Official Title: A Phase 1 Study of INCB099280 in Combination With Adagrasib in Adults With Advanced Solid Tumors Harboring a KRASG12C Mutation

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Clinical Study Protocol

INCB 99280-204

A Phase 1 Study of INCB099280 in Combination With Adagrasib in Adults With Advanced Solid Tumors Harboring a KRAS^{G12C} Mutation

Product:	**INCB099280**
IND Number:	[redacted]
EU CT Number:	**2023-503223-26-00**
Phase of Study:	**1**
Sponsor:	**Incyte Corporation** **1801 Augustine Cut-Off** **Wilmington, DE 19803 USA**
Original Protocol:	**22 FEB 2023**
Amendment 1:	**12 MAY 2023**
Amendment 2:	**16 MAY 2023**
Amendment 3:	**17 OCT 2023**
Amendment 4:	**21 FEB 2024**

INVESTIGATOR'S AGREEMENT

I have read the INCB 99280-204 Protocol Amendment 4 (dated 21 FEB 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.

_____

(Printed Name of Investigator)

_____ _____

(Signature of Investigator) (Date)

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LIST OF ABBREVIATIONS

Abbreviations and Special Terms	Definition
ACTH	adrenocorticotropic hormone
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
ART	antiretroviral therapy
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the plasma concentration curve
BCG	Bacillus Calmette-Guerin
BCRP	breast cancer resistance protein
BID	twice daily
$C_{avg,ss}$	average plasma concentration at steady state
CFR	Code of Federal Regulations
CHF	congestive heart failure
CI	confidence interval
CL/F	apparent oral dose clearance
CL_{ss}/F	apparent oral dose clearance at steady state
C_{max}	maximum plasma concentration
$C_{max,ss}$	maximum plasma concentration at steady state
C_{min}	minimum plasma concentration
$C_{min,ss}$	minimum plasma concentration at steady state
CNS	central nervous system
COVID-19	coronavirus disease 2019
CR	complete response
CRC	colorectal cancer
CrCl	creatinine clearance
CSF	cerebrospinal fluid
CSR	Clinical Study Report
CT	computed tomography
C_{tau}	plasma concentration at time tau (ie, 12 hours for twice daily regimens) at steady state
CTCAE	Common Terminology Criteria for Adverse Events

Abbreviations and Special Terms	Definition
ctDNA	circulating tumor DNA
C_{trough}	trough plasma concentration
CXCL	chemokine ligand
CYP	cytochrome P450
DCR	disease control rate
DDI	drug-drug interaction
DILI	drug-induced liver injury
DLCO	diffusing capacity for carbon monoxide
DLT	dose-limiting toxicity
dMMR	deficient mismatch repair
DNA	deoxyribonucleic acid
DOR	duration of response
DRESS	drug reaction with eosinophilia and systemic symptoms
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EMG	electromyography
EOT	end of treatment
ESMO	European Society for Medical Oncology
FAS	full analysis set
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
FT4	free thyroxine
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GGT	gamma-glutamyltransferase
GI	gastrointestinal
HBV	hepatitis B virus
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
IB	Investigator Brochure

Abbreviations and Special Terms	Definition
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
ID	identification
IEC	independent ethics committee
IFN	interferon
IL	interleukin
ILD	interstitial lung disease
INR	international normalized ratio
irAE	immune-related adverse event
IRB	institutional review board
iRECIST	immune Response Evaluation Criteria in Solid Tumors
IRT	interactive response technology
IV	intravenous
KRAS	Kirsten rat sarcoma viral oncogene homologue
$KRAS^{G12C}$	KRAS glutamine to cysteine mutation at codon 12
LVEF	left ventricular ejection fraction
MAP/ERK	mitogen-activated protein/extracellular signal–related kinase
MATE	multidrug and toxic extrusion
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
MTD	maximum tolerated dose
mTPI	modified toxicity probability interval
MSI-H	high microsatellite instability
NE	not evaluable
NSCLC	non–small cell lung cancer
ORR	objective response rate
PD-1	programmed death-1
PD-L1	programmed death-ligand 1
PFS	progression-free survival
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
PPI	proton pump inhibitor

Abbreviations and Special Terms	Definition
PR	partial response
PT	prothrombin time
QD	once daily
QTcF	QT interval corrected using Fridericia's formula
QxW	every x weeks
RANKL	receptor activator of nuclear factor kappa-B ligand
RAS	rat sarcoma
RDE	recommended dose for expansion
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
RSI	Reference Safety Information
SAE	serious adverse event
SCC	squamous cell carcinoma
SD	stable disease
SJS	Stevens-Johnson syndrome
SoA	schedule of activities
SOP	standard operating procedure
Study treatment	This term refers to all medications that the participant is required to receive as part of this study.
T3	triiodothyronine
T4	thyroxine
TEAE	treatment-emergent adverse event
TEN	toxic epidermal necrolysis
$T_{max,ss}$	time to maximum plasma concentration at steady state
TMB-H	tumor mutational burden-high
TME	tumor microenvironment
TRAE	treatment-related adverse event
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
V_z/F	apparent oral dose volume of distribution at steady state
WBC	white blood cell
WOCBP	woman of childbearing potential

1. PROTOCOL SUMMARY

Protocol Title: A Phase 1 Study of INCB099280 in Combination With Adagrasib in Adults With Advanced Solid Tumors Harboring a $KRAS^{G12C}$ Mutation

Protocol Number: INCB 99280-204

Objectives and Endpoints:

Table 1 presents the primary and secondary objectives and endpoints.

Table 1: Primary and Secondary Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of INCB099280 in combination with adagrasib. • To establish the MTD or identify RDE(s) for the combination of INCB099280 and adagrasib.	• DLTs. • TEAEs. • Impact of TEAEs on study drug administration, assessed by treatment interruptions, dose reductions, and permanent discontinuation.
Secondary	
• To characterize the PK of INCB099280 and adagrasib when administered in combination. • To assess whether clinically effective dose(s) of INB099280 can be coadministered with adagrasib.	• Descriptive summary of PK concentration data for INCB099280 and adagrasib. • INCB099280 PK parameters including $C_{max,ss}$, $T_{max,ss}$, $C_{min,ss}$, AUC_{0-12h}, CL/F, and V_z/F from observed INCB099280 plasma concentration-time profiles, summarized and analyzed [redacted]
To assess the antitumor activity of INCB099280 in combination with adagrasib in participants with $KRAS^{G12C}$-mutant advanced solid tumors, including NSCLC and CRC.	• Objective response, defined as having a best overall response of CR or PR assessed per RECIST v1.1 by the investigator. • Disease control, defined as having a best overall response of CR, PR, or SD ≥ 15 weeks (from the start of treatment) assessed per RECIST v1.1 by the investigator. • DOR, defined as the time from the first CR or PR until disease progression (assessed per RECIST v1.1 by the investigator) or death from any cause, whichever occurs earlier. • Six-month and 12-month PFS, defined as absence of disease progression (assessed per RECIST v1.1 by the investigator) or death from any cause from start of treatment to 6 or 12 months.

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
Clinical Indication	Adults with $KRAS^{G12C}$-mutated advanced solid tumors, including NSCLC or CRC, whose disease has progressed after at least 1 prior line of systemic therapy.
Population	• Part 1: Adults with previously treated advanced $KRAS^{G12C}$-mutant advanced solid tumors. • Part 2: Adults with previously treated advanced NSCLC or CRC harboring the $KRAS^{G12C}$ mutation.
Number of Participants	Approximately 125 participants are planned to be enrolled. • Part 1 (dose finding) will include approximately 45 DLT-evaluable participants. • Part 2 (dose expansion) will include up to 80 participants with previously treated $KRAS^{G12C}$-mutant NSCLC (Cohort A) or previously treated $KRAS^{G12C}$-mutant CRC (Cohort B).
Study Design	This is a Phase 1 multicenter, open-label study conducted in 2 parts: a dose-finding part followed by a dose-expansion part. In Part 1, the safety, tolerability, and PK of escalating doses of INB099280 in combination with adagrasib will be evaluated in approximately 45 DLT-evaluable participants with previously treated $KRAS^{G12C}$-mutant advanced solid tumors. [redacted]. These data will support the identification of an MTD and/or RDE(s) for further evaluation in the dose-expansion part of the study. In Part 2, up to 3 RDEs will be evaluated to expand on the clinical experience with these RDEs in 2 disease-specific cohorts: previously treated $KRAS^{G12C}$-mutated NSCLC and previously treated $KRAS^{G12C}$-mutated CRC. Up to 80 participants will be enrolled in Part 2. If only 1 dose regimen is selected for expansion, then up to 40 participants will be enrolled in each of the 2 disease cohorts. If more than 1 dose regimen is selected for expansion, participants will be randomized to the dose levels within each disease-specific cohort (see Figure 1 for further details).

Table 2: Key Study Design Elements (Continued)

Estimated Duration of Study Participation	Up to 28 days for screening, [redacted], continuous combination treatment in consecutive 28-day cycles as long as participants are receiving benefit and have not met any criteria for study withdrawal, and 30 (+ 7) to 90 (+ 14) days for safety follow-up after the last dose of study drug. Participants who discontinue study treatment for a reason other than disease progression should continue to have efficacy assessments performed until disease progression, new anticancer therapy is started, death, withdrawal of consent, lost to follow-up, for 12 months after the EOT, or the end of study, whichever occurs first. It is estimated that an individual will participate for approximately 9 months.
DSMB	Yes (external)
Coordinating Principal Investigator	To be determined

Treatment Groups and Duration:

INCB099280 will be administered in combination with adagrasib. INCB099280 may be administered for up to 2 years or until a criterion for treatment discontinuation described in Section 7.1 is met. Adagrasib may be administered until the participant meets the criteria for treatment discontinuation as described in Section 7.1.

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

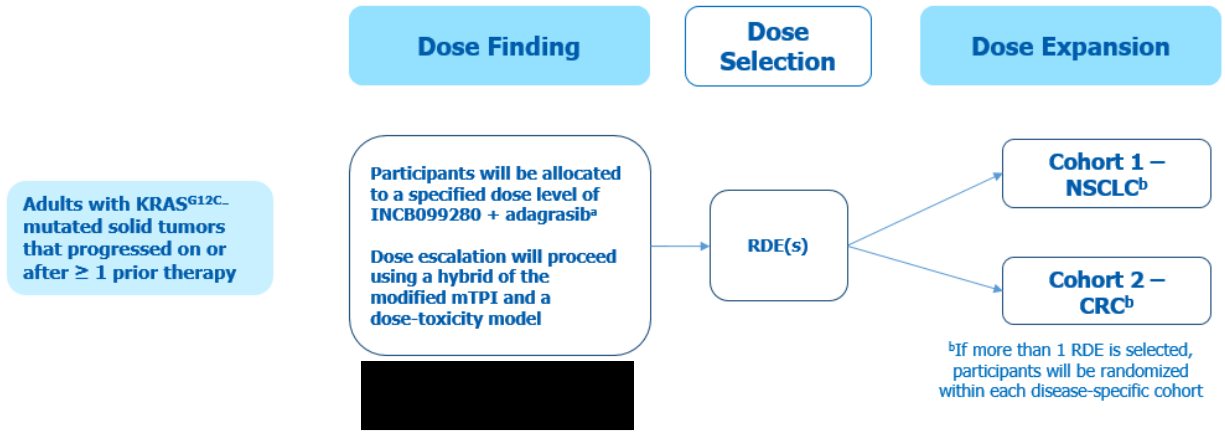

Table 3: Schedule of Activities

	Prescreening	Screening	INCB099280 [redacted]		Cycles 1 and 2					Cycles 3 and 4				Cycles 5+			Safety Follow-Up		Disease Status	
Window (Days)	**If Needed**	**28 Days**	[redacted]	[redacted]	**D1**	**D4 (±1d)**	**D8 (±3d)**	**D15 (±3d)**	**D22 (±3d)**	**D1 (±3d)**	**D8 (±3d)[b]**	**D15 (±3d)**	**D22 (±3d)[b]**	**D1 (±3d)**	**D15 (±3d)[b]**	**EOT**	**EOT +30d (+7d)**	**EOT +90d (+14d)**	**Q8W/ Q12W After EOT**	**Notes**
Documentation																				
Informed consent	X	X																		Section 8.1.1
Inclusion/exclusion criteria		X	X		X															Section 5
Clinical examination																				
Medical history		X																		Section 8.1.5
Cancer history		X																		Section 8.1.5.2
Prior/concomitant medications		X	X		X		X	X	X	X		X		X		X	X	X		Section 6.7
ECOG performance status		X	X		X					X				X		X	X			Section 8.3.6
Vital signs/body weight		X	X		X		X	X	X	X		X		X		X	X			Section 8.3.3
Physical examination		X	X*		X*		X*	X*	X*	X*		X*		X*		X				Section 8.3.2 Includes height at screening. *Symptom directed.
12-Lead ECG		X			X		X*			X†				X†		X	X			Section 8.3.4 See Table 17 for required ECG timepoints. *Cycle 1 only. †Every other cycle beginning with Cycle 4.

Table 3: Schedule of Activities (Continued)

Window (Days)	Prescreening If Needed	Screening 28 Days	INCB099280 [redacted] [redacted]	 [redacted]	Cycles 1 and 2 D1	 D4 (±1d)	 D8 (±3d)	 D15 (±3d)	 D22 (±3d)	Cycles 3 and 4 D1 (±3d)	 D8 (±3d)[b]	 D15 (±3d)	 D22 (±3d)[b]	Cycles 5+ D1 (±3d)	 D15 (±3d)[b]	 EOT	Safety Follow-Up EOT +30d (+7d)	 EOT +90d (+14d)	Disease Status Q8W/ Q12W After EOT	Notes
Clinical examination (continued)																				
Echocardiogram		X			X*					X*				X*						Section 8.3.5 *Every other cycle beginning with Cycle 1.
Laboratory-based investigations																				
KRAS^{G12C} testing and sponsor confirmation	X*	X																		Section 8.1.5.2.1 Assay tested locally using tissue and/or ctDNA using validated molecular testing methods. *If status is unknown.
PD-L1 expression		X																		If needed, see Section 8.1.5.2.2.
Hematology panel		X	X		X		X	X	X	X		X		X		X	X			Section 8.3.7
Chemistry panel		X	X		X		X	X	X	X		X		X		X	X			Section 8.3.7
Endocrine panel		X*								X†				X†		X	X			Section 8.3.7 *ACTH and cortisol collected in the morning at screening and as clinically indicated. †Cycle 3 and every other cycle. If a participant has an endocrine irAE, additional assessments may be performed.

Table 3: Schedule of Activities (Continued)

	Prescreening	Screening	INCB099280 [redacted]		Cycles 1 and 2					Cycles 3 and 4				Cycles 5+			Safety Follow-Up		Disease Status	
Window (Days)	**If Needed**	**28 Days**	[redacted]	[redacted]	**D1**	**D4 (±1d)**	**D8 (±3d)**	**D15 (±3d)**	**D22 (±3d)**	**D1 (±3d)**	**D8 (±3d)[b]**	**D15 (±3d)**	**D22 (±3d)[b]**	**D1 (±3d)**	**D15 (±3d)[b]**	**EOT**	**EOT +30d (+7d)**	**EOT +90d (+14d)**	**Q8W/ Q12W After EOT**	**Notes**
Laboratory-based investigations (continued)																				
Pregnancy testing		X*	X†		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 (up to 190 days after the last dose of study drug).
Coagulation panel		X														X				Section 8.3.7 Additional assessments should be performed if clinically indicated.
Hepatitis screening		X																		Section 8.3.7.2
Urinalysis		X								X*				X*		X	X			Section 8.3.7 *Cycle 3 and every other cycle.
Adverse events																				
AE assessments		X	X	X	X		X	X	X	X		X		X		X	X	X		Section 8.3.1
Telephone AE assessments						X*					X		X		X					Section 8.3.1.1 *Cycle 1 only.

Table 3: Schedule of Activities (Continued)

Window (Days)	Prescreening If Needed	Screening 28 Days	INCB099280 [redacted] [redacted]	 [redacted]	Cycles 1 and 2 D1	 D4 (±1d)	 D8 (±3d)	 D15 (±3d)	 D22 (±3d)	Cycles 3 and 4 D1 (±3d)	 D8 (±3d)[b]	 D15 (±3d)	 D22 (±3d)[b]	Cycles 5+ D1 (±3d)	 D15 (±3d)[b]	 EOT	Safety Follow-Up EOT +30d (+7d)	 EOT +90d (+14d)	Disease Status Q8W/ Q12W After EOT	Notes
Radiology and disease assessments																				
Radiologic tumor imaging and response assessment		X								X*				X*		X			X†	Section 8.2.1 *Q8W (56 ± 7 days) until disease progression. After 12 months of treatment, frequency may be reduced to Q12W (84 ± 14 days). Imaging should not be delayed for delays in cycle starts. †Participants who discontinue therapy due to a reason other than progressive disease should be followed for disease status (see Section 8.8.2).
Study treatment																				
Contact IRT		X	X		X					X				X		X				Section 8.1.3
Dispense INCB099280			X*		X					X				X						Section 6.1, Section 6.3, and Section 8.1.3 [redacted]
Dispense adagrasib					X					X				X						Section 6.1, Section 6.3, and Section 8.1.3

Table 3: Schedule of Activities (Continued)

Window (Days)	Prescreening If Needed	Screening 28 Days	INCB099280 [redacted] [redacted]	 [redacted]	Cycles 1 and 2 D1	 D4 (±1d)	 D8 (±3d)	 D15 (±3d)	 D22 (±3d)	Cycles 3 and 4 D1 (±3d)	 D8 (±3d)[b]	 D15 (±3d)	 D22 (±3d)[b]	Cycles 5+ D1 (±3d)	 D15 (±3d)[b]	EOT	Safety Follow-Up EOT +30d (+7d)	 EOT +90d (+14d)	Disease Status Q8W/ Q12W After EOT	Notes
Study treatment (continued)																				
Administer INCB099280 in clinic			X	X	X		X*			X†				X‡						Section 6.1 *Cycle 1 only. †Cycle 4 only. ‡Cycles 6, 8, and 12 and every fourth cycle thereafter.
Administer adagrasib in clinic					X		X*			X†				X‡						Section 6.1 *Cycle 1 only. †Cycle 4 only. ‡Cycles 6, 8, and 12 and every fourth cycle thereafter.
Distribute participant information cards		X																		Section 8.1.4
Distribute reminder cards		X	X	X	X		X	X	X	X		X		X		X	X		X	Section 8.1.4
Distribute dosing diaries			X	X	X		X	X	X	X		X		X						Section 8.1.4
Collect study drug and review dosing diary					X*		X	X	X	X		X		X		X				Section 6.4 *Cycle 2 only.
Assess compliance					X*		X	X	X	X		X		X		X				Section 6.4 *Cycle 2 only.

