Assessments); Section 8.3.3, Physical Examinations**

    Description of change: Clarified when height is to be measured during physical examinations.

    Rationale for change: Clarification.

11. **Section 1, Protocol Summary (Table 3: Schedule of Assessments); Section 8.3.7, Laboratory Assessments (Table 18: Required Laboratory Analytes)**

    Description of change: Removed mean corpuscular hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin concentration, and reticulocyte count from the hematology analytes; removed HbA_{1c} from the blood chemistry analytes; and removed ACTH and cortisol from the endocrine function analytes.

    Rationale for change: The hematology panel has been limited to standard analytes. ACTH, cortisol, and HbA_{1c} will be analyzed to work up potential endocrine abnormalities and are not required at baseline as per irAE management guidance (ASCO and ESMO Clinical Practice Guidelines).

12. **Section 1, Protocol Summary (Table 3: Schedule of Assessments); Section 5.2, Exclusion Criteria (Criterion 26); Section 8.3.7.2, Serology**

    Description of change: Updated eligibility and monitoring for participants with HBV and HCV infection.

    Rationale for change: Clarification and alignment with the ASCO guidelines.

13. **Section 2.2, INCB099280; Section 2.4.5, Clinical Safety Profile of INCB099280**

    Description of change: Revised background information on INCB099280.

    Rationale for change: Update.

14. **Section 2.4.3, Justification for INCB099280 Dose Selection**

    Description of change: Updated the justification for the dose selected (400 mg BID), including the addition of subsections on safety/efficacy, pharmacodynamic and translational data, pharmacokinetics, and exposure/response data.

    Rationale for change: Updated study design.

15. **Section 4.1.1, Dose Finding; Section 6.5.2, Procedures for Cohort Review and Dose Finding; Section 6.6, Dose Modifications; Section 6.6.2, Dose Reductions; Section 6.6.3, Criteria and Procedures for Dose Interruptions and Adjustments of Study Drug; Section 6.6.4, Management of Non–Immune-Related Adverse Events (Table 10: Non–Immune-Related Adverse Event Management Guidelines for INCB099280); Section 10.1, Sample Size Determination; Appendix E, A Hybrid Design for Dose-Escalation Oncology Clinical Trials**

    Description of change: Updated text regarding INCB099280 dose selection and dose modification, including incorporating original Table E1 into Section 4.1.1, revising the corresponding text regarding DLTs, adding that the RDE selected for evaluation in Part 2 will not exceed the MTD, and deleting original Appendix E.

    Rationale for change: Removal of the INCB099280 600 mg BID and 800 mg BID dose levels.

16. **Section 4.1.3, Safety Monitoring**

    Description of change: Clarified the safety monitoring rules for Part 2.

    Rationale for change: Elimination of redundant language and to allow for flexibility in safety monitoring, given the high rate of approximately 60% of Grade 3 or higher AEs with these classes of agents in combination and the overall favorable risk/benefit with appropriate dose modification per Protocol in previous clinical study experience.

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

    Description of change: Added guidance on prior permitted therapies for each cohort.

    Rationale for change: Updated study design.

18. **Section 5.1, Inclusion Criteria (Criterion 6)**

    Description of change: Added text that if participants have only 1 measurable lesion per RECIST v1.1, the biopsy specimen must be obtained from a nontarget lesion or archival tissue.

    Rationale for change: Clarification.

19. **Section 5.2, Exclusion Criteria (Criterion 6)**

    Description of change: Updated the interval between first administration of study treatment and anticancer therapies to include at least 5 half-lives from receipt of prior anti–PD-L1 therapy.

    Rationale for change: Clarification.

20. **Section 5.2, Exclusion Criteria (Criterion 31); Section 6.7.3, Prohibited Medications and Procedures**

    Description of change: Reduced the washout of prior antibiotics from 28 days to 14 days.

    Rationale for change: Current clinical evidence does not suggest that a longer washout period improves participant outcomes, and decreasing the washout period allows for increased flexibility supporting participant enrollment.

21. **Section 5.2, Exclusion Criteria (Criterion 35); Section 6.7.3, Prohibited Medications and Procedures**

    Description of change: Added that COVID-19 vaccines are allowed as long as they are not live vaccines.

    Rationale for change: Clarification.