Table 3: Schedule of Activities (Continued)

	Prescreening	Screening	INCB099280 [redacted]		Cycles 1 and 2					Cycles 3 and 4				Cycles 5+			Safety Follow-Up		Disease Status	
Window (Days)	If Needed	28 Days	[redacted]	[redacted]	D1	D4 (±1d)	D8 (±3d)	D15 (±3d)	D22 (±3d)	D1 (±3d)	D8 (±3d)[b]	D15 (±3d)	D22 (±3d)[b]	D1 (±3d)	D15 (±3d)[b]	EOT	EOT +30d (+7d)	EOT +90d (+14d)	Q8W/ Q12W After EOT	Notes
PK sampling																				
PK plasma (predose)				X*	X		X†			X‡				X§						Section 8.4.1 [redacted] †Cycle 1 only. ‡Cycle 4 only. §Cycles 6, 8, and 12 and every fourth cycle thereafter.
PK plasma timed (postdose)				X*			X†													Section 8.4.1 [redacted] †Cycle 1 only.
Pharmacodynamic sampling																				
Plasma biomarker			X		X					X*										Section 8.5.1 *Cycle 3 Day 1 only.
Plasma cell-free DNA			X		X					X*										Section 8.5.2 *Cycle 3 Day 1 only.
Tumor tissue collection		X																		Section 8.5.3 Fresh or archival; required only if PD-L1 expression is not known.

Note: Each cycle is 28 days.
[a] For participants in lead-in cohort only.
[b] Assessments by telephone only.

2. INTRODUCTION

2.1. Background

Immune evasion, one of the hallmarks of cancer, is a pivotal mechanism exploited by tumor cells to evade detection by the immune system and facilitate tumor progression. Tumors achieve this through several mechanisms; one such mechanism engages the PD-1/PD-L1 immune checkpoint inhibitory interaction that regulates the immune response, particularly of cytotoxic T cells, resulting in their immune downregulation and exhaustion. On this basis, blocking the PD-L/PD-L1 pathway has been exploited therapeutically and there is now substantial evidence for the use of these immune checkpoint inhibitors 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).

However, 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.

2.2. $KRAS^{G12C}$ Inhibition

KRAS, one of the members of the RAS family of genes, is one of the most frequently mutated proto-oncogenes in cancer. Activating mutations in KRAS are found in 95% of pancreatic ductal adenocarcinomas, nearly half of colon cancers, and approximately one-third of non–squamous cell NSCLCs (Bailey et al 2018, Moore et al 2020, Simanshu et al 2017).

Among cancers in which somatic KRAS mutations are most common, the vast majority of KRAS genomic alterations involve the single nucleotide variation with glycine substituted by cysteine at codon 12 (Wiesweg et al 2019). These missense mutations occur in approximately 13% of patients with non–squamous cell NSCLC (Biernacka et al 2016) and 3% of all patients with CRC (Sanchez-Vega et al 2018).

Since the seminal discovery of RAS oncogenes 40 years ago, the majority of these studies focused on the cell-autonomous contribution of these oncogenes to cell proliferation, survival, and metabolism. However, accumulating evidence suggests that oncogenic signaling can engage host cells within the TME and dampen immune responses that, given the clinical success of immunotherapy with PD-(L)1 inhibitors, have been recognized as having powerful antitumoral functions. Pioneering work over the past 10 years has resulted in the development of mutant-specific KRAS inhibitors by binding to the thiol group of the novel cysteine residue resulting from the KRAS (G12C) mutation, trapping $KRAS^{G12C}$ in an inactive state (Ostrem et al 2013). Of these allele-specific $KRAS^{G12C}$ inhibitors, adagrasib and sotorasib have shown clinical promise.

Adagrasib is an irreversible inhibitor of $KRAS^{G12C}$ that covalently binds to the mutant cysteine in KRAS and locks the mutant KRAS protein in its inactive, guanosine diphosphate–bound state, resulting in the inhibition of downstream MAP/ERK signaling. Adagrasib inhibits the viability in cells harboring $KRAS^{G12C}$ mutations by potent binding to mutant $KRAS^{G12C}$ (cellular IC_{50} ≈5 nM) and with high selectivity (> 1000×) for the mutant $KRAS^{G12C}$ protein without affecting wild-type KRAS protein. It results in tumor growth inhibition in $KRAS^{G12C}$-mutated tumor xenograft models with minimal off-target activity. Adagrasib has also been shown to have favorable PK properties, including oral bioavailability, long half-life (≈24 hours), and extensive tissue distribution. As of 27 NOV 2021, [redacted] participants ([redacted] adult healthy volunteers or special populations and [redacted] participants with cancer) have been exposed to 1 or more doses of adagrasib, of which [redacted] were participants with cancer treated with adagrasib as monotherapy. Refer to the adagrasib IB for further information.

2.3. Clinical Experience With Allele-Specific Inhibitors of $KRAS^{G12C}$

Clinical data from studies of sotorasib and adagrasib have shown that $KRAS^{G12C}$ inhibition translates into clinical efficacy with manageable toxicities in patients with $KRAS^{G12C}$-mutant advanced NSCLC and CRC.

Sotorasib was the first covalent allele-specific $KRAS^{G12C}$ inhibitor approved by the FDA and European Commission in 2021 and 2022, respectively, as monotherapy for the treatment of adults with $KRAS^{G12C}$-mutated advanced NSCLC who have disease progression after at least 1 prior line of systemic therapy. Data from the Phase 2 portion of the single-arm, open-label, global, multicenter, CodeBreaK100 study with sotorasib as monotherapy showed substantial antitumor effects in 124 evaluable adult patients with $KRAS^{G12C}$-mutated NSCLC that progressed on prior therapies. At a median follow-up of 15.3 months, major efficacy outcomes in participants with > 1 measurable lesion at baseline were ORR of 37.1% (95% CI: 28.6, 46.2; CR: 3.2%; PR: 33.9%), median DOR of 11.1 months (95% CI: 6.9, NE), median PFS of 6.8 months (95% CI: 5.1, 8.2), and median overall survival of 12.5 months (95% CI: 10.0, NE) (Skoulidis et al 2021).

In DEC 2022, the FDA approved adagrasib as monotherapy for the same therapeutic indication. The approval was based on the primary outcome measures of ORR and response duration observed in 112 evaluable participants from Cohort A of the KRYSTAL-1 study. Results showed comparable efficacy with an ORR of 42.9% (95% CI: 33.5, 52.6) and an estimated median DOR of 8.5 months (95% CI: 6.2, 13.8) with a median follow-up of 12.9 months; responses lasted for more than 6 months in more than 58% of participants (Krazati™ 2022). Additionally, subgroup analysis revealed responses to adagrasib in participants with stable and/or previously treated CNS disease and offered exploratory insights into potential biomarkers of response (Jänne et al 2022a). Notably, participants in both studies had received a $KRAS^{G12C}$ inhibitor after having received prior platinum-doublet chemotherapy and a PD-1/PD-L1 inhibitor (98.3% of participants in the KRYSTAL-1 study and 81% in the CodeBreaK100 study).

Adverse events, regardless of attribution to adagrasib, were observed in all participants; the most common events were diarrhea (70.7%), nausea (69.8%), fatigue (59.5%), vomiting (56.9%), anemia (36.2%), dyspnea (35.3%), increased blood creatinine (34.5%), and decreased appetite (31.9%). Adverse events that were attributed by the investigators to the treatment were reported in 97.4% of participants; the most common were diarrhea (62.9%), nausea (62.1%), vomiting

(47.4%), fatigue (40.5%), increased ALT (27.6%), increased blood creatinine (25.9%), and increased AST (25.0%). Most of the frequently observed TRAEs were Grade 1 or 2. A total of 52 participants (44.8%) had Grade 3 or higher TRAEs; the most common were fatigue, nausea, and increased ALT (each in 4.3%) and increased AST (3.4%). Two fatal events were reported (1 cardiac failure in a participant with a medical history of pericardial effusion and 1 pulmonary hemorrhage). Treatment-related AEs led to dose reduction in 51.7% of participants and dose interruption in 61.2% of participants; the most common reasons were GI-related events, hepatic events (increased ALT and AST levels), and fatigue. Eight participants (6.9%) discontinued adagrasib because of TRAEs (Jänne et al 2022a).

Serious cutaneous reactions have been seen in patients receiving adagrasib. As reported publicly by a health authority, there was a case of fatal TEN, also known as Lyell syndrome, in a patient treated with adagrasib for NSCLC as part of the compassionate program in France. This patient was previously treated with pembrolizumab. This patient's other medications included amoxicillin discontinued 3 weeks prior to the onset of clinical presentation and pravastatin started 15 days prior to the onset. Additionally, a health authority analysis identified 4 other cases of serious skin reactions and 1 nonserious case of "skin toxicity" related to the use of adagrasib alone or in combination. The serious skin reactions included dermatitis in a patient receiving adagrasib and pembrolizumab, SJS in a patient receiving adagrasib and cetuximab and in a patient receiving adagrasib and afatinib, and DRESS in a patient receiving adagrasib monotherapy.

Adagrasib has demonstrated promising clinical efficacy and favorable tolerability as monotherapy in previously treated patients with advanced CRC harboring a $KRAS^{G12C}$ mutation. Of 43 evaluable patients who received adagrasib as monotherapy, the investigator-assessed confirmed ORR was 19% and the DCR was 86%. The median DOR was 4.3 months (95% CI: 2.3, 8.3), and the median PFS was 5.6 months (95% CI: 4.1, 8.3) (Klempner et al 2022).

2.4. Rationale for Combining an Inhibitor of $KRAS^{G12C}$ With a PD-L1 Inhibitor

Only a subset of patients benefit from treatment with $KRAS^{G12C}$ inhibitors, and early results indicate that drug resistance frequently arises (Awad et al 2021, Tanaka et al 2021). Therefore, while these results confirm that $KRAS^{G12C}$ is a targetable alteration, combination therapies aimed at augmenting the efficacy of these therapies are needed in patients with $KRAS^{G12C}$-mutant tumors.

There are rational arguments in support of combining PD-1/PD-L1 inhibitors with targeted inhibition of KRAS. As oncogenic KRAS signaling has been shown to play a role in orchestrating an immunosuppressive environment (Cullis et al 2018), $KRAS^{G12C}$ inhibitors can indirectly affect antitumor immunity in addition to affecting the survival of cancer cells. $KRAS^{G12C}$ inhibition has been shown to have both direct and indirect effects on the TME, including up-regulation of IFN signaling via Myc inhibition resulting in enhanced intrinsic and extrinsic IFN responses, reduced expression of chemokines leading to reduced tumor infiltration by immunosuppressive myeloid cells, enhanced infiltration and activation of cytotoxic T cells, and increased antigen presentation (Canon et al 2019, Van Maldegem et al 2021, Mugarza et al 2022). Initial data showed durable responses following $KRAS^{G12C}$ inhibition in mice dependent on T cells, and $KRAS^{G12C}$ inhibition with adagrasib combined with anti–PD-1 therapy led to

improved survival in a genetically engineered $KRAS^{G12C}$-mutant CT26 syngeneic mouse model when compared to either agent administered as monotherapy. Notably, adagrasib demonstrated acquired adaptive tumor immunity and durable complete responses in this model (Briere et al 2021).

2.4.1. Clinical Results for Combination of Adagrasib With a PD-1 Inhibitor

The current clinical experience with adagrasib in combination with the anti–PD-1 monoclonal antibody pembrolizumab includes data from Cohorts 1a and 2 of the KRYSTAL-7 Phase 2 study and the KRYSTAL-1 Phase 1b study in which this combination therapy was administered as the primary systemic therapy to participants with $KRAS^{G12C}$-mutant advanced, unresectable, or metastatic NSCLC. Preliminary results from the KRYSTAL-7 study including 53 evaluable participants showed an ORR of 49% (95% CI: 35, 63) regardless of the level of PD-L1 expression and a DCR of 89% (95% CI: 77, 96) at a median follow-up of 3.5 months. This preliminary clinical activity was seen across all 3 PD-L1 subgroups: ORR was 59%, 48%, and 30% and the estimated 6-month PFS rates were 70%, 50%, and 60% for a tumor proportion score of ≥ 50%, 1% to 49% and < 1%, respectively. Treatment-related AEs of any grade, Grade 3 severity, and Grade 4 severity were observed in 83%, 40%, and 4% of participants, respectively. The most common TRAEs reported in ≥ 15% of participants that were attributed to the combination treatment by the investigators were nausea (48%), diarrhea (43%), vomiting (24%), fatigue, increased ALT and AST (21% each), decreased appetite (20%), and increased amylase (20%). The treatment-related liver TEAEs were predominantly low-grade events and occurred early after the initiation of treatment. No treatment-related deaths were reported. Treatment-related AEs led to adagrasib dose reduction in 31% of participants and dose interruption in 41% of participants. Two participants (3%) discontinued both adagrasib and pembrolizumab and 3% discontinued pembrolizumab only due to TRAEs.

Additionally, data from the KRYSTAL-1 Phase 1b cohort including 7 evaluable participants treated with the same combination therapy showed comparable activity with objective responses in 57% of participants noted across all PD-L1 subgroups and a DCR of 100% with a median follow-up of 19.3 months. All 4 participants who responded had a durable response of more than 9 months, with 2 continuing on treatment for more than 18 months. The safety of this cohort was consistent with what has been observed in the KRSTYAL-7 study, and a manageable safety profile with no Grade 4 or 5 TRAEs was demonstrated (Jänne et al 2022b).

These results suggest that the concurrent combination of adagrasib with a PD-(L)1 inhibitor may provide a chemotherapy-free option for treatment-naïve NSCLC and supports further investigation of adagrasib in combination with a PD-(L)1 inhibitor.

2.5. Rationale for Study

The hypothesis is that adagrasib could be safely administered with INCB099280, an orally administered small-molecule inhibitor of PD-L1, and result in improved outcomes in participants with $KRAS^{G12C}$-mutant malignant solid tumors whose disease has progressed after at least 1 prior line of systemic therapy.

The overall aim of this multicenter, open-label Phase 1 study is to evaluate the safety, tolerability, and antitumor activity of INCB099280 administered in combination with adagrasib in participants with selected $KRAS^{G12C}$-mutant advanced solid tumors. The dose-expansion part

of the study will further evaluate the RDE(s) of INCB099280 in combination with adagrasib in participants with $KRAS^{G12C}$-mutant advanced NSCLC and CRC.

2.6. INCB099280

INCB099280, an investigational inhibitor of PD-L1, potentially offers advantages over therapeutic monoclonal 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.

Preliminary data from an ongoing Phase 1 study (INCB 99280-112) in participants with advanced solid malignancies indicates that INCB099280 is well tolerated, has a favorable safe profile, and shows promising antitumor activity (Prenen et al 2023).

2.6.1. Justification for INCB099280 Dose for Further Evaluation

As of 08 JUL 2022, 86 participants with advanced solid malignancies received INCB099280 as monotherapy (Study INCB 99280-112) with total daily doses ranging from 100 mg to 800 mg, administered either QD or BID. Overall, 80 of 86 participants (93%) were evaluable for response, having had at least 1 postbaseline disease assessment. These 80 evaluable participants were assigned to 1 of 7 dose cohorts: 100 mg QD (n = 3; 3.8%), 200 mg QD (n = 3; 3.8%), 200 mg BID (n = 3; 3.8%), 300 mg BID (n = 28; 35%), 600 mg QD (n = 9; 11.3%), 400 mg BID (n = 24; 30%), and 800 mg QD (n = 10; 12.5%).

With a median follow-up of 17 weeks (range: 0.6-45.7 weeks), 33 (41.3%) of these 80 evaluable participants had disease control on INCB099280. Nine (11.3%) had an objective response (1 [1.3%] had a CR and 8 [10%] had a PR), and 24 (30%) had SD. Responses were dose dependent, with 6 of the 9 objective responses observed after a median follow-up of 10.8 weeks (range: 0.6-45.7 weeks) in participants who received 400 mg BID. The onset of responses has frequently been seen on the first postbaseline disease assessment performed 8 weeks after the initiation of INCB099280, and responses were durable in 8 of the 9 participants who achieved an objective response to treatment. Responding participants had molecularly diverse and clinically heterogeneous malignancies. The diagnoses of 6 of 24 participants (25%) who responded to treatment with 400 mg BID included MSI-H SCC of the cervix, anaplastic carcinoma thyroid, cutaneous SCC, adnexal carcinoma of the scalp, SCC of the anal canal, and TMB-H colon cancer. A further 3 responding participants included 2 with a diagnosis of dMMR endometrial adenocarcinoma and MSI-H, TMB-H adenocarcinoma of the prostate who received 300 mg BID and 1 participant with a diagnosis of TMB-H adenocarcinoma of the colon who received 600 mg QD. None of the responding participants had previously received treatment with a checkpoint inhibitor targeting the PD-1/PD-L1 pathway. In a further case of TMB-H (217 mut/Mb) poorly differentiated sebaceous carcinoma of the scalp, continued treatment with 400 mg BID beyond disease progression was characterized by a continuing regression of disease with a durable partial response per iRECIST. Further, treatment with INCB099280 was characterized by disease stabilization or regression of measurable disease in 5 of 24 participants (20.8%) who received 400 mg BID and 6 of 28 participants (21.4%) who received 300 mg BID. This additional antitumor activity is clinically meaningful given that participants were eligible following progression on or after having received systemic anticancer therapy for advanced disease.

Additional support of [redacted] mg [redacted] as a biologically active dose includes PK and pharmacodynamic data. All responding participants who received treatment with [redacted] mg [redacted] and [redacted] mg [redacted] as well as the participant who received [redacted] mg [redacted] and had a PR per [redacted] had [redacted] above the [redacted] for PD-L1 inhibition on human monocytes. The highest tumor growth inhibition in established humanized mouse tumor models and the level of PD-L1 inhibition as well as increases in T-cell populations were also seen [redacted]. Furthermore, computational noncompartmental analysis showed that there is a significant overlap in exposure between INCB099280 [redacted] mg [redacted] and [redacted] mg [redacted] but that [redacted] mg [redacted] has a [redacted] for both [redacted] and [redacted] when compared to [redacted] mg [redacted] An exploratory pharmacodynamic analysis bioanalytically evaluated the effects of INCB099280 on immune activation by measuring plasma levels of cytokines, soluble PD-L1, and T-cell proliferation and activation. Overall, preliminary pharmacodynamic biomarker data demonstrate that INCB099280 has immunomodulatory activity during the first [redacted] days of treatment and that [redacted] mg [redacted] may be associated with higher pharmacodynamic effects compared to lower doses, findings that are consistent with approved monoclonal antibody PD-(L)1 inhibitors. Moreover, an interim exposure pharmacodynamic biomarker assessment showed a moderate, positive correlation between increases in CXCL10, IFNγ, IL-18, IL-18BP, IL-27 and soluble PD-L1 from baseline and [redacted], a finding that was also statistically significant.

Based on this dose- and exposure-response evaluation together with a favorable safety profile (see Section 2.8 for further details), [redacted] mg [redacted] was selected as the minimally effective dose for further evaluation.

2.6.2. Justification for Duration of Treatment

Anti–PD-(L)1 therapies have improved outcomes across multiple tumor types. Clinical studies evaluating anti–PD-(L)1 therapies have provided mature data to evaluate DOR and the long-term safety profile. Melanoma was the initial tumor to enter late-stage clinical studies and obtain an approval for an anti–PD-1 therapy. In melanoma, approximately one-third of patients have long-term benefit with durable responses to single-agent or combination immunotherapy. Despite the extensive clinical investigation with checkpoint inhibitors that has been done to date, the optimal duration of treatment for checkpoint inhibitors has not been defined (Banks and Sullivan 2020, Marron et al 2021). In the KEYNOTE-001 study, participants with melanoma who received pembrolizumab and achieved a CR were allowed to discontinue therapy once Protocol-specified criteria were met; among the 72 participants who discontinued treatment, responses were maintained in 90% (Hamid et al 2019). In the KEYNOTE-006 study, 19% of participants with melanoma completed the Protocol-specified 2-year limit of treatment. Responses continued in 76% of participants who achieved a CR, 77% of those who achieved a PR, and 54% of those who achieved SD. Additionally, 8% of participants with best overall response of PR converted to CR after stopping pembrolizumab. In the group of participants who completed 2 years of treatment and had SD or response, 78% of participants had sustained disease control and did not have disease progression 2 years after completing pembrolizumab treatment (Robert et al 2019). Clinical studies evaluating anti–PD-(L)1 therapies have taken differing approaches in regard to maximum duration of treatment. Some studies allowed treatment until disease progression or unacceptable toxicity was observed, and others specified a maximum duration of 12 or 24 months. Current evidence suggests that patients may obtain

benefit from less treatment compared to what is specified in clinical studies and the approved indications. There is also a consideration that prolonged treatment with immunotherapy may lead to an increased risk of clinically significant irAEs as well as a financial burden to patients and healthcare providers (Marron et al 2021). Based on the available evidence from initial clinical studies evaluating anti–PD-(L)1 therapies, participants may be treated with INCB099280 for up to 2 years.

2.7. INCB099280 in Combination With Adagrasib

The adagrasib dose of 400 mg [redacted] has been studied in combination with pembrolizumab and has shown clinical benefit with acceptable safety and tolerability (see Section 2.4.1). In addition, preliminary clinical PK of adagrasib administered in combination with [redacted] showed favorable PK properties and demonstrated that adagrasib 400 mg BID resulted in a [redacted] ng/mL). Therefore, the adagrasib dose that will be used in this study is [redacted] mg [redacted]

2.7.1. Rationale for the INCB009280 Starting Dose in Combination With Adagrasib

In this study, the starting dose of INCB099280 administered in combination with adagrasib will be [redacted] mg [redacted] This dose was selected after accounting for the effect of adagrasib on [redacted].

Preclinical data suggest that INCB099280 is [redacted] in humans and may be subject to [redacted] when coadministered with [redacted]

Based on the observed dose proportionality in INCB099280 [redacted] from [redacted] mg [redacted] to [redacted] mg [redacted] it is anticipated that a dose of [redacted] mg [redacted] calculated as [redacted] mg [redacted], would result in an approximately equivalent INCB099280 [redacted] in the presence of adagrasib. Therefore, the [redacted] mg [redacted] regimen in the presence of adagrasib was chosen as not to exceed the [redacted].

2.7.2. Rationale for Escalating the Dose of INCB099280 to [redacted] mg [redacted]

The dose escalation for INCB099280 (as outlined in Table 6) will proceed based on emerging PK, safety, and tolerability data according to the algorithm provided in Table 8 and will mirror the equivalent effective monotherapy doses of INCB099280. The rationale for escalating the INCB099280 dose above the estimated equivalent dose to [redacted] mg [redacted] is based on preliminary population PK modeling and simulation using the [redacted] available to date. It is projected that the percentage of participants with a [redacted] threshold could be increased from [redacted]% with 400 mg [redacted] to [redacted]% for [redacted] mg [redacted] and [redacted] mg [redacted] respectively. Further, it is estimated that the proportion of participants with an average plasma concentration above the IC_{90} could be increased with doses [redacted] mg [redacted] from [redacted]% and [redacted]% at a dose of [redacted] mg [redacted] and [redacted] mg [redacted] respectively.

Therefore, INCB099280 dose escalation will start with [redacted] mg [redacted] and INCB099280 dose(s) with an acceptable benefit/risk ratio will be identified for expansion based on safety, tolerability, and [redacted] from Part 1, enriched by pharmacometric modeling and simulation utilizing clinical data from studies conducted with INCB099280.

2.8. Clinical Safety Profile of INCB099280

The foreseeable risks associated with the administration of INCB099280 are currently based on the clinical safety information from 2 studies in which INCB099280 has been administered as monotherapy: a completed adult healthy participant study (INCB 99280-101) and the ongoing Phase 1 study (INCB 99280-112).

2.8.1. First-in-Human Study in Healthy Adult Participants

A total of [redacted] participants were enrolled in the healthy adult participant study and received single doses of INCB099280 or placebo orally: [redacted]. Additionally, there were no meaningful differences in the incidence of individual TEAEs across treatment groups. Additional details are provided in the INCB099280 IB.

2.8.2. First-in-Participant Study in Advanced Solid Malignancies

As of 22 JUN 2023, 172 participants with cancer have been treated with INCB099280 at doses ranging from 100 mg QD to 800 mg BID. Across all dose levels, 95.3% of participants experienced a TEAE, the majority of which were Grade 1 or 2. The most frequent TEAEs of any grade across dose levels were asthenia (30.2%), decreased appetite (27.3%), and nausea (25.0%). The most frequent treatment-related AEs of any grade across all dose levels were asthenia (22.7%), nausea (16.3%), fatigue (13.4%), decreased appetite (12.8%), pruritus (12.2%), and diarrhea (10.5%). Treatment with INCB099280 has been well tolerated across all dose levels tested. INCB099280 was escalated to a maximum of 800 mg BID, and a maximum tolerated dose was not identified. Preliminary response data with a data cutoff date of 22 JUN 2023 that included 159 response-evaluable participants showed an ORR of 7.5%. Two participants

achieved CR, and 10 had PR. Disease control (SD plus PR plus CR) was seen in 57 participants (35.8%) across multiple dose levels of INCB099280. The highest ORR observed was 17.8% at the 400 mg BID dose level (Prenen et al 2023). For further information, refer to the INCB099280 IB.

2.9. Benefit/Risk Assessment

Even though immune checkpoint inhibitors 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 inhibitor monotherapy. This unmet medical need is reflected in these agents being effective in a minority of unselected patients and many patients with common types of tumors who have progressive disease as their best response.

There is a robust biological rationale supported by preclinical data for the addition of a $KRAS^{G12C}$ inhibitor to INCB099280 in adults with solid tumors harboring mutant $KRAS^{G12C}$. Results in participants with recurrent advanced NSCLC and CRC have been encouraging and have led to an ongoing randomized Phase 3 study as the primary therapy in NSCLC, where it is hoped that, in addition to its antiproliferative and antiapoptotic effects, there will also be a potential for a synergistic/additive effect with PD-(L)1 inhibition.

Clinical experience with the combination of adagrasib and pembrolizumab has shown a manageable safety profile, overall consistent with either agent administered as monotherapy, and with a low rate of TRAEs leading to discontinuation (Jänne et al 2022b). There is the potential risk of serious adverse skin reactions with adagrasib, which are more commonly observed when adagrasib is combined with active substances with an identified risk of serious adverse skin reactions or soon after their withdrawal. In order to minimize the risk of serious adverse skin reactions, adagrasib dose modifications for any grade skin toxicity as well as serious skin reactions including bullous lesions, SJS, and TEN have been implemented and are detailed in Table 16.

For these reasons, this Phase 1 study to evaluate the addition of adagrasib to INCB099280 in adults with tumors that harbor $KRAS^{G12C}$ mutations has been designed to determine whether the concurrent administration of these 2 agents is safe and tolerable and confers meaningful clinical benefit. Based on the available preclinical and clinical data and the measures implemented to minimize risks with INCB099280 and adagrasib, this combination is expected to have a positive benefit/risk profile in this study.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of INCB099280 and adagrasib may be found in the INCB099280 IB and adagrasib 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 adagrasib. • To establish the MTD or identify RDE(s) for the combination of INCB099280 and adagrasib.	• DLTs. • TEAEs. • Impact of TEAEs on study drug administration, assessed by treatment interruptions, dose reductions, and permanent discontinuation.
Secondary	
• To characterize the PK of INCB099280 and adagrasib when administered in combination. • To assess whether clinically effective dose(s) of INB099280 can be coadministered with adagrasib.	• Descriptive summary of PK concentration data for INCB099280 and adagrasib. • INCB099280 PK parameters including $C_{max,ss}$, $T_{max,ss}$, $C_{min,ss}$, AUC_{0-12h}, CL/F, and V_z/F from observed INCB099280 plasma concentration-time profiles, summarized and analyzed [redacted].
To assess the antitumor activity of INCB099280 in combination with adagrasib in participants with $KRAS^{G12C}$-mutant advanced solid tumors, including NSCLC and CRC.	• Objective response, defined as having a best overall response of CR or PR assessed per RECIST v1.1 by the investigator. • Disease control, defined as having a best overall response of CR, PR, or SD ≥ 15 weeks (from the start of treatment) assessed per RECIST v1.1 by the investigator. • DOR, defined as the time from the first CR or PR until disease progression (assessed per RECIST v1.1 by the investigator) or death from any cause, whichever occurs earlier. • Six-month and 12-month PFS, defined as absence of disease progression (assessed per RECIST v1.1 by the investigator) or death from any cause from start of treatment to 6 or 12 months.
[redacted]	
[redacted]	[redacted]

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 1 multicenter, open-label study conducted in 2 parts: a dose-finding part followed by a dose-expansion part. The study will enroll adults with $KRAS^{G12C}$-mutated advanced solid tumors whose disease has progressed after at least 1 prior line of systemic therapy. In Part 2 (dose expansion), enrollment will be limited to adults with $KRAS^{G12C}$-mutated NSCLC or CRC.

The study will include a 28-day screening period to determine eligibility, an [redacted] a treatment period of up to 2 years for INCB099280 or until the participant meets Protocol-specified criteria for discontinuation of treatment for INCB099280 and/or adagrasib, an EOT visit, and 30-day and 90-day safety follow-up visits.

Tumor assessments will be performed at baseline and subsequently Q8W (± 7 days) for the first year of treatment and Q12W (± 14 days) thereafter by site investigator review according to RECIST v1.1. Participants who discontinue study treatment for a reason other than disease progression will continue to be assessed for their disease status during the follow-up period of the study and should continue to have tumor assessments Q8W (± 7 days) for the first 12 months and then Q12W (± 14 days) thereafter until a new anticancer therapy is started, disease progression, withdrawal of consent, lost to follow-up, death, for 12 months after the EOT, or the end of the study, whichever occurs first.

Safety will be evaluated from the time the participant signs informed consent until the 90-day safety follow-up visit. In Part 2, safety data will also be reviewed by a DSMB.

4.1.1. Part 1 – Dose Finding

In Part 1, the safety, tolerability, and PK of escalating doses of INCB099280, coadministered with adagrasib, will be evaluated in approximately 45 participants with $KRAS^{G12C}$-mutant advanced solid tumors. These data will support the identification of an MTD and/or RDE(s) of the combination for further evaluation in the dose-expansion part of the study. No more than 1 participant per dose level will begin study treatment within a 24-hour period.

[redacted], the starting dose regimen (Dose Level 1) will be INCB099280 50 mg QD and adagrasib 400 mg BID (see the rationale for this starting dose in Section 2.7.1). Dose-escalation decisions will be guided by emergent safety and tolerability data, taking the [redacted] into consideration.

Early [redacted] will be performed for Part 1 Dose Level 1. One participant will initially be enrolled into the cohort and [redacted] will be performed (within 1 week of [redacted]) following the [redacted] before further participants are treated. An additional 2 participants may be enrolled after the [redacted] and reviewed. The [redacted] from these second and third participants will also be analyzed prior to further enrollment in the dose level cohort.

The [redacted] for the participants enrolled in Dose Level 1 will be reviewed and the assignment of the next dose-escalation level (Dose Level 2) will be selected according to Table 5, providing

the safety of the combination for Dose Level 1 is acceptable as assessed by the hybrid model described in Section 4.1.1.2. If the [redacted] for the first 3 participants treated have an [redacted], additional participants may not be treated at this dose level.

Table 5: Potential Dose Levels to Be Explored in Dose Level 2

Scenarios of INCB099280 [redacted] (When Administered With adagrasib 400 mg BID)	**INCB099280 Dose Level 2 Options (in Combination With Adagrasib 400 mg BID)**	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

If further dose escalation is warranted, subsequent dose levels to be explored are described (see Table 6). No matter which INCB099280 dose is selected for Dose Level 2, the subsequent dose levels described in Table 6 will be followed.

Table 6: Potential Dose Levels to Be Explored in Part 1

Dose Level	**INCB099280 Dose**[a]	**Adagrasib Dose**
−1	[redacted]	400 mg BID
1 (starting dose)	[redacted]	**400 mg BID**
2	See Table 5	400 mg BID
The appropriate dose level below will be selected following available data generated from the second dose level explored (eg, if [redacted] mg [redacted] is selected for the second dose level per Table 5, the third dose level will be [redacted] mg [redacted]		
	[redacted]	400 mg BID
	[redacted]	400 mg BID
	[redacted]	400 mg BID
	[redacted]	400 mg BID
	[redacted]	400 mg BID
	[redacted]	400 mg BID

Note: Guided by findings from Table 5.

[a] Intermediate dose levels may be explored based on emerging safety and [redacted].

[b] If the MTD has not been reached and there is no clear efficacy-related signal at the highest dose level, then the dose-escalation procedure may be continued with additional participants enrolled at a higher dose level.

Alternate dose levels for INCB099280 [redacted] may be evaluated based on [redacted] but will not exceed the highest [redacted] dose that has cleared the DLT period; possible alternative doses of INCB099280 are included in Table 7.

Table 7: Potential Alternate Dose Levels to Be Explored in Part 1

Dose Level	INCB099280 Dose[a]	Adagrasib Dose
A	[redacted]	400 mg BID
B	[redacted]	400 mg BID
C	[redacted]	400 mg BID
C	[redacted]	400 mg BID
E	[redacted]	400 mg BID
F	[redacted]	400 mg BID
G	[redacted]	400 mg BID

[a] Intermediate dose levels may be explored based on emerging safety and [redacted].

4.1.1.1. [redacted] Treatment Period

Dose Level 1 will start with a [redacted] treatment period of INCB099280 as [redacted]

If 9 participants are enrolled in Dose Level 1, additional dose levels will not include a lead-in treatment period. However, if < 9 participants are included in Dose Level 1, participants enrolled in Dose Level 2 will also [redacted]. This will ensure at least 9 participants can be evaluated [redacted].

4.1.1.2. DLT Evaluation Using the Hybrid Model

For dose-level cohorts that [redacted], adagrasib will be coadministered with INCB099280 starting on Cycle 1 Day 1. The DLT observation period will start when coadministration of adagrasib and INCB099280 has been initiated and will last for 28 days.

Participants will be considered DLT evaluable if they have received at least 75% of the planned doses of both INCB099280 and adagrasib during the first 28 days of treatment or had a DLT during this observation period.

A hybrid of the modified mTPI design and a dose-toxicity model will be used to make dose-escalation, de-escalation, and dose-elimination decisions. For each tested dose regimen, dose-escalation decisions will be based on a minimum cohort of 3 DLT-evaluable participants and will take a target DLT rate of 30% during the first 28 days of combination treatment into consideration. However, even if an observed DLT rate would support dose escalation, a tested dose regimen may be retained and the RDE may be guided by PK and other clinical data (such as

lower-grade treatment-related toxicities and AEs meeting DLT criteria that occurred after the DLT observation period).

The hybrid design (Liao et al 2022) is a hybrid of the modified mTPI design and a dose-toxicity model, and it has 3 steps.

Step 1: An mTPI design (Ji et al 2010) with a target DLT rate p_T of 30% (equivalence interval [0.27, 0.33]) and a dose-exclusion cutoff of 0.95 is firstly modified to control the overdosing toxicity using the posterior probability of DLT rate in the overdosing interval (0.33, 1) to be less than 0.75. With this rule, if 3 DLTs are observed out of 6 participants, which is a DLT rate of approximately 50%, then the mTPI will guarantee a dose de-escalation instead of staying at the current dose level when the observed toxicity rate is high. Table 8 shows the dose-escalation rules based on the number of DLTs observed in a dose-level cohort.

Step 2: A frequentist logistic dose-toxicity model is used by pooling all observed safety information from all previous dose cohorts to estimate the DLT rate for the current dose level and predict the DLT rate for the next INCB099280 and adagrasib dose level in the provisional dose list. The estimated DLT rate at the current dose level is used together with the decision rules from the modified mTPI design to make a decision jointly about dose escalation. Note that if the dose-toxicity model is not feasible (eg, no DLT is observed at any tested doses), then no action is needed at this step.

Step 3: If the decision in Table 8 is to have a dose escalation (E) at the next INCB099280 dose (to be given in combination with adagrasib) level in the provisional dose list, then the predicted DLT rate using the dose-toxicity model from Step 2 is used to judge whether the next dose level is feasible or not by checking if the predicted DLT rate at the next INCB099280 dose level is over the prespecified targeted DLT rate. If the predicted DLT rate is over the targeted DLT rate, then the next dose level in the provisional dose list cannot be used. Instead, an intermediate dose from the earlier used dose-toxicity model will be calibrated so that the DLT rate is below the targeted DLT rate. Similarly, if the decision in Table 8 is to have a dose de-escalation (D) to a lower INCB099280 dose level in the provisional dose list, an intermediate dose from the earlier used dose-toxicity model will be calibrated so that the DLT rate is below the targeted DLT rate. If the decision in Table 8 is to stay (S) at the current dose and the estimated DLT rate at the current INCB099280 dose is greater than the prespecified targeted DLT rate, then the decision is to de-escalate (D) to an intermediate dose level; otherwise, it is a stay (S). Note that choosing the intermediate dose level will take into consideration what is clinically and operationally feasible.

A minimum of 3 evaluable participants are required at each dose level. However, depending on the minimal threshold of PK sampling needed, 3, 4, 5, or 6 participants may be enrolled. Approximately 45 evaluable participants may be treated in the dose-finding part of the study, and the dose-escalation procedure may be stopped if the number of evaluable participants treated at any dose level is ≥ 9. If emerging data support de-escalation of an unacceptable dose (D or DU) at the lowest dose level, the study will evaluate the data to determine whether a lower dose (or alternative schedule) should be considered.