22. **Section 5.2, Exclusion Criteria (Criterion 36); Section 6.7.3, Prohibited Medications and Procedures**

    Description of change: Changed the washout period for prior treatment with moderate or potent [redacted] inducers and inhibitors to ≥ 10 days.

    Rationale for change: Clarification.

23. **Section 5.2, Exclusion Criteria (Criterion 38 [Table 6: Exclusionary Laboratory Values])**

    Description of change: Updated exclusionary hepatic laboratory values to remove 3 × ULN liver function tests (ALT/AST) in the presence of liver metastases, removed the option of glomerular filtration rate and serum creatinine to determine renal function, and clarified the institutional ULN results for coagulation tests (INR, PT, aPTT).

    Rationale for change: Clarification.

24. **Section 5.3.1, Meals and Dietary Restrictions; Section 6.1, Study Treatments Administered (Table 7: Study Treatment Information); Section 8.4.1, Blood Sample Collection; Appendix B, Instructions to Participants for Handling Study Drug (INCB099280)**

    Description of change: Clarified guidance for meal restrictions around dosing administration and PK sample collection.

    Rationale for change: Clarification.

25. **Section 5.5, Recruitment Strategy and Retention of Participants; Section 8.6, Storage and Future Use of Biological Samples**

    Description of change: Added information on recruitment strategy and retention of participants as well as sample collection and storage.

    Rationale for change: Updated Protocol template.

26. **Section 5.6, Replacement of Participants; Section 7.1.1, Reasons for Discontinuation**

    Description of change: Removed requirement that participants must be discontinued from the study if found to not have met eligibility criteria.

    Rationale for change: If continuing on study treatment is not considered by the investigator as harmful to the participant, they should not be deprived of potential benefit.

27. **Section 6.1, Study Treatments Administered (Table 7: Study Treatment Information)**

    Description of change: Added [redacted]-mg tablet.

    Rationale for change: New tablet strength.

28. **Section 6.5, Dose-Limiting Toxicity and Determination of a Recommended Dose for Expansion; Section 6.6, Dose Modifications; Section 6.6.1, Dose Interruptions; Section 6.6.3, Criteria and Procedures for Dose Interruptions and Adjustments of Study Drug; Section 6.6.6, Dose-Modification Guidelines for Adverse Events Potentially Associated with Axitinib Treatment (Table 12: Axitinib Toxicity Management Guidelines; Table 13: Management Guidelines for Specific Adverse Events Common to Both INCB099280 and Axitinib; Table 14: Algorithms of Decision on INCB099280/Axitinib Rechallenge After Recovery From Drug-Related ALT/AST Elevations)**

    Description of change: Clarified guidance regarding axitinib dose modifications.

    Rationale for change: Clarification and to provide additional rechallenge guidance for liver function test (ALT/AST) elevation.

29. **Section 6.6.5, Management of Immune-Related Adverse Events (Table 11: Management Guidelines for Immune-Related Adverse Events)**

    Description of change: Clarified guidance related to INCB099280 in the event of Grade 3 hepatitis and in the event of myocarditis, pericarditis, and elevated troponin.

    Rationale for change: To align dose modification guidance throughout the Protocol.

30. **Section 6.7.2.3, Acid-Reducing Agents**

    Description of change: Removed antacids from section heading and removed the recommendation that [redacted] blockers be administered > [redacted] hours before or after administration of study treatment.

    Rationale for change: Clarification.

31. **Section 6.7.3, Prohibited Medications and Procedures**

    Description of change: Updated text regarding prohibited medications and/or procedures.

    Rationale for change: Clarification.

32. **Section 8.3.7, Laboratory Assessments (Table 18: Required Laboratory Analytes); Appendix B, COVID-19 Pandemic Guidance**

    Description of change: Removed COVID-19 pandemic guidance.

    Rationale for change: No longer applicable.

33. **Section 10.2, Population for Analysis (Table 23: Primary and Secondary Endpoints and Analysis Populations)**

    Description of change: Listed all PK outputs to be evaluated.

    Rationale for change: Clarification.

34. **Section 10.5, Interim Analysis**

    Description of change: Updated the statistical design of the study so that in Part 2, for each cohort, a nonbinding futility analysis after the first 20 participants either complete the Week 12 efficacy assessment or have disease progression or discontinue study treatment will be performed.

    Rationale for change: Updated study design.

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

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