When adding participants to a dose level in response to a stay (S) decision, the number of additional participants to be enrolled is capped to minimize the exposure to a dose that may have

unacceptable toxicity (denoted as "dose unacceptable [DU]" in Table 8). To determine how many more participants can be enrolled at the dose level, steps can be counted in a diagonal direction (down and to the right) from the current cell to the first cell marked DU. For example, if 1 of 3 participants experienced a DLT at a given dose level, no more than 3 additional participants should be enrolled at this dose level until additional DLT data are available. This is because that dose level would be considered unacceptably toxic if all 3 of the additional participants experience a DLT (ie, 4 of 6 participants with a DLT in Table 8).

If the MTD has not been reached and there is no clear efficacy-related signal at the highest dose level, then the dose-escalation procedure may be continued with additional participants enrolled at a higher dose level.

At the end of the dose-escalation procedure, the DLT rates at all tested dose levels will be estimated based on the aforementioned dose-toxicity model if it is feasible or the pool-adjacent violators algorithm if the parametric dose-toxicity model is not feasible. The dose with an estimated DLT rate closest to [redacted]% will be treated as a MTD. However, the totality of the available data, such as the emerging safety and [redacted], will be considered before deciding on the dose(s) to carry forward to Part 2.

Table 8: Dose-Finding Rules per Modified mTPI Design

Participants With at Least X DLT	Number of Participants Evaluable for DLT						
	3	4	5	6	7	8	9
0	E	E	E	E	E	E	E
1	S	S	S	E	E	E	E
2	D	D	S	S	S	S	S
3	DU	DU	D	D	S	S	S
4		DU	DU	DU	D	D	D
5			DU	DU	DU	DU	DU
6				DU	DU	DU	DU
7					DU	DU	DU
8						DU	DU
9							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: Target toxicity rate p_T = [redacted]%.
Note: Flat noninformative prior Beta(1,1) is used as a prior and $\varepsilon_1 = \varepsilon_2 = 0.03$ (Ji et al 2010, Ji and Wang 2013).
Note: Posterior toxicity probability cut = 0.75.

4.1.2. Part 2 – Dose Expansion

In Part 2, up to 80 participants will be enrolled into 2 disease-specific cohorts ($KRAS^{G12C}$-mutated NSCLC and $KRAS^{G12C}$-mutated CRC) to further evaluate the safety and tolerability of the combination therapy as well as to continue characterizing the PK and antitumor activity. Part 2 will not begin until all RDE(s) are identified. Up to 3 INCB099280 and

adagrasib dose regimens (selected as RDE[s]) will be chosen to facilitate dose optimization. The RDE(s) for evaluation in Part 2 will be determined based on an integrated assessment of safety, tolerability, and PK, supplemented by antitumor activity and biomarkers; it will not exceed the MTD of the combination identified in Part 1.

If only 1 dose regimen is selected for expansion, then up to 40 participants will be initially enrolled in each of the 2 disease cohorts. However, if more than 1 RDE is to be used, then participants will be randomly assigned equally to the selected RDEs for each disease-specific cohort. If an RDE proves to be suboptimal based on the totality of the emerging data, that RDE cohort may be dropped as described in Section 10.5.

4.1.3. Safety Monitoring

In Part 1, approximately biweekly telephone conferences with study investigators will be scheduled by the sponsor in order to review dose-level and cohort-specific data and overall safety data, to agree on dose escalation, to adjudicate individual high-grade AEs as potentially dose limiting, and to guide other major study decisions. Continuous evaluation for toxicity events will be performed throughout Part 1 and Part 2 to assess for any late-onset immune-related toxicities that occur beyond the 28-day DLT observation period up to a minimum of 90 days after the last dose of study drug. In Part 2, teleconferences will continue with study investigators; therefore, participants will be continually evaluated for safety. The data will be reviewed by a DSMB as detailed in the charter. The DSMB will evaluate the data during the conduct of Part 2 and will determine whether it is appropriate for the study to continue as planned. If more than [redacted]% of participants (when [redacted] or more participants have been enrolled) have an AE ≥ Grade 4 that is attributable to either study treatment, then further enrollment of participants may be suspended until the sponsor, investigators, and DSMB have determined the appropriate course of action. In addition, if more than [redacted] participants enrolled or if [redacted]% of participants (when [redacted] or more participants have been enrolled) have an AE of interstitial lung disease/pneumonitis ≥ Grade 3, then further enrollment of participants may be suspended until the sponsor, investigators, and DSMB have determined the appropriate course of action. If an expansion cohort is discontinued because of toxicity, a new cohort may be initiated at a previously tested lower dose level.

See Section 5.6 for additional information on the Part 2 DSMB.

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's last visit has occurred.

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.

The study will include up to 28 days for screening, 8-day PK lead-in of INCB099280 monotherapy (described in Section 4.1.1.1), continuous combination treatment in consecutive 28-day cycles as long as participants are receiving benefit and have not met any criteria for study withdrawal, 30 (+ 7) to 90 (+ 14) days for safety follow-up after the last dose of study drug, and disease status follow-up for participants who discontinue study treatment for reasons other than progressive disease. It is estimated that an individual will participate for approximately 9 months.

The end of study is defined as when the last participant completes the last study-related telephone call or visit, 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 visit of the last participant in the study globally to ensure the results are robust, meaningful, and representative of all multiregions by having complete follow-up data determined by the statistical hypotheses for the objectives established.

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 DSMB. If the study is terminated prematurely, the sponsor will notify the investigators, the IRBs and IECs, and regulatory bodies of the decision and reason for termination of the study. The DSMB will recommend termination of the study if warranted, as described in Section 5.6.

5. STUDY POPULATION

Deviations from eligibility criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability, and/or participant safety. Therefore, adherence to the criteria as specified in this Protocol is essential. Prospective approval of Protocol deviations to recruitment and enrollment criteria, also known as Protocol waivers or exemptions, are not permitted. Thought should be given to all relevant medical and nonmedical conditions as well as the risks and benefits of study treatment in deciding whether this Protocol is suitable for a particular participant.

5.1. Inclusion Criteria

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

1. Ability to comprehend the participant information and willingness to sign a written ICF for the study.
2. Men and women 18 years of age or older at the time of signing the ICF.
3. $KRAS^{G12C}$-mutated solid malignancy determined by a sponsor-approved assay using either tumor tissue or ctDNA.
4. Histologically confirmed malignant solid tumor with locally advanced and/or metastatic disease.
   a. Only participants with NSCLC will be enrolled into Part 2 Cohort A.
   b. Only participants with CRC will be enrolled into Part 2 Cohort B.
5. Part 1: Disease progression on or after at least 1 prior systemic treatment. Participants must have received all available local standard of care therapies.
6. Part 2 (Cohort A - NSCLC): Received an anti–PD-(L)1—containing regimen and platinum-based chemotherapy regimen either concurrently or sequentially.

   Note: As described in Exclusion Criterion 4, if a participant has received prior PD-L1 therapy, 6 months must have elapsed between the last dose of the anti–PD-L1 antibody and the first dose of study treatment.
7. Part 2 (Cohort B - CRC): Received at least 1 line of systemic therapy that includes the combination of fluoropyrimidine-based chemotherapy with oxaliplatin and irinotecan (given concurrently or sequentially) and either a vascular endothelial growth factor–targeting monoclonal antibody or an anti–epidermal growth factor receptor monoclonal antibody (if RAS wild-type). Participants with MSI-H/dMMR CRC must also have received a prior immune checkpoint inhibitor approved for this indication.
8. Measurable disease according to RECIST v1.1.

9. Known PD-L1 expression level in tumor. Note: There is no minimum level of PD-L1 expression required for enrollment into the study. The PD-L1 expression level may have been determined at any point in the disease course using a commercially available assay or can be tested locally during the screening process (using a commercially available assay) and the results reported to the sponsor. If PD-L1 expression is unknown or cannot be tested locally, participants must be willing to provide tumor tissue (fresh or archival) for central laboratory assessment of PD-L1 expression.
10. ECOG performance status of 0 or 1.
11. Estimated life expectancy > 3 months.
12. Willingness to avoid pregnancy or fathering children based on the criteria below.
    a. Men must agree to take appropriate precautions to avoid fathering children (with at least 99% certainty) from screening through 190 days after the last dose of study drug (or longer as appropriate based on country-specific requirements) and must refrain from donating sperm during this period. Permitted methods that are at least 99% effective in preventing pregnancy (see Appendix A) should be communicated to the participants and their understanding confirmed.
    b. Women of childbearing potential must do the following:
        – 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 30 days before the first dose of study drug until 190 days after the last dose.
    c. 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. Another malignancy that is progressing or has progressed within the past 3 years and/or that requires treatment.

   Note: Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin, in situ cervical cancer, early-stage endometrial cancer that has been definitively treated, superficial bladder cancer, Gleason 6/7 treated prostate cancer, and ductal carcinoma in situ or lobular carcinoma in situ of the breast.

2. CNS metastases requiring treatment and/or leptomeningeal disease.
    a. Participants with untreated CNS metastases that are symptomatic, who require increasing doses of steroids and/or a steroid dose of more than 1 mg of dexamethasone daily (or equivalent), or with lesions with a significant amount of surrounding edema.
    b. Participants with previously treated CNS metastases that are progressing, who are not clinically stable within 2 weeks of the initiation of study treatment, or who require increasing doses of steroids and/or a steroid dose of more than 1 mg of dexamethasone daily (or equivalent).

Prior Cancer Therapy

3. Part 2 only: Prior treatment with an approved or investigational agent targeting $KRAS^{G12C}$.
4. Prior receipt of an anti–PD-L1—containing therapy and 6 months has not elapsed prior to the first dose of study treatment.
5. Toxicity from prior therapy that has not recovered to ≤ Grade 1 or baseline (with the exception of anemia not requiring transfusion support and any grade of alopecia). Endocrinopathy not adequately controlled on replacement therapy should be discussed with the medical monitor.
6. Received thoracic radiation of > 30 Gy within 6 months of the first dose of study treatment.

    Note: Participants must have recovered from all radiation-related toxicities to ≤ Grade 1 and not require corticosteroids.
7. Participation in another interventional clinical study.
8. Treatment with anticancer medications or investigational drugs within the following intervals before the first administration of study drug:
    a. At least 14 days for chemotherapy or targeted small-molecule therapy.
    b. At least 28 days for a prior monoclonal antibody.
    c. At least 28 days or 5 half-lives (whichever is longer) for all other investigational study drugs or devices.

Medical History

9. Impaired cardiac function or clinically significant cardiac disease, including unstable angina, acute myocardial infarction within 6 months before the start of study treatment, New York Heart Association Class III or IV CHF, clinically significant or uncontrolled arrhythmias, or a cerebrovascular accident within 6 months of the start of study treatment.
10. History or evidence of interstitial lung disease, including noninfectious pneumonitis.
11. Presence of a GI condition that may affect drug absorption.
12. Active autoimmune disease requiring systemic treatment, including corticosteroids exceeding a daily dose of 10 mg of prednisone or equivalent.

13. A diagnosis of immunodeficiency or receiving chronic systemic steroid therapy exceeding a daily dose of 10 mg of prednisone or equivalent.
14. HIV infection with a CD4+ T-cell count < 200 cells/µL and/or a detectable viral load per parameters of assay and/or on an ART regimen containing [redacted] and/or on a new ART regimen for less than 28 days prior to the initiation of study treatment.
15. Active infection, including tuberculosis, requiring systemic therapy, with the exception of HIV as noted in Exclusion Criterion 14.
16. History of organ transplantation, including allogeneic stem cell transplantation.
17. Known hypersensitivity or severe reaction to any component of study drug or formulation components.
18. Major surgery within 4 weeks of the start of study therapy or postoperative complications preventing the participant from adhering to protocol assessments and procedures.
19. Presence of GI conditions that may affect drug absorption, as well as those that interfere with GI transit, including gastric bypass surgery, gastric sleeve, or gastric band.
20. Inability to swallow tablets.

Medications

21. Receipt of systemic antibiotics within 28 days of the first dose of study treatment.
22. Probiotic usage during screening and throughout the study treatment period.
23. Receipt of a live-attenuated vaccine (such as measles, mumps, and rubella; chickenpox; some zoster; yellow fever; rabies; BCG; and typhoid vaccines) within 28 days of the planned start of study drug.

    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.

    Note: If enrolled, participants should not receive live-attenuated vaccines during the study and up to 90 days after the last dose of study treatment (see Section 6.7.3).
24. Medication with any of the following characteristics that cannot be discontinued prior to the start of study treatment: [redacted] (see Appendix B), [redacted], P-gp substrates with a narrow therapeutic index, [redacted], or known risk of torsades de pointes.

    Note: A washout period ≥ 14 days before the first dose of INCB099280 is required for prior treatment with [redacted].
25. Unable to be weaned off of a prohibited medication as described in Section 6.7.3 before the initiation of study treatment.

Organ Function

26. Participants with laboratory values at screening as defined in Table 9.

Table 9: Exclusionary Laboratory Values

Laboratory Parameter		Exclusion Criterion
Hematology		
a	Platelets	≤ 100 × 10^9/L
b	Hemoglobin	≤ 9 g/dL or < 5.6 mmol/L (transfusion is acceptable to meet this criterion)
c	ANC	≤ 1.5 × 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] (estimated glomerular filtration rate may also be used in place of CrCl)	CrCl < 50 mL/min
Coagulation		
i	INR	> 1.5 × institutional ULN for participants not receiving anticoagulant therapy
j	PT	> 1.5 × institutional ULN for participants not receiving anticoagulant therapy
k	aPTT	> 1.5 × institutional ULN for participants not receiving anticoagulant therapy

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

Diagnostic Assessments

27. Clinically significant ECG abnormality.

28. An average QTcF interval > 450 milliseconds on triplicate ECG.

    a. Presence of conditions that are considered risk factors for QT prolongation, including but not limited to electrolyte imbalances that cannot be managed with supplementation (hypokalemia, hypomagnesemia, hypocalcemia), clinically significant bradycardia in the opinion of the investigator, family history of sudden cardiac death prior to the age of 50 years, and congenital long QT syndrome.

29. Systolic dysfunction with an LVEF < 53%.

30. Active HBV or HCV infection defined as follows (testing must be performed to determine eligibility):
    a. Detectable HBV DNA
    b. Chronic HBV infection with active disease meeting the criteria for anti-HBV therapy in participants who are not on a suppressive antiviral therapy prior to initiation of or while receiving study treatment.
    c. A positive HCV antibody and quantitative HCV RNA result greater than the lower limit of detection for the assay.

Other Exclusions

31. Is pregnant or expecting to conceive or breastfeeding starting with the screening visit through 190 days after the last dose of study treatment or expecting to father children starting with the screening visit through 190 days after the last dose of study treatment.
32. Any condition that would, in the investigator's judgment, interfere with full participation in the study, including administration of study treatment and attending all planned study visits; pose a significant risk to the participant; or interfere with interpretation of study data.
33. Known history of DILI; alcoholic liver disease; nonalcoholic steatohepatitis; primary biliary cirrhosis; or ongoing extrahepatic obstruction caused by stones, cirrhosis of the liver, or portal hypertension.
34. 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

5.3.1.1. Suggested Meal With Study Drug Administration

INCB099280 and adagrasib should be administered with a [redacted] (see Table 10 for further details).

5.3.1.2. Dietary Restrictions

Participants will refrain from consuming [redacted], and juice containing those restricted fruits from 72 hours before the first dose of study drug and throughout the treatment period.

5.4. Screen Failures

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

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened 1 time, if appropriate. Participants who rescreen must reconsent and be assigned a new participant number.

Abnormal laboratory tests with results that fail eligibility requirements may be repeated once during screening.

5.5. Replacement of Participants

Participants may be replaced as described in the following text:

- In Part 1, a participant who withdraws from study treatment before receiving at least 75% of the planned doses of INCB099280 or adagrasib during the DLT observation period for reasons other than a DLT (eg, not evaluable for DLT) may be replaced to ensure a minimum number of evaluable participants.
- Participants who do not meet the eligibility requirements of the study may be replaced.

5.6. Data Safety Monitoring Board

This study will use a DSMB to monitor safety throughout the study and at the planned analyses. The DSMB will make recommendations to the study team and sponsor executive team regarding steps to ensure both participant safety and the continued ethical integrity of the study. The DSMB will consider the overall risk and benefit to study participants and recommend to the sponsor if the study should continue in accordance with the Protocol. Specific details regarding composition, responsibilities, and governance, including the roles and responsibilities of the various members, executive team, and Protocol team, and requirements for and proper documentation of DSMB reports, minutes, and recommendations, will be described in the DSMB charter that is reviewed and approved by all DSMB members.

6. STUDY TREATMENT

INCB099280 and adagrasib will be administered orally on a continuous daily dosing schedule. The study treatment will be administered in 28-day treatment cycles.

INCB099280 may be administered for up to 2 years (26 cycles) from the first dose of INCB099280, while adagrasib may be administered until a criterion for treatment discontinuation has been met (see Section 7.1.1). Participants who stop INCB099280 for reasons other than confirmed disease progression may continue on treatment with adagrasib monotherapy until a criterion for treatment discontinuation has been met. Participants who stop adagrasib for reasons other than confirmed disease progression may continue on treatment with INCB099280 until a criterion for treatment discontinuation has been met.

6.1. Study Treatments Administered

A dosing diary (electronic or paper) will be provided to the participants to provide guidance for the prescribed use of the 2 study drugs. Participants must be instructed to record all doses (missed or vomited doses) in the dosing diary (see Section 8.1.4 for more information). If a participant inadvertently takes an extra dose during a day, they should not take the next dose.

INCB099280 and adagrasib will be administered in the clinic at the visits specified in Table 3.

Table 10 presents the study treatment information.

Table 10: Study Treatment Information

	Study Treatment 1	Study Treatment 2
Study treatment name	INCB099280	Adagrasib
Mechanism of action	PD-L1 inhibitor	$KRAS^{G12C}$ inhibitor
Dosage formulation	Tablets	Tablets
Unit dose strength(s)/dosage level(s)	[redacted] mg or [redacted] mg / starting dose for escalation [redacted] mg [redacted]	200 mg / 400 mg BID
Administration instructions	• Adagrasib: Administered orally BID at approximately the same time in the morning and evening each day. • INCB099280: May be administered orally BID (at approximately the same time in the morning and evening each day) or QD (administered once per day in the morning). • BID doses should be taken approximately 12 hours apart. • Study drugs should be given with a [redacted] and with at least 240 mL (1 cup) of water. [redacted] • The study drugs must be swallowed whole and not chewed before swallowing. • [redacted] • Participants must be instructed that if they miss a dose or vomit after taking a dose, they must not take an extra dose, but instead resume with the subsequent doses as prescribed. If a dose is taken more than 4 hours after the usual time (morning or evening), it should be skipped and dosing resumed with the next scheduled dose.	
Packaging and labeling	INCB099280 will be provided as tablets in a bottle. Each container will be labeled as required per country requirement.	Adagrasib will be provided as tablets in a bottle. Each container will be labeled as required per country requirement.
Storage	Must be refrigerated. Store at 2°C-8°C (36°F-46°F).	May be stored in the carton at room temperature or refrigerated conditions according to instructions on the label. Acceptable temperature range for storage is 2°C-25°C (36°F-77°F).
Status of treatment in participating countries	Investigational	Investigational

6.2. Preparation, Handling, and Accountability

The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit for all study treatments upon receipt and any discrepancies are reported and resolved before the study treatment is dispensed.

Only participants who have been enrolled in the study may receive study treatment, and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access that is 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 or designee will also maintain records adequately documenting that the participants were provided the specified study drug. These records should include dates, quantities, and any available batch or serial numbers or unique code numbers assigned to 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 Study Reference Manuals.

6.3. Measures to Minimize Bias: Randomization and Blinding

All participants will be centrally assigned to study treatment using an IRT. Before the study is initiated, the telephone number and call-in directions for the IRT and/or the log-in information

and directions for the IRT will be provided to each site. Full details will be provided in the IRT Reference Manual.

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

Returned study treatment should not be redispensed to any participant.

If multiple RDEs are identified for dose expansion in Part 2, participants will be randomized to a dose within each disease-specific cohort. In this scenario, on Cycle 1 Day 1, participants will be assigned a unique number (randomization number) in ascending numerical order. The randomization number encodes the participant's assignment to one of the open-label treatment groups in one of the 2 disease-specific cohorts, according to the randomization schedule generated before the start of the study by the sponsor's statistics department. Once randomized to the assigned dose, participants will complete the study at the dose assigned unless criteria are met for dose reduction of either agent as described in Section 6.6.

This is an open-label study; blinding is not applicable.

6.4. Study Treatment Compliance

Participants need to be reminded of the importance of being compliant with the administration of study treatment.

Participants must bring their diaries (if using a paper diary; see Section 8.1.4) and unused study drugs to the clinic at each visit in order for site personnel to assess compliance and perform drug accountability. Compliance with INCB099280 and adagrasib will be calculated by the sponsor based on the drug accountability (eg, tablet counts) documented by the site staff and monitored by the sponsor/designee.

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

6.5. Dose-Limiting Toxicity and Determination of Maximum Tolerated Dose

For the purpose of dose finding, any AE that occurs during the DLT observation period (ie, the first 28 days of treatment) will be assessed and the severity graded according to the National Cancer Institute CTCAE v5.0 to determine whether it is a DLT.

The sponsor should be notified as soon as possible and within 24 hours of becoming aware that an AE met a criterion for a DLT.

Further experience in the dose-expansion phase may result in the need to explore a lower dose of either INCB099280 or adagrasib in combination.

6.5.1. Definition of a Dose-Limiting Toxicity

Dose-limiting toxicity will be defined as the occurrence of any of the toxicities in Table 11 occurring up to and including Day 28, except those with a clear alternative explanation. 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. Participants who receive at least 75% of the doses of each study drug (ie, 42 doses each for INCB099280 and adagrasib) at the level assigned or have a DLT will be considered evaluable for determining tolerability of the dose.

Individual participant dose interruptions or reductions may be made based on events observed at any time during treatment with study drugs; however, for the purposes of cohort dose escalation/de-escalation, expanding a dose cohort, and determining the MTD of INCB099280 in combination with adagrasib, decisions will be made based on events that are observed from the first day of study drug administration through and including the final day of Cycle 1 (Day 28). A lower MTD may subsequently be determined based on relevant toxicities that become evident after Day 28.

Table 11: Definition of Dose-Limiting Toxicity

Toxicity	Definition
Nonhematologic	• Any ≥ Grade 3 nonhematologic toxicity EXCEPT the following: – Grade 3 or higher electrolyte abnormality that lasts up to 72 hours, is not clinically complicated, and resolves spontaneously or responds to conventional medical interventions. – Grade 3 nausea, vomiting, or diarrhea for less than 72 hours with adequate antiemetic and other supportive care. – Grade 3 fatigue for less than 1 week. – Grade 3 amylase or lipase elevations that is not associated with symptoms, clinical manifestations, or radiologic imaging confirming pancreatitis.
Hematologic	• Grade 3 thrombocytopenia with clinically significant bleeding (ie, requires hospitalization, transfusions 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 persists for ≥ 7 days. • Grade 4 anemia not explained by underlying disease or some other concomitant disorder.

Table 11: Definition of Dose-Limiting Toxicity (Continued)

Toxicity	Definition
Immune-related toxicity	• ≥ Grade 2 ocular irAEs. • ≥ Grade 2 myocarditis or pericarditis • ≥ Grade 2 myasthenia gravis, Guillain-Barré syndrome • Grade 3 irAEs that do not improve to baseline or at least Grade 1 in < 5 days with appropriate care or with corticosteroid therapy. • Grade 4 irAEs, regardless of duration. • Any grade encephalitis and/or demyelinating disease. Exception: • Grade 3 or 4 endocrinopathy that is adequately controlled with hormone supplementation.
General	
Participant being unable to receive ≥ 75% of either study drug doses during the DLT observation period because of a TRAE, even if the AE does not meet DLT criteria mentioned above. Participant discontinued study treatment because of a DLT or TRAE after receiving at least 1 dose of INCB099280, even if they did not start the combination with adagrasib. Note: Exceptions include the DLT exclusions mentioned above.	
MTD	
• In Part 1 of the study, the MTD will be defined as described in Section 4.1.1 and according to Table 8. • In Part 2, participants will be continually evaluated for AEs that meet the definition of a DLT. The DSMB will evaluate the data every 3 months during the conduct of Part 2 and will determine whether it is appropriate for the study to continue as planned.	

6.5.2. Follow-Up of Dose-Limiting Toxicities

All DLTs should be monitored until resolution, improvement to the baseline state, or stabilization and no further improvement is clinically expected or the participant discontinues from the study.

During follow-up, participants should be seen as often as medically indicated to ensure their health and well-being.

6.5.3. Procedures for Cohort Review and Dose Escalation

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

The decision to proceed to the next dose level will be made by the study team and the investigators based on safety, tolerability, and preliminary [redacted] obtained. The dose and/or schedule may also be adjusted to further evaluate safety or PK findings as described in Section 4.1. The study procedures will be the same as those described for other study participants.

6.6. Dose Modifications

The management of some AEs may require dose modifications, including treatment interruptions, dose reductions, or the permanent discontinuation of one or both study drugs. All dose modifications should be documented in the source with clear reasoning, including the medical management.

No intraparticipant dose escalation to a higher dose cohort than that in which the participant was initially enrolled will be allowed.

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

Management guidelines for AEs requiring dose modifications are described in Section 6.6.1.2 and Section 6.6.1.3. Dose interruptions and reductions are allowed for INCB099280 and adagrasib following the dose-modification guidelines and according to the clinical judgment of the investigator. Treatment with INCB099280 and/or adagrasib may be delayed for up to 28 days to allow for resolution of toxicity. Participants may resume treatment once the AE improves 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. The treating investigator should contact the medical monitor to discuss the case of any participant whose treatment has been interrupted for more than 28 days before restarting treatment with INCB099280 or adagrasib.

Individual decisions regarding dose modifications should be made using clinical judgment and in consultation with the medical monitor, taking into account relatedness of the AE to the study drug and the underlying condition of the study participant. Adverse events that have a clear alternative explanation, or transient (≤ 72 hours) abnormal laboratory values without associated clinically significant signs or symptoms, may be exempt from dose-reduction or dose-interruption rules.

6.6.1.1. Management of Adverse Events

The guidance provided in Section 6.6.1.3 should be followed as best practice for decisions regarding management of treatment-related AEs that are not suspected to be irAEs. At their onset, AEs should be evaluated to consider if they are immune related and the investigator should use their best judgment in determining which guidance to follow based on the symptoms and workup. If the participant has an AE where conflicting guidance is available in the subsequent sections of the Protocol, the most conservative approach should be taken until the cause of the AE has been established.

The management of AEs considered immune related should be based on the guidance provided in Section 6.6.1.2, whereas the management of AEs believed to be attributable to adagrasib should follow the guidance provided in Section 6.6.1.3.

6.6.1.2. Management of Adverse Events Attributable to INCB099280

For all study participants, recommended dose reductions of INCB099280 are described in Table 12. If a participant is enrolled in a dose level not described in Table 12, the following principle for dose reduction should be followed:

- The first INCB099280 dose reduction should be approximately a [redacted]% dose reduction, accounting for available tablet sizes.
- The second INCB099280 dose reduction should be a [redacted]% dose reduction, accounting for available tablet sizes.

Table 12: INCB099280 Recommended Dose-Reduction Scheme

INCB099280 Starting Dose	First Dose Reduction	Second Dose Reduction
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

In the event a participant has 1) an increase in ALT or AST elevation ≥ 3 × ULN, 2) total bilirubin ≥ 2 × ULN, and 3) ALP < 2 × 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, the administration of other drug(s) known to be hepatotoxic, or confirmed DILI. If DILI is confirmed, INCB099280 must be discontinued.

6.6.1.2.1. 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 may be 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 are outlined in Table 13. 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.

Immune-related AEs should be managed according to international guidelines such as the ASCO or ESMO Clinical Practice Guidelines (Haanen et al 2022, Schneider et al 2021).

Table 13: Management Guidelines for Immune-Related Adverse Events

irAE	CTCAE v5 Grade	Guidance for Restarting INCB099280	Monitoring and/or Supportive Care
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 prednisone, treat as Grade 3. • Consultation with pulmonary and infectious disease specialists as necessary.

Table 13: Management Guidelines for Immune-Related Adverse Events (Continued)

irAE	CTCAE v5 Grade	Guidance for Restarting INCB099280	Monitoring and/or Supportive Care
Pneumonitis (continued)	Grade 3, Grade 4, or recurrent Grade 2	Permanently discontinue INCB099280.	• Administer IV methylprednisolone 1-2 mg/kg or equivalent with taper. • Empirical antibiotics may be considered. • 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 13: Management Guidelines for Immune-Related Adverse Events (Continued)

irAE	CTCAE v5 Grade	Guidance for Restarting INCB099280	Monitoring and/or Supportive Care
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.

Table 13: Management Guidelines for Immune-Related Adverse Events (Continued)

irAE	CTCAE v5 Grade	Guidance for Restarting INCB099280	Monitoring and/or Supportive Care
Diarrhea/colitis (continued)	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.
	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	Consider permanently discontinuing INCB099280 if asymptomatic; permanently discontinue INCB099280 if symptomatic.	• 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.

Table 13: Management Guidelines for Immune-Related Adverse Events (Continued)

irAE	CTCAE v5 Grade	Guidance for Restarting INCB099280	Monitoring and/or Supportive Care
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, SJS, TEN, drug reaction with eosinophilia and systemic symptoms/drug-induced hypersensitivity syndrome).
	Grade 4 or recurrent Grade 3	Permanently discontinue INCB099280.	
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).

Table 13: Management Guidelines for Immune-Related Adverse Events (Continued)

irAE	CTCAE v5 Grade	Guidance for Restarting INCB099280	Monitoring and/or Supportive Care
Nephritis or renal dysfunction (creatinine increased) (continued)	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.
	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.

Table 13: Management Guidelines for Immune-Related Adverse Events (Continued)

irAE	CTCAE v5 Grade	Guidance for Restarting INCB099280	Monitoring and/or Supportive Care
Diabetes mellitus (continued)	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. • 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 13: Management Guidelines for Immune-Related Adverse Events (Continued)

irAE	CTCAE v5 Grade	Guidance for Restarting INCB099280	Monitoring and/or Supportive Care
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 3-4 • Consultation with an endocrinology specialist advised. • Maintenance therapy as in Grade 1.
	Grade 3 or Grade 4	Withhold INCB099280 until improvement to ≤ Grade 1.	

Table 13: Management Guidelines for Immune-Related Adverse Events (Continued)

irAE	CTCAE v5 Grade	Guidance for Restarting INCB099280	Monitoring and/or Supportive Care
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. • Consultation with a cardiology specialist strongly is advised. • Initial diagnostic workup should include a clinical evaluation, ECG, and telemetry monitoring as well as cardiac imaging, ie, 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 WBC 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).

Table 13: Management Guidelines for Immune-Related Adverse Events (Continued)

irAE	CTCAE v5 Grade	Guidance for Restarting INCB099280	Monitoring and/or Supportive Care
Myocarditis or pericarditis (continued)	Grade 1 (pericarditis or elevated troponin)	Withhold INCB099280	• Early initiation of steroids is recommended if clinical suspicion of an immune-mediated pericarditis is high. • Consider resuming INCB099280 upon complete resolution of clinical findings consistent with pericarditis. • Consider resuming INCB099280 once Grade 1 troponin has normalized or if believed not to be related to INCB099280. • The decision to reinitiate INCB099280 will be based upon the treating physician's clinical judgment and, where applicable, after completion of steroid taper. • Close monitoring for deterioration in cardiac function is recommended, specifically in participants with baseline cardiopulmonary disease and reduced cardiac function.
	Grade 2, Grade 3, and Grade 4 as well as biopsy proven immune-mediated myocarditis and pericarditis	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.

Table 13: Management Guidelines for Immune-Related Adverse Events (Continued)

irAE	CTCAE v5 Grade	Guidance for Restarting INCB099280	Monitoring and/or Supportive Care
Nervous system disorders (These are general guidelines, and the exact management will depend on the presentation. Close monitoring and consultation with neurology is highly recommended.)	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.
	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.	

Table 13: Management Guidelines for Immune-Related Adverse Events (Continued)

irAE	CTCAE v5 Grade	Guidance for Restarting INCB099280	Monitoring and/or Supportive Care
Other irAEs (continued)	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.	

6.6.1.3. Management of Adverse Events Attributable to Adagrasib

General guidance for management of AEs attributable to adagrasib is as follows:

- The severity of all AEs must be graded according to National Cancer Institute CTCAE v5; in the event that > 1 AE occurs, dose modification for adagrasib should be based on the clinical judgment of the investigator.
- Participants should be thoroughly evaluated, and appropriate efforts should be made to rule out alternative etiologies.
- A specialist referral is strongly encouraged.
- Supportive care should be provided as clinically indicated and in accordance with local practice guidelines; the prescription of supportive medication should take the potential DDIs and any known risk to prolong QT interval into consideration (see Appendix B for further details).
- In the event a participant has 1) an increase in ALT or AST elevation ≥ 3 × ULN, 2) total bilirubin ≥ 2 × ULN, and 3) ALP < 2 × 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, the administration of other drug(s) known to be hepatotoxic, or confirmed DILI. If DILI is confirmed, adagrasib must be discontinued.
- Management of some AEs may require adagrasib dose modifications (outlined in Table 15 and Table 16); these include treatment interruptions, dose reductions (described in Table 14), or the permanent discontinuation of adagrasib.
  - All dose modifications should be documented with clear reasoning and documentation of the approach taken.
  - In the event that > 1 AE occurs, dose modification for adagrasib will be based on the organ system exhibiting the greatest degree of toxicity or otherwise on the clinical judgment of the investigator.

– Any participants requiring a toxicity-related treatment interruption of > 4 weeks should permanently discontinue adagrasib unless further clinical benefit is anticipated; continued administration of study treatment should be discussed with and approved by the sponsor.

– A maximum of 2 dose reductions outlined in Table 14 will be allowed. Permanently discontinue adagrasib in participants who are unable to tolerate 400 mg QD.

Table 14: Adagrasib Dose-Reduction Scheme

Adagrasib Starting Dose	First Dose Reduction	Second Dose Reduction
400 mg BID	[redacted] mg [redacted]	[redacted] mg [redacted]

[a] May be divided into [redacted] dosing for improved tolerability.

Table 15: Adagrasib Dose Modifications for Hematologic Toxicities

Adverse Reaction	Severity	Adagrasib Dose Modifications
Any	Grade 1 or 2	None
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	
Any other events	Grade 3 or 4	Hold treatment until ≤ Grade 1 or returned to baseline May resume treatment at the same dose

Table 16: Adagrasib Dose Modifications for Nonhematologic Toxicities

Adverse Reaction	Severity	Adagrasib Dose Modifications
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Table 16: Adagrasib Dose Modifications for Nonhematologic Toxicities (Continued)

Adverse Reaction	Severity	Adagrasib Dose Modifications
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	
[redacted] ALT or AST elevations	Grade 2	Hold treatment until ≤ Grade 1 or returned to baseline Resume treatment at the next lower dose level
Nausea [redacted] hours despite supportive care Vomiting [redacted] hours despite supportive care (or [redacted] hours [redacted] [redacted] hours despite supportive care [redacted] ALT or AST elevations [redacted] days QTcF prolongation on [redacted] t [redacted] All other toxicities	Grade 3	
Vomiting > 24 hours despite supportive care (or 72 hours while optimizing treatment) Any non–life-threatening toxicity	Grade 4	
[redacted]	Grade 4	Hold treatment until ≤ Grade 1 or returned to baseline. For AEs that are not life-threatening and that can be managed, treatment may resume at a lower dose level. Otherwise, discontinue study treatment.

Table 16: Adagrasib Dose Modifications for Nonhematologic Toxicities (Continued)

Adverse Reaction	Severity	Adagrasib Dose Modifications
DILI	Grade 2	Discontinue
[redacted] DILI	Grade 3	
[redacted] DILI [redacted]	Grade 4	

6.6.2. Criteria for Permanent Discontinuation of Study Drug Due to Unacceptable Toxicity

Unacceptable toxicity or the inability to tolerate study treatment will require the permanent discontinuation of one or both study drug(s).

- Participants who are required to discontinue INCB099280 may continue treatment with adagrasib until an adagrasib discontinuation criterion is met.
- Participants who are required to discontinue adagrasib may continue to receive treatment with INCB099280 after a [redacted]. After the treatment break, participants must resume treatment with [redacted]

Unacceptable toxicity and intolerance to study treatment include the following:

- Any AE that compromises the participant's ability to continue study-specific procedures or is considered not in the participant's best interest if they continue with study treatment.
- An AE requiring treatment discontinuation as described in Section 6.6.1.2 or Section 6.6.1.3.

- An AE requiring more than the allowed dose reductions of INCB099280 described in Table 12 or adagrasib described in Table 14.
- A persistent AE requiring an interruption of study treatment for more than 28 days unless a further pause in treatment has been discussed with and agreed to by the sponsor.

See Section 7 for discontinuation procedures.

6.6.3. Treatment Beyond Initial Radiologically Determined Progressive Disease per RECIST v1.1

Immunotherapeutic agents 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.

When progressive disease has been determined per RECIST v1.1 by the investigator, participants who are clinically unstable must discontinue study treatment. However, participants who are clinically stable may continue to receive study treatment at the discretion of the investigator in consultation with the participant until a subsequent follow-up evaluation. Clinically stable is defined by the following criteria:

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

Participants must have the opportunity to be reconsented if treatment beyond initial RECIST v1.1 progression is planned. The follow-up evaluation should be performed 4 to 8 weeks later. If the initial disease progression is confirmed by a subsequent follow-up disease assessment (ie, there is a further increase in the target sum of diameters of ≥ 5 mm, any further progression in nontarget lesion[s], and/or progression of the new lesions either in number or in size [sum ≥ 5 mm]), the participant should discontinue study treatment unless 1) further clinical benefit is anticipated, 2) there are no alternative treatment options, and 3) they do not have any ≥ Grade 2 TRAEs. Continued administration of study treatment should be discussed with and approved by the sponsor.

If the initial disease progression per RECIST v1.1 is not confirmed, the participant may continue on study treatment and subsequent follow-up evaluation should be performed according to the protocol imaging schedule.

6.7. Concomitant Medications and Procedures

All concomitant treatments administered (both prescription and over-the-counter medicines including vitamins, vaccines, and/or herbal supplements) and concomitant procedures that were

performed must be recorded in the eCRF. Additionally, all medication that was administered and procedures performed within 28 days of the initiation of study treatment and until 90 days after the last dose of study treatment or until the participant begins a new anticancer therapy, whichever occurs first, must be recorded in the eCRF. Any changes in any of these treatments must also be recorded.

Concomitant medications administered or procedures that are performed as part of treatment of SAEs (as defined in Section 9.2) should be recorded for any SAE that is reported beyond 90 days after the last dose of study treatment. Guidance about concomitant medications that should be used with caution or avoided during treatment with adagrasib is provided in the following text and Appendix B.

6.7.1. Permitted Medications and Procedures

With the exception of those treatments specifically prohibited per this Protocol outlined in Section 6.7.3, all treatments that the investigator considers clinically indicated may be provided in accordance with local, national, or international guidelines.

In particular:

- Administration of COVID-19 vaccines (eg, mRNA) is allowed provided they do not meet criteria for exclusion as outlined in Section 6.7.3.
- Use of prophylactic growth factors is permitted and should be based on the investigator's clinical judgment (refer to the ASCO guidelines for the use of WBC growth factors [Smith et al 2015]).
- Female participants using hormonal contraceptives should be made aware of the potential for adagrasib to inhibit hepatic CYP3A4 and increase exposure of hormonal contraceptives, with an increased risk of venous thromboembolism (eg, deep vein thrombosis or pulmonary embolism). Therefore, precautions should be taken in participants with recent, clinically significant thromboembolic events, and all participants using hormonal contraceptives should be closely monitored for thromboembolic events.

6.7.2. Restricted Medications and Procedures

6.7.2.1. Systemic Glucocorticoids

Systemic glucocorticoids may be used with doses of prednisone ≤ 10 mg or equivalent. Higher doses of systemic glucocorticoids may be used as part of the treatment of irAEs (see Section 6.6.1.2 for further details).

6.7.2.2. [redacted]

The use of [redacted] or [redacted] regardless of indication is allowed provided participants have been on stable oral doses for at least 2 weeks prior to study entry or stable with at least 2 parenteral injections prior to study entry; this stable dose should be maintained during the treatment period. Participants requiring initiation of [redacted] or an [redacted] during the course of the study should be evaluated to rule out disease progression.

6.7.2.3. [redacted]

A clinical DDI study in which INCB099280 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] Additionally, because [redacted]

In view of the above, the concomitant use of [redacted] with study treatment should be avoided. If there is a need for the continued use of [redacted] are preferred over [redacted]. If [redacted] are prescribed, then they should be administered more than 2 hours before and 2 hours after dosing with [redacted] If [redacted] are prescribed, they should be administered [redacted] hours [redacted] dosing with adagrasib (which is [redacted] hours before the next [redacted] dose).

6.7.2.4. Moderate/Sensitive CYP2C9 or CYP2D6 Substrates Without a Narrow Therapeutic Index

Since adagrasib coadministered with medications that are [redacted]/sensitive CYP2C9 or CYP2D6 substrates may cause increased exposure to these medications, the concomitant use of such medication should be administered with caution. Further consideration may also include reducing the dose of these medications when coadministered with adagrasib. Examples of [redacted]/sensitive CYP2C9 or CYP2D6 substrates are provided in Appendix C.

6.7.2.5. Strong Inhibitors of [redacted]

Since the concomitant use of medications that are strong inhibitors of [redacted] may increase the exposure of [redacted] they should be administered with caution during the treatment period. Examples of strong inhibitors of [redacted] are provided in Appendix C.

6.7.2.6. Substrates of MATE-1 and MATE-2K Transporters

Since adagrasib may inhibit MATE-1/MATE-2K,substrates of these transporters should be used with caution during the treatment period. Examples of MATE-1/MATE-2K transporters are provided in Appendix C.

6.7.3. Prohibited Medications and Procedures

Medications and vaccines that are exclusionary per this Protocol (see Section 5.2) are also prohibited after the initiation of study treatment. If there is a clinical indication for the use of one of these medications or administration of these vaccines during the study, study treatment should be discontinued; however, the decision to continue with study treatment lies with the investigator in consultation with the sponsor. The following medications are prohibited on this Protocol:

- Any anticancer medications, including chemotherapy or biologic therapy other than study treatment
- [redacted]
- Medications that are known to result in QT interval prolongation and pose a risk of torsades de pointes (see Appendix B)

- P-gp substrates with a narrow therapeutic index (see Appendix B)
- Inhibitors of [redacted] (see Appendix B)
- [redacted] CYP3A4/CYP3A5 inducers and inhibitors (see Appendix B)
- Substrates of [redacted] CYP2C9, and CYP2D6 with a narrow therapeutic index (see Appendix B)
- Immunosuppressive agents (from the start of screening through the EOT)

  Note: Inhaled or topical steroids, systemic glucocorticoids (eg, prednisone or equivalent) at doses ≤ 10 mg/day, immunosuppressive agents used as part of the management of irAEs (as described in Section 6.6.1.2), or premedication with corticosteroids as prophylaxis for an established contrast allergy for imaging procedures are permitted.
- Investigational agents other than study treatment (from the start of screening through the follow-up period)
- Concomitant radiation therapy

  Note: Palliative radiation therapy may be permitted after consultation with the medical monitor.
- Vaccination with live-attenuated vaccines administered from 28 days before the initiation of study treatment until 90 days after the last dose of study drug.
  - Examples of common live-attenuated vaccines include, but are not limited to, measles, mumps, and rubella; chickenpox/zoster; yellow fever; rabies; BCG; typhoid (oral) vaccines; and live-attenuated influenza vaccines.

    Note: Inactivated/killed seasonal influenza vaccines are allowed.
- Probiotic dietary supplements

7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT WITHDRAWAL

7.1. Discontinuation of Study Treatment

7.1.1. Criteria for Permanent Discontinuation of Study Treatment

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

- Radiographically determined progressive disease according to RECIST v1.1 that has been confirmed
  - *Note:* In select instances, participants may continue on treatment past confirmed disease progression. See Section 6.6.3 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 progression and survival.
- Further participation would be injurious to the participant's health or well-being, in the investigator's medical judgment.
- Unacceptable toxicity or intolerance to study treatment (as noted in Section 6.6.2).
- The study is terminated by the sponsor or the DSMB.
- The study is terminated by the local health authority, IRB, or IEC.

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

- If, during the course of the study, a participant is found not to have met eligibility criteria, the medical monitor, in collaboration with the investigator, will determine whether the participant should be withdrawn from study treatment.

7.1.2. Discontinuation Procedures

In the event that the decision is made to permanently discontinue 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 Section 8.8. 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 staff despite repeated attempts.

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

- The site staff must attempt to contact the participant and schedule a follow-up visit as soon as possible. The participant should be reminded of the importance of adhering to the planned visit schedule and their wish to continue participation in the study should be ascertained.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to reestablish contact with the participant (where possible, 3 telephone calls, a letter to the participant's last known mailing address, contact with the participant's primary healthcare provider, or any other locally permitted method). Every attempt to establish contact should be documented in the participant's medical record.
- Should repeated attempts to re-establish contact with the participant fail, they will be considered lost to follow-up.

8. STUDY ASSESSMENTS AND PROCEDURES

Recognizing the very dynamic nature of the COVID-19 pandemic and the flexibility required to manage the impact of the pandemic on ongoing clinical studies, details and additions may need to be added into respective study manuals and site-specific monitoring plans as applicable, with institutional and health authority requirements and approvals as warranted, and communicated and discussed with investigative sites as needed.

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 or their legally authorized representative and answer all questions regarding the study.
  - Informed consent must be obtained before any study-related procedures are conducted, unless otherwise specified by the Protocol.
  - Informed consent must be obtained using the IRB/IEC-approved version in a language that is native and understandable to the participant. 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. 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 or their legally authorized representative will be required to sign a statement of informed consent that meets the applicable requirements and regulations for the countries in which the study is being conducted as well as the IRB/IEC or study center.
- The participant must be informed that 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. Prescreening and Screening Procedures

Prescreening outside of the Protocol-specified 28-day screening window is allowed for participants whose $KRAS^{G12C}$-mutation status is unknown. A separate prescreening consent form should be used for blood or tumor tissue collection and local testing for the $KRAS^{G12C}$ mutation.

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 enrollment or the administration of study treatment. Tests with results that fail eligibility requirements may be repeated once during screening. 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 5.5 for information regarding screen failures and replacement of participants, respectively.

8.1.3. Interactive Response Technology Procedure

Each participant will be identified in the study by a participant ID number, which is a combination of the site ID and 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 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. Reminder cards will be provided at each visit through the end of the study. The reminder card will indicate the date and time of the next visit and will also remind the participant if they should not take their morning dose of study drug 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 first treatment visit and each visit thereafter, a study drug–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 study visit, and data entered in the paper diary or uploaded from the electronic diary (ie, device or app) 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 will be collected (except in countries not permitted; see additional guidance below) where allowed per local and national regulations.

As race and ethnicity data are not to be analyzed from a scientific or medical justification perspective, but rather are to be reported in a descriptive format only in the CSR, data on race and ethnicity from France will 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 (including baseline mutation or biomarker status), and prior treatments, including systemic treatments, radiation, and surgical procedures, will be recorded.

8.1.5.2.1. $KRAS^{G12C}$ Testing and Documentation of $KRAS^{G12C}$ Status

The presence of tumor $KRAS^{G12C}$ mutation for the purpose of participant eligibility must be established using sponsor-approved methods and laboratories. Genotyping to determine the mutation status can be performed using tumor tissue and/or ctDNA. Results previously determined may be accepted provided the results are from a sponsor-approved method and laboratory. Participants with unknown $KRAS^{G12C}$ mutation status can use the prescreening process (see Section 8.1.2) to determine if they are eligible for the study using a local laboratory prior to signing the full study consent.

8.1.5.2.2. PD-L1 Expression Status in the Tumor

The level of PD-L1 expression in the tumor (and surrounding immune cells, if available), determined using a commercially available assay, should be known before treatment on this Protocol is initiated. The PD-L1 expression result will also be captured in the eCRF. However, where commercial assays are not available, fresh or archival tumor tissue may be submitted to the sponsor for PD-L1 testing (see Section 8.5.3).

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 8-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 by 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 positron emission tomography/CT scan uses higher energy and thinner slices, it may be acceptable with medical monitor approval.

Imaging must capture all known sites of disease and include images of the chest, abdomen, and pelvis. Additional imaging of anatomical sites (eg, head, neck) of known disease or suspected metastases 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 disease assessment should be performed 8 weeks (56 ± 7 days) after Cycle 1 Day 1 and then Q8W (56 ± 7 days) thereafter for the first year (11 cycles). After 1 year of study treatment, disease assessment frequency may be reduced to Q12W (84 ± 14 days). Imaging assessments may be performed more frequently if clinically indicated.

Imaging should follow calendar days and should <u>not</u> be delayed for delays in cycle starts.

Disease progression may be confirmed at least 4 weeks but no more than 8 weeks after the first scan indicating disease progression in clinically stable participants as per guidelines in Section 6.6.3. A positron emission tomography 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 6.6.3.

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, for 12 months after the EOT, death, or the end of the study, whichever occurs first.

8.2.2. Medical Resource Utilization and Health Economics

Not applicable.

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, surrogate, or the participant's legally authorized representative). The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up on AEs that are serious, 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 within 24 hours. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

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

8.3.1.1. Telephone Adverse Event Assessments

Adverse event assessments will be performed by telephone according to the schedule detailed in Table 3. Participants may be directed to report to the clinic for further assessment. At least 3 attempts should be made to contact the participant for these telephone AE assessments and documented if unsuccessful.

8.3.2. Physical Examinations

At the screening visit and the EOT visit, a physical examination should be conducted (including height measurement at screening only).

During the study, participants will have a symptom-directed physical examination at the visits specified in Table 3. Participants will be assessed by the investigator or medically qualified designee per institutional standard of care. These assessments should be an evaluation as indicated by participant symptoms, AEs, or other findings and documented on the Adverse Events Form in the eCRF.

8.3.3. Vital Signs

Vital signs (to be taken before blood collection for laboratory tests) include blood pressure, pulse, respiratory rate, and body temperature and will be measured along with body weight as outlined in Table 3. 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.

Abnormal vital sign results identified after the first dose of study treatment constitute an AE if they are considered clinically meaningful, induce clinical signs or symptoms, require concomitant therapy, or require changes in study treatment.

8.3.4. Electrocardiograms

Twelve-lead ECGs will be obtained as outlined in the SoA (see Table 3) and Table 17 using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. On days of timed blood collections, ECGs are to be collected before any blood draws. 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 (at screening and during the study treatment

period) will be collected from a single measurement. In the event that a single QTc is > 450 milliseconds, 2 additional ECGs will be measured and the average ECG from the triplicates will be reported for the occasion (ie, visit and/or timepoint if applicable).

The 12-lead ECGs will be interpreted by the investigator at the site to be used for immediate participant management and transmitted to a central ECG laboratory. Additional 12-lead ECGs may be performed as clinically indicated to manage participant safety. The decision to include or exclude a participant or withdraw a participant from 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.

Table 17: Electrocardiogram Collection Schedule

	Timing of Sample		
Study Visit	**Any Time**	**Before the Morning Dose of INCB099280 and Adagrasib[a,b]**	**1 (± 10 min), 2 (± 15 min), and 4 Hours (± 30 min) After the Morning Dose of INCB099280 and Adagrasib**
Screening	X		
Cycle 1 Day 1		X	X
Cycle 1 Day 8		X	X
Cycle 2 Day 1 and every 2 cycles thereafter (eg, Cycle 4, Cycle 6)	X		
EOT	X		
30-Day safety follow-up	X		

[a] INCB099280 and adagrasib will be administered in the clinic on days of timed ECGs.
[b] To be collected within 15 minutes before blood draws.

8.3.5. Echocardiograms

Left ventricular systolic function as measured by LVEF will be assessed by echocardiography at the timepoints described in Table 3. 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.

8.3.6. Eastern Cooperative Oncology Group Status

The ECOG performance status will be assessed as outlined in Table 3 and according to the criteria in Table 18.

Table 18: 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.

8.3.7. Laboratory Assessments

See Table 19 for the list of clinical laboratory tests to be performed and Table 3 for the timing and frequency. A certified laboratory local to the investigative site will perform all clinical laboratory assessments for safety (ie, blood chemistries, hematology assessments, coagulation tests, endocrine function, and urinalysis). The investigative site will enter the laboratory results and laboratory normal ranges into the eCRF. Additional testing may be required by the sponsor based on emerging safety data. Additional tests may also be performed if clinically indicated.

Clinically significant abnormal laboratory findings are those that are clinically meaningful, induce clinical signs or symptoms, require concomitant therapy, require changes in study treatment, 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 7 days before the first dose of study treatment. If performed more than 7 days before the first dose of study treatment, then the tests must be repeated and eligibility confirmed before study treatment administration begins. After Cycle 1, predose laboratory procedures can be conducted up to 72 hours before study treatment administration (within the 3-day study window), and results should be reviewed by the investigator or qualified designee and found to be acceptable before a new cycle of treatment is initiated.

Table 19: Required Laboratory Analytes

Chemistry	Hematology	Dipstick Urinalysis (With Microscopic Examination [Where Indicated[a]])	Serology	Coagulation
Albumin ALP ALT AST Amylase Bicarbonate or CO_2 Blood urea nitrogen or urea Calcium Chloride Creatinine Glucose Lactate dehydrogenase Lipase Magnesium Phosphate Potassium Sodium Total bilirubin Direct bilirubin (if total bilirubin is elevated above ULN) Total protein Uric acid	Complete blood count, including: • Hemoglobin • Hematocrit • Platelet count • Red blood cell count • White blood cell count • Reticulocytes • Mean corpuscular volume • Mean corpuscular hemoglobin concentration • Mean corpuscular hemoglobin Absolute values must be provided for: • WBC differential laboratory results Differential count if indicated, including: • Basophils • Eosinophils • Lymphocytes • Monocytes • Neutrophils	Color and appearance pH and specific gravity Bilirubin Glucose Ketones Leukocytes Nitrite Occult blood Protein	Hepatitis B surface antigen Hepatitis B surface antigen antibody Hepatitis B core antibody HBV DNA HCV antibody HCV RNA	PT aPTT INR
			Endocrine Function	**Pregnancy Testing**
			TSH FT4 (total T4, total T3, and free T3 as clinically indicated) ACTH (baseline only) Cortisol (baseline only)	Female participants of childbearing potential only require a serum test at screening and EOT and a urine pregnancy test before the first dose on Cycle 1 Day 1. Pregnancy tests (serum or urine) should be repeated if required by local regulations.

Note: Additional tests may be required, as agreed upon by the investigator and sponsor, based on emerging safety data or to rule out a diagnosis.
Note: Alternative tests are also allowed as per regional standard of care.
[a] Microscopic examination only if blood is suspected in urine.

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 will be performed locally as outlined in 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.

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 19. Generally, hepatitis tests should be performed early in the screening process due to the length of time needed to obtain the results. Additional tests may be performed if clinically indicated.

8.4. Pharmacokinetic Assessments

Blood samples will be collected from all participants to perform PK analyses as specified in Table 3 and Table 20. Samples collected for analyses of study drug plasma concentrations may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

8.4.1. Blood Sample Collection

Venous blood samples will be collected to assess the PK of INCB099280 and adagrasib. The timing of blood PK assessments is outlined in Table 20. After the predose PK sample is drawn, participants will begin study treatment. During the [redacted] During the treatment period, INCB099280 and adagrasib will be coadministered. Predose is defined as within 60 minutes before administration of morning study treatment. Study drugs should be administered in the clinic on days when PK samples are collected. Participants should [redacted] with their study drug administration as detailed in Section 6.1. Adjustments to the timing of blood sampling may be made based on emerging [redacted].

The actual date and time (24-hour clock time) of each sample collection will be recorded. The actual date and time of the study drug administration at the clinic will also be recorded. In addition, the actual date/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 Laboratory Manual.

Table 20: Pharmacokinetic Blood Sample Timing

Dose Level/Cohort	Study Visit	Timing of Sample – INCB099280	Timing of Sample – Adagrasib
Cohort/dose level with a [redacted] (see Section 4.1.1.1)	[redacted]	[redacted]	[redacted]
	Cycle 1 Day 1	Predose	Predose
	[redacted]	[redacted]	Predose
	Cycle 2 Day 1	Predose	Predose
	Cycle 4 Day 1	Predose	Predose
	Cycle 6 Day 1	Predose	Predose
	Cycle 8 Day 1	Predose	Predose
	Cycle 12 Day 1 and every fourth cycle thereafter	Predose	Predose
Cohort/dose level [redacted]	Cycle 1 Day 1	Predose	Predose
	[redacted]	[redacted]	Predose
	Cycle 2 Day 1	Predose	Predose
	Cycle 4 Day 1	Predose	Predose
	Cycle 6 Day 1	Predose	Predose
	Cycle 8 Day 1	Predose	Predose
	Cycle 12 Day 1 and every fourth cycle thereafter	Predose	Predose

[a] Predose sample to be taken within 60 minutes prior to morning administration of study treatment.

8.4.2. Bioanalytical Methodology, Sample Analysis, and Pharmacokinetic Analysis

Plasma samples will be analyzed for analytes by the sponsor or their designee using a validated assay. Additionally, residual samples may be used for exploratory analyses to identify metabolites and residual pharmacodynamic and translational samples may be utilized for PK testing. Details on the PK analyses to be performed are found in Section 10.4.3.

8.5. Pharmacodynamic and Translational Assessments

Plasma and tumor tissue will be collected for assessments as outlined in Table 3 and correlated with compound presence and clinical outcome(s) as appropriate. Biomarker assessments beyond those listed may be evaluated at the discretion of the sponsor using excess biomarker or PK samples. Analyses will be conducted by Incyte Corporation (Wilmington, DE) or Incyte's designee.

For information regarding handling/shipping of specimens, please refer to the Laboratory Manual for the study.

8.5.1. Plasma Biomarker Assessments

A number of tumor- and immune response–derived proteins can be released from tumors or activated normal cells into the blood. Plasma analytes may include cytokines and other markers of inflammation and immune status and tumor markers. Other assays relevant to the objectives of the study may be performed based on emerging data.

8.5.2. Plasma for Cell-Free DNA

Plasma will be collected to prepare cell-free DNA to confirm KRAS mutation status and identify gene alterations in ctDNA at baseline. It will also be used to assess ctDNA as a potential predictor of response and a marker of response during treatment.

8.5.3. Tumor Biopsy

The collection of tumor tissue is required at screening only if PD-L1 tumor expression has not been or cannot be determined locally by a commercially available assay (see Section 8.1.5.2.2). Fresh or archival tissue may be submitted. The tumor tissue will be assessed for PD-L1 expression.

8.6. Unscheduled Visits

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

8.7. End of Treatment

When a participant permanently discontinues study drug, whether the participant is withdrawing from the study early or 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.

8.8. 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 described in Table 3.

8.8.1. Safety Follow-Up

The safety follow-up period is the interval between the EOT visit and the scheduled follow-up visit, which should occur 30 (+ 7) and 90 (+ 14) days after the EOT visit (or after the last dose of study drug 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 method of communication for assessment of any AEs; this contact should be documented in the source.

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.

8.8.2. Post-Treatment Disease Status Follow-Up

Participants who discontinue study treatment for a reason other than progressive disease will move into the disease status follow-up period and should be assessed by radiologic imaging as follows:

- If before 1 year from the first dose of study treatment: Q8W (56 ± 7 days)
- If after 1 year from the first dose of study treatment: Q12W (84 ± 14 days)

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

- Start of new anticancer therapy
- Disease progression
- 12 months from the EOT
- Withdrawal of consent
- Lost to follow-up
- Death
- 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 disease progression of the underlying disease studied) 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 signs and symptoms due to the study disease that develop after the administration of the first dose of study treatment are to be reported as an AE. • Signs, symptoms, or the clinical sequelae of a suspected DDI 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 or conditions with expected fluctuations in signs or symptoms should be reported as an AE only if the investigator judges the fluctuation to have worsened more than expected during study participation.

9.2. Definition of Serious Adverse Event

If an event is not an AE per the definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for disease progression, 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 (secondary malignancies); intensive treatment in an emergency department or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse. Secondary malignancies should always be considered SAEs.

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

Adverse Event and Serious Adverse Event Recording

- An AE/SAE that begins or worsens after informed consent is signed should be recorded on the Adverse 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 one 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. The relationship to each study drug must be assessed and entered into the eCRF.
- 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 each study drug 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 eCRF) 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 (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, 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 IB 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 and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements or Regulation EU No. 536/2014 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 ≥ 3 × ULN, 2) a total bilirubin ≥ 2 × ULN, and 3) an ALP < 2 × 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, 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 (female participants only).
  - If the female participant is no longer pregnant and meets the treatment continuation criteria within 28 days of the scheduled start of a cycle, study treatment may be resumed after approval has been received from the sponsor'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 and should include an assessment of the possible causal relationship to the sponsor's study drug to any pregnancy outcome, as well as follow-up to the first well-baby visit or the duration specified in local regulations, whichever is later. Refer to the Incyte Reference Guide for Completing the Clinical Trial Pregnancy Form or Study Reference Manual 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 treatment, derived from safety information collected by the sponsor or its designee, are presented in the IB. Additional safety information collected between IB updates will be communicated in the form of Investigator Notifications.

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 adagrasib 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 should do the following:

- Contact the medical monitor immediately.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities until INCB099280 or adagrasib can no longer be detected systemically.
- Obtain a plasma sample for [redacted] within 2 days from the date of the last dose of study treatment if requested by the medical monitor or if possible (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.

10. STATISTICS

This section outlines the statistical analysis strategy and procedures for this study. If, after the study has begun, but before the final database lock, changes are made to primary efficacy and safety and/or secondary efficacy hypotheses or the statistical methods related to those hypotheses, the Protocol will be amended, consistent with ICH E9 (EMA 1998) and ICH E9 (R1) (EMA 2020). The detailed statistical analyses will be documented in the Statistical Analysis Plan.

10.1. Sample Size Determination

10.1.1. Part 1 – Dose Escalation

The primary objective of Part 1 of the study is to determine the MTD and/or RDE(s) of INCB099280 in combination with adagrasib. Dose escalation will follow a hybrid design (Liao et al 2022) with a target DLT rate of [redacted]%. The hybrid design incorporates optimal properties from 2 existing dose-finding designs: a model-assisted design (the modified mTPI) and a dose-toxicity model-based design.

Cohorts of at least 3 DLT-evaluable participants will be initially enrolled into each dose level in Part 1, and the dose-escalation procedure may be stopped if the number of evaluable participants treated at any dose level is ≥ 9. The planned total sample size for Part 1 is approximately 45 evaluable participants, and the exact number of participants treated will depend on the number of participants required per dose level and the number of dose levels tested before the RDE(s) is established.

10.1.2. Part 2 – Dose Expansion

Part 2 is an open-label dose expansion that will include 2 tumor cohorts: one for NSCLC and one for CRC. A maximum of 80 participants will be enrolled into Part 2. Up to 3 combination dose regimens (RDEs) may be selected to further characterize the safety, tolerability, PK profile, and preliminary antitumor activity of INCB099280 in combination with adagrasib in designated tumor populations and to facilitate initial dose optimization.

A sample size of up to 20 participants per tumor cohort dose level is chosen to detect important signals in safety. If only 1 dose level is selected for expansion, up to 40 participants per tumor cohort may be enrolled. The probabilities of observing different numbers of clinically determined safety events with a true event rate at 0.05, 0.1, 0.15, and 0.2 are listed in Table 21.

Table 21: Distributions of Observed Safety Events Under Different Event Rates

Event Rate	0.05	0.1	0.15	0.2
Assuming a sample size of 20 participants				
≥ 1 event	64.2%	87.8%	96.1%	98.8%
≥ 2 events	26.4%	60.8%	82.4%	93.1%
≥ 3 events	7.5%	32.3%	59.5%	79.4%
Assuming a sample size of 40 participants				
≥ 1 event	87.1%	98.5%	99.8%	> 99.9%
≥ 3 events	32.3%	77.7%	95.1%	99.2%
≥ 5 events	4.8%	37.1%	73.7%	92.4%

The 95% exact binomial CIs for the true event rate given different numbers of observed events are shown in Table 22.

Table 22: Precision of 95% Exact Binomial Confidence Interval for Event Rate

Assuming a sample size of 20 participants					
No. of Events	**1**	**2**	**3**	**4**	**5**
Estimate	0.05	0.10	0.15	0.20	0.25
95% CI	0.00, 0.25	0.01, 0.32	0.03, 0.38	0.06, 0.44	0.09, 0.49
Assuming a sample size of 40 participants					
No. of Events	**2**	**4**	**6**	**8**	**10**
Estimate	0.05	0.10	0.15	0.20	0.25
95% CI	0.01, 0.17	0.03, 0.24	0.06, 0.30	0.09, 0.36	0.13, 0.41

10.2. Populations for Analysis

The populations for analysis are provided in Table 23.

Table 23: Populations for Analysis

Population	Description
FAS	The FAS will include all participants who received at least 1 dose of INCB099280 or adagrasib. Participants will be analyzed according to the treatment to which they have been assigned. The FAS will be used for the summary of demographics, baseline characteristics, participant disposition, and analyses of all efficacy data.
DLT-evaluable	The DLT-evaluable population will include all participants in Part 1 that meet one of the following criteria: • Had a DLT by the end of the first treatment cycle (ie, Day 1 to Day 28 inclusive) • Received at least 75% of the planned doses (ie, ≥ 42 doses) of both INCB099280 and adagrasib during the first treatment cycle (ie, Day 1 to Day 28 inclusive) • Discontinue study treatment due to a DLT or TRAE after receiving at least 1 dose of INCB099280, even if adagrasib was not started
Safety	The safety population will include all enrolled participants who received at least 1 dose of INCB099280 or adagrasib. Treatment groups for this population will be determined according to the actual treatment the participant received regardless of assigned study drug treatment. All safety analyses will be conducted using the safety population.
PK-evaluable	The PK-evaluable population will include all participants who received at least 1 dose of INCB099280 and provided at least 1 postbaseline plasma sample (1 PK measurement).
Pharmacodynamic-evaluable	The pharmacodynamic-evaluable population will include all participants who received at least 1 dose of INCB099280 and provided the baseline and at least 1 postbaseline pharmacodynamic measurement.
PK/pharmacodynamic-evaluable	The PK/pharmacodynamic-evaluable population will include all participants who were both PK evaluable and pharmacodynamic evaluable.

The safety and efficacy endpoints, the population that will be used for each analysis, and population-level summary metrics are summarized in Table 24.

Table 24: Population Information for Primary Safety and Exploratory Efficacy Endpoints

Endpoint	Analysis Population	Population-Level Summary Metric
DLTs	DLT-evaluable	DLT incidence rate
• TEAEs • Impact of TEAEs on study drug administration, assessed by treatment interruptions, dose reductions, and permanent discontinuation	Safety	• Incidence rates of TEAEs • Incidence rates of treatment interruptions, dose reductions, and discontinuations for both INCB099280 and adagrasib due to TEAEs
• Objective response: best overall response of CR or PR, per RECIST v1.1 as determined by the investigator by radiographic disease assessment • Disease control: best overall response of CR, PR, or SD ≥ 15 weeks (from start of treatment) per RECIST v1.1 as determined by the investigator by radiographic disease assessment • DOR: time from the earliest date of disease response (CR or PR) per RECIST v1.1 until earliest date of disease progression as determined by the investigator by radiographic disease assessment or death due to any cause if occurring sooner than progression • Six-month and 12-month PFS, defined as absence of disease progression (assessed per RECIST v1.1 by the investigator) or death from any cause, from start of treatment to 6 or 12 months	FAS	• ORR • DCR • Median DOR • 6-month PFS • 12-month PFS

10.3. Level of Significance

This is an exploratory study, and no formal statistical tests will be performed. All CIs will be 95%.

10.4. Statistical Analyses

10.4.1. Primary Analysis

The DLT-evaluable participants will be summarized by dose level. The DLT incidence rate along with a 95% 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 DLTs will be listed by dose level.

The tolerability of the study drug combination will be assessed by summarizing the number of study drug dose interruptions, dose reductions, and treatment discontinuations due to AEs for both INCB099280 and adagrasib. The reasons for dose interruptions, dose reductions, and treatment discontinuations will be listed and summarized by dose level.

Safety analyses will be conducted for the safety population. Adverse events will be coded according to the MedDRA dictionary, and TEAEs (ie, AEs reported for the first time or worsening of a pre-existing event after the first dose of study drug until 90 days after the last dose of study treatment or the start of new anticancer therapy) will be tabulated by preferred term and system organ class for all events, related events, and events of ≥ Grade 3. Quantitative safety variables (eg, laboratory assessments, vital signs) and their changes from baseline will be summarized with descriptive statistics. Clinically notable abnormal values will be flagged and tabulated based on predefined criteria.

The clinical laboratory data will be analyzed using summary statistics; no formal treatment group comparisons are planned. In addition, distributions of key laboratory parameters may be plotted over time; these values will also be classified into CTCAE v5 toxicity grades when applicable and tabulated. Descriptive statistics and mean change from baseline will be determined for vital signs at each assessment time. Vital sign results will be reviewed for clinically notable abnormalities.

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

Measures of exposure (eg, days of exposure, dose intensity, etc) of both INCB099280 and adagrasib will be summarized by means of summary statistics.

10.4.2. Secondary and Exploratory Efficacy Analyses

Objective response rate is defined as the proportion of participants with a best overall response of CR or PR, as determined by the investigator by radiographic disease assessment according to RECIST v1.1 (Eisenhauer et al 2009). The ORR and its 95% CI will be summarized by disease type and dose level.

Disease control rate is defined as the proportion of participants with a best overall response of CR, PR, or SD ≥ 15 weeks (from the start of treatment as determined by the investigator by radiographic disease assessment according to RECIST v1.1. The DCR and its 95% exact binomial CI will be summarized by disease type and dose level.

Duration of response is defined as the time from earliest date of CR or PR until earliest date of disease progression as determined by the investigator according to RECIST v1.1 or death due to any cause if occurring sooner than progression. The Kaplan-Meier estimate of median DOR and its 95% CI will be provided if there are at least 5 responders in a tumor cohort at some dose level. Censoring for DOR will follow FDA guidance (FDA 2015, FDA 2018).

Progression-free survival is defined as the time from the treatment start date to the earliest date of disease progression according to RECIST v1.1 as determined by investigator review or death due to any cause if occurring sooner than progression. The Kaplan-Meier estimates for 6-month

and 12-month PFS rate and their 95% CIs will be summarized by disease type and dose level. Censoring for PFS will follow FDA guidance (FDA 2015, FDA 2018).

10.4.3. Pharmacokinetic Analysis

10.4.3.1. Noncompartmental Analysis and Descriptive Analysis

Standard noncompartmental PK methods will be used to analyze the plasma concentration data using Phoenix WinNonlin v8.3.4 or higher (Certara USA, Princeton, NJ) or other functionally equivalent software applications. The actual times of postdose sample collections will be used. Predose PK samples will be assigned time 0.

The following steady-state PK parameters will be calculated from the plasma concentrations of INCB099280:

- $C_{max,ss}$ – Maximum plasma concentration at steady state
- $T_{max,ss}$ – Time to maximum plasma concentration at steady state
- $C_{min,ss}$ – Minimum plasma concentration at steady state
- $AUC_{0\text{-}12h}$ – Area under the plasma concentration-time curve during 1 dosing interval (ie, 12 hours for [redacted] regimens) at steady state
- $C_{ave,ss}$ – Average plasma concentration at steady state. Derived as $AUC_{0\text{-}12h}$ divided by 12 (hours)
- C_{tau} – The plasma concentration at time tau (ie, 12 hours for [redacted] regimens) at steady state
- CL_{ss}/F – Apparent oral dose clearance at steady state
- V_z/F – Apparent oral dose volume of distribution at steady state

The plasma concentrations will be summarized by cohort/dose levels, visit, and time. The PK parameters estimated by noncompartmental analysis methods will be summarized by cohort/dose levels and visit.

The descriptive summary statistics include but are not limited to the number of observations, mean, standard deviation, standard error of the mean, coefficient of variation, median, minimum, maximum, geometric mean, and geometric coefficient of variation.

10.4.3.2. [redacted]

[redacted]

This analysis will be done in a stepwise manner and limit further participant enrollment into the dose level as described in Section 4.1.1.

10.4.4. Translational Assessments

Descriptive statistics will be performed for exploratory biomarkers and correlative assessments planned to evaluate known and/or potential prognostic and/or predictive biomarkers associated with a clinical benefit for participants treated with INCB099280.

10.5. Interim Analysis

In Part 1, dose-escalation decisions from the hybrid design based on the current available data will be made before the end of the study. In other words, after each dose-level cohort in the dose-escalation procedure, the next dose level has to be chosen depending on the observed accumulated data.

In Part 2, preplanned analyses of safety will be provided to the DSMB as specified in the charter. The process by which the DSMB will review data and make recommendations and decisions will be documented in the charter.

Periodic data review will review the safety and efficacy of each of the RDEs. If any RDE is not tolerable (as described in Section 4.1.3), that RDE may be dropped. A nonbinding futility stopping rule for each cohort using Bayesian predictive probability of success will be applied. This will ensure a reasonable number of objective responses have been observed in the individual disease cohort to ensure reasonable benefit of the combination treatment compared to adagrasib monotherapy data. If any RDE has inferior efficacy based on the aforementioned rules, that RDE may be dropped.

11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

11.1. Investigator Responsibilities

- The Protocol, Protocol Amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC and health authorities before the study is initiated.
- The investigator is responsible for ensuring that the safety reports provided by the sponsor are reviewed and processed in accordance with regulatory requirements, the policies and procedures established by the IRB/IEC, and institutional requirements.
- Any amendments to the Protocol will require approval from both health authorities and the IRB/IEC before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
  - Providing oversight of the conduct of the study at the site and adherence to GCP, IRB/IEC requirements, institutional requirements, and applicable laws and country-specific regulations.
- Adhering to the Protocol as described in this document and agreeing that changes to the Protocol procedures, with the exception of medical emergencies, must be discussed and approved, first, by the sponsor or its designee and, second, by the IRB/IEC. Each investigator is responsible for enrolling participants who have met the specified eligibility criteria.
- Retaining records in accordance with all local, national, and regulatory laws but for a minimum period of at least 2 years after the last marketing application approval in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or if not approved, 2 years after the termination of the test article for investigation to ensure the availability of study documentation should it become necessary for the sponsor or a regulatory authority to review.
  - The investigator must not destroy any records associated with the study during the retention period without receiving approval from the sponsor. The investigator must notify the sponsor or its designee in the event of accidental loss or destruction of any study records. If the investigator leaves the institution where the study was conducted, the sponsor or its designee must be contacted to arrange alternative record storage options.

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

11.1.1. Identification of the Coordinating Principal Investigator

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

11.2. Data Management

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

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

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

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

The investigator will be responsible for the following:

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

- Maintaining adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial participants. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail). Source data are, in general, all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).
- Verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- Maintaining accurate documentation (source data) that supports the information entered in the eCRF, sent to a central vendor designated by the sponsor, or as described in other study and data flow manuals.
  - Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed 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 trial).
  - Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Current applicable medical records must be available.
- Sending participants' data, either as unique samples, copies, or photographs, to be evaluated centrally or analyzed centrally, or both, by a qualified vendor designated by the sponsor.
  - As required by privacy and data protection regulations and Incyte's privacy policies, if any photographs of participants are to be taken, the photographs must be limited to the area of the face or the body that is strictly necessary and the photographs should be masked (ie, identifying features such as eyes, mouth, scars, tattoos, or unique markings or features should be either obscured with a black bar or digitally pixelated so as to not permit the reidentification of the participants and preserve their confidentiality) by a specially designated photography vendor prior to sending the photographs to Incyte or any other third-party vendors for analysis or further processing.

  - 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 Monitoring Plan or equivalent.

Quality tolerance limits will be predefined in the project management plan for the trial 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 for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

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

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

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

12. REFERENCES

Adagrasib Investigator's Brochure. San Diego, CA: Mirati Therapeutics, Inc.

Awad MM, Liu S, Rybkin II, et al. Acquired resistance to KRASG12C inhibition in cancer. N Engl J Med 2021;384:2382-2393.

Bailey MH, Tokheim C, Porta-Pardo E, et al. Comprehensive characterization of cancer driver genes and mutations. Cell 2018;173:371-385.

Banks LB, Sullivan RJ. When is it OK to stop anti-programmed death 1 receptor (PD-1) therapy in metastatic melanoma? Am J Clin Dermatol 2020;21:313-321.

Biernacka A, Tsongalis PD, Peterson JD, et al. The potential utility of re-mining results of somatic mutation testing: KRAS status in lung adenocarcinoma. Cancer Genet 2016;209:195-198.

Briere DM, Li S, Calinisan A, et al. The KRASG12C inhibitor MRTX849 reconditions the tumor immune microenvironment and sensitizes tumors to checkpoint inhibitor therapy. Mol Cancer Ther 2021;20:975-985.

Canon J, Rex K, Saiki AY, et al. The clinical KRAS(G12C) inhibitor AMG 510 drives anti-tumour immunity. Nature 2019;575:217-223.

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

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

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

Cullis J, Das S, Bar-Sagi, D. Kras and tumor immunity: friend or foe?. Cold Spring Harb Perspect Med 2018;8:a031849.

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

European Medicines Agency. ICH E9 statistical principles for clinical trials. CPMP/ICH/363/96. 1998.

European Medicines Agency. ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials. EMA/CHMP/ICH/436221/2017. 2020.

Food and Drug Administration. Guidance for Industry: Clinical Trial Endpoints for the Approval of Non-Small Cell Lung Cancer Drugs and Biologics. 2015.

Food and Drug Administration. Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics. 2018.

Haanen J, Obeid M, Spain L, et al. Management of toxicities from immunotherapy: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol 2022;33:1217-1238.

Hamid O, Robert C, Daud A, et al. Five-year survival outcomes for patients with advanced melanoma treated with pembrolizumab in KEYNOTE-001. Ann Oncol 2019;30:582-588.

Haslam A, Prasad V. Estimation of the percentage of US patients with cancer who are eligible for and response to checkpoint inhibitor immunotherapy drugs. JAMA Netw Open 2019;2:e192535.

INCB099280 Investigator's Brochure. Wilmington, DE: Incyte Corporation.

Jänne PA, Riely GJ, Gadgeel SM, et al. Adagrasib in non-small-cell lung cancer harboring a KRASG12C mutation. N Engl J Med 2022a;387:120-131.

Jänne PA, Smit EF, de Marinis F, et al. Preliminary safety and efficacy of adagrasib with pembrolizumab in treatment-naïve patients with advanced non-small cell lung cancer (NSCLC) harboring a KRASG12C mutation. Immunooncol Technol 2022b;16(suppl 1):1-2 [abstr LBA4].

Ji Y, Liu P, Li Y, Bekele N. A modified toxicity probability interval method or dose-finding trials. Clin Trials 2010;7:653-663.

Ji Y, Wang S-J. Modified toxicity probability interval design: a safer and more reliable method than the 3 + 3 design for practical Phase I trials. J Clin Oncol 2013;31:1785-1791.

Klempner SJ, Weiss J, Pelster M, et al. KRYSTAL-1: updated efficacy and safety of adagrasib (MRTX849) with or without cetuximab in patients with advanced colorectal cancer (CRC) harboring a KRASG12C mutation. Ann Oncol 2022;33(suppl 7):S1391 [abstr LBA24].

Krazati (adagrasib) [prescribing information]. Mirati Therapeutics, Inc; December 2022.

Liao JJZ, Z Zhou F, Zhou H, Petruzzelli L, Hou K, Asatiani E. A hybrid design for dose-finding oncology clinical trials. Int J Cancer 2022;151:1602-1610.

Marron TU, Ryan AE, Reddy SM, et al. Considerations for treatment duration in responders to immune checkpoint inhibitors. J Immunother Cancer 2021;9:e001901.

Moore AR, Rosenberg SC, McCormick F, Malek S. RAS-targeted therapies: is the undruggable drugged?. Nat Rev Drug Discov 2020;19:533-552.

Mugarza E, van Maldegem F, Boumelha J, et al. Therapeutic KRASG12C inhibition drives effective interferon-mediated antitumor immunity in immunogenic lung cancers. Sci Adv 2022;8:eabm8780.

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

Ostrem JM, Peters U, Sos ML, Wells JA, Shokat KM. K-Ras(G12C) inhibitors allosterically control GTP affinity and effector interactions. Nature 2013;503:548-551.

Prenen H, Lesimple T, Robert M, et al. A phase 1 study exploring the safety and tolerability of the small-molecule PD-L1 inhibitor INCB099280 in patients with select advanced solid tumors. Ann Oncol 2023;20(suppl 1):100589.

Robert C, Ribas A, Schachter J, et al. Pembrolizumab versus ipilimumab in advanced melanoma (KEYNOTE-006): post-hoc 5-year results from an open-label, multicentre, randomised, controlled, phase 3 study. Lancet Oncol 2019;20:1239-1251.

Sanchez-Vega F, Mina M, Armenia J, et al. Oncogenic signaling pathways in the cancer genome atlas. Cell 2018;173:321-337.

Schneider BJ, Naidoo J, Santomasso BD, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: ASCO guideline update [erratum in J Clin Oncol 2022;40:315]. J Clin Oncol 2021;39:4073-4126.

Simanshu DK, Nissley DV, McCormick F. RAS proteins and their regulators in human disease. Cell 2017;170:17-33.

Skoulidis F, Li BT, Dy GK, et al. Sotorasib for lung cancers with KRAS p.G12C mutation. N Engl J Med 2021;384:2371-2381.

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

Tanaka N, Lin JJ, Li C, et al. Clinical acquired resistance to KRASG12C inhibition through a novel KRAS Switch-II pocket mutation and polyclonal alterations converging on RAS-MAPK reactivation. Cancer Discov 2021;11:1913-1922.

van Maldegem F, Valand K, Cole M, et al. Characterisation of tumour microenvironment remodelling following oncogene inhibition in preclinical studies with imaging mass cytometry. Nat Commun 2021;12:5906.

Vilgelm AE, Johnson DB, Richmond A. Combinatorial approach to cancer immunotherapy: strength in numbers. J Leukoc Biol 2016;100:275-290.

Wiesweg M, Kasper S, Worm K, et al. Impact of RAS mutation subtype on clinical outcome – a cross-entity comparison of patients with advanced non-small cell lung cancer and colorectal cancer. Oncogene 2019;38:2953-2966.

Yonezawa A, Inui K. Importance of the multidrug and toxin extrusion MATE/SLC47A family to pharmacokinetics, pharmacodynamics/toxicodynamics and pharmacogenomics. Br J Pharmacol 2011;164:1817-1825.

APPENDIX A. INFORMATION REGARDING EFFECTIVENESS OF CONTRACEPTIVE METHODS AND DEFINITIONS

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 one of the nonhormonal, highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

For male participants of reproductive potential[b]

The following methods during the Protocol-defined timeframe in Section 5.1 are highly effective:

- Use of a male condom plus partner use of an additional contraceptive method when having penile-vaginal intercourse with a WOCBP who is not currently pregnant
- Vasectomy with medical assessment of the surgical success (verified by site personnel's review of the participant's medical records)
- Sexual abstinence[c]
  - Abstinence from penile-vaginal intercourse

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

For female participants who are WOCBP

The following methods during the Protocol-defined timeframe in Section 5.1 that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods:

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

[a] Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
[b] If the male participant has a partner of childbearing potential, the partner should also use contraceptives.
[c] In the context of this guidance, sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study 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.
[d] 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.
[e] Contraception methods that in the context of this guidance are considered to have low user dependency.
[f] 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.

Source: Clinical Trials Facilitation and Coordination Group 2014 and 2020.

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

Examples of contraindicated medications are provided below.

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
P-gp substrates with a narrow therapeutic index
Colchicine, dabigatran, digoxin
[redacted]
[redacted]
[redacted] **inhibitors of CYP3A4/**[redacted]
Aprepitant, atazanavir, boceprevir, [redacted], clarithromycin, cobicistat, danoprevir, diltiazem, erythromycin, fluconazole, grapefruit, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir, [redacted] nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, troleandomycin, voriconazole
Moderate and potent/strong inducers of CYP3A4/[redacted]
Apalutamide, bosentan, carbamazepine, efavirenz, enzalutamide, etravirine, mitotane, phenobarbital, phenytoin, primidone, rifampin, St John's wort
[redacted]
[redacted]
CYP2C9 substrate with a narrow therapeutic index
Warfarin
CYP2D6 substrates with a narrow therapeutic index
Thioridazine, pimozide

Compiled from https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers, https://drug-interactions.medicine.iu.edu/MainTable.aspx, and https://go.drugbank.com/categories/DBCAT002667 (accessed JUL 2021). This list of examples is not exhaustive; refer to the sources for additional examples.

APPENDIX C. MEDICATIONS TO BE USED WITH CAUTION DURING STUDY TREATMENT

Examples of medications and substances to be used with caution during study treatment are listed below.

Moderate/sensitive CYP2C9 substrates
Celecoxib, glimepiride, tolbutamide
Moderate/sensitive CYP2D6 substrates
Encainide, imipramine, metoprolol
[redacted]
[redacted]
Substrates of MATE-1/MATE-2K
Acyclovir, cimetidine, cephalexin, cephradine, creatinine, estrone sulphate, fexofenadine, flecainide, ganciclovir, guanidine, metformin, procainamide, tetraethylammonium, thiamine, 1-methyl-4-phenylpyridinium

Sources: Compiled from https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers, https://drug-interactions.medicine.iu.edu/MainTable.aspx, https://go.drugbank.com/categories/DBCAT002667 (accessed JUL 2021), and Yonezawa and Inui 2011. This list of examples is not exhaustive; refer to the sources for additional examples.

APPENDIX D. PROTOCOL AMENDMENT SUMMARY OF CHANGES

Document	Date
Amendment 1	12 MAY 2023
Amendment 2	16 MAY 2023
Amendment 3	17 OCT 2023
Amendment 4	21 FEB 2024

Amendment 4 (21 FEB 2024)

Overall Rationale for the Amendment:

The primary purpose of this amendment is to address queries raised by a health authority.

1. **Section 2.3, Clinical Experience With Allele-Specific Inhibitors of $KRAS^{G12C}$; Section 2.9, Benefit/Risk Assessment**

   Description of change: Added information about serious skin toxicity occurring in patients who received treatment with adagrasib and the updated benefit/risk assessment of the study.

   Rationale for change: Addition of emerging data.

2. **Section 2.8.2, First-in-Participant Study in Advanced Solid Malignancies**

   Description of change: Updated background information on the safety and efficacy of INCB099280.

   Rationale for change: Update to the safety and efficacy data.

3. **Section 5.1, Inclusion Criteria (Criteria 5, 7, and 9)**

   Description of change: Modified the inclusion criteria specifying prior treatment required for participants in Part 1 (Criterion 5) and Part 2 CRC (Criterion 7) and clarified that there is no minimum level of PD-L1 expression required for enrollment in the study (Criterion 9).

   Rationale for change: Health authority comment.

4. **Section 5.2, Exclusion Criteria (Criterion 28)**

   Description of change: Added Criterion 28a, which prohibits participants with risk factors for QT prolongation from enrolling in the study.

   Rationale for change: Health authority comment**.**

5. **Section 6.5.1, Definition of a Dose-Limiting Toxicity (Table 11: Definition of Dose-Limiting Toxicity)**

   Description of change: Added text to the DLT definition stating that Grade 3 amylase or lipase elevations with radiologic imaging showing pancreatitis constitutes a DLT.

   Rationale for change: Health authority comment.

6. **Section 6.6.1.2, Management of Adverse Events Attributable to INCB099280; Section 6.6.1.3, Management of Adverse Events Attributable to Adagrasib (Table 16: Adagrasib Dose Modifications for Nonhematologic Toxicities)**

   Description of change: Added text instructing sites on how to handle potential DILI cases. Any event that is determined to be a DILI case would require study treatment discontinuation.

   Revised the dose-modification guidelines for adagrasib to clarify that adagrasib [redacted]

   Revised the dose-modification guidance for adagrasib to add guidance for [redacted]

   Rationale for change: Health authority comment.

7. **Section 6.7.2.6, Substrates of MATE-1 and MATE-2K Transporters; Appendix C: Medications To Be Used With Caution During Study Treatment**

   Description of change: Added a section instructing sites to use drugs that are substrates of the MATE-1 and MATE-2K transporters with caution.

   Rationale for change: Adagrasib is an inhibitor of MATE-1 and MATE-2K and the use of adagrasib in combination with MATE-1 and MATE-2K substrates could result in increased exposure of these drugs and should be used with caution.

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

Amendment 3 (17 OCT 2023)

Overall Rationale for the Amendment:

The primary purpose of this amendment is to update the length of time required to prevent pregnancy and refrain from donating oocytes due to comments by a health authority.

1. **Section 5.1, Inclusion Criteria (Inclusion Criterion 12); Section 5.2, Exclusion Criteria (Exclusion Criterion 31)**

   Description of change: Updated Inclusion Criterion 12a to require men to take precautions to avoid fathering children for 190 days from the last dose, Inclusion Criterion 12b to indicate that women must refrain from donating oocytes until 190 days after the last dose, and Exclusion Criterion 31 to exclude men from enrolling if expecting to father children within 190 days after the last dose of study drug.

   Rationale for change: Health authority comment.

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

Amendment 2 (16 MAY 2023)

Overall Rationale for the Amendment:

The primary purpose of this amendment is to address queries raised by a health authority.

1. **Section 1, Protocol Summary (Table 2: Key Study Design Elements; Table 3: Schedule of Activities); Section 4.1, Overall Design; Section 4.1.1, Part 1 – Dose Finding; Section 4.1.1.1, [redacted]; Section 4.2, Overall Study Duration; Section 8.4.1, [redacted]; Section 10.4.3.2, [redacted]**

   Description of change: Clarified the [redacted] and added text that allows participants in Dose Level 2 to receive INCB099280 as monotherapy in the [redacted] if < 9 participants are enrolled in Dose Level 1.

   Rationale for change: To allow further [redacted] in Dose Level 2 if needed.

2. **Section 1, Protocol Summary (Figure 1: Study Design Schema); Section 2.7.1, Rationale for the INCB099280 Starting Dose in Combination With Adagrasib; Section 2.7.2, Rationale for Escalating the Dose of INCB099280 to [redacted] mg [redacted] Section 4.1.1, Part 1 – Dose Finding (Table 5: Potential Dose Levels to Be Explored in Dose Level 2; Table 6: Potential Dose Levels to Be Explored in Part 1; Table 7: Potential Alternate Dose Levels to Be Explored in Part 1); Section 6.1, Study Treatments Administered (Table 10: Study Treatment Information); Section 6.6.1.2, Management of Adverse Events Attributable to INCB099280 (Table 12: INCB099280 Recommended Dose-Reduction Scheme)**

   Description of change: Amended the starting dose of INCB099280 in combination with adagrasib to [redacted] mg [redacted] As the [redacted] is unknown, the algorithm for selecting the dose of INCB099280 to be explored in Dose Level 2 was added, the table for potential dose levels in Part 1 was updated, and an alternate dose-level table was added.

   Rationale for change: Health authority comment. Additional changes were made to allow data to inform dose-escalation decisions.

3. **Section 1, Protocol Summary (Table 3: Schedule of Activities); Section 4.1.1, Part 1 – Dose Finding**

   Description of change: Added a telephone contact at Cycle 1 Day 4 to the SoA and added a rule that only allows 1 participant to start dosing per day in Part 1 of the study.

   Rationale for change: The telephone contact on Cycle 1 Day 4 allows for early safety monitoring for participants. The rule only allowing 1 participant to start dosing per day in each dose level in Part 1 provides guidance and sufficient time between participant dosing in the dose-finding part of the study.

4. **Section 1, Protocol Summary (Table 3: Schedule of Activities); Section 8.4.1, Blood Sample Collection (Table 20: Pharmacokinetic Blood Sample Timing)**

   Description of change: Sparse PK samples were added predose at Cycles 6, 8, and 12 and every fourth cycle thereafter.

   Rationale for change: Health authority comment.

5. **Section 4.1.1, Part 1 – Dose Finding; Section 10.4.3.2, Effect of Adagrasib on INCB099280 Pharmacokinetic Parameters**

   Description of change: Specified limited enrollment in Dose Level 1 to allow for [redacted] after 1 and then 2 additional participants are enrolled prior to exposing additional participants to that dose level.

   Rationale for change: To characterize the [redacted] when limited participants have been enrolled.

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

   Description of change: Updated the exclusion criterion for renal function to be based on calculated CrCl.

   Rationale for change: Health authority comment.

7. **Section 8.3.4, Electrocardiograms (Table 17: Electrocardiogram Collection Schedule)**

   Description of change: Added timed postdose ECG collection at Cycle 1 Day 1 and updated to include postdose ECG assessments to be performed at 4 hours for all participants in the study.

   Rationale for change: Further monitoring of cardiac safety.

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

Amendment 1 (12 MAY 2023)

Overall Rationale for the Amendment:

The primary purpose of this amendment is to address queries raised by a health authority.

1. **Section 1, Protocol Summary (Table 2: Key Study Design Elements; Table 3: Schedule of Activities); Section 4.1, Overall Design; Section 4.1.1, Part 1 – Dose Finding; Section 4.2, Overall Study Duration;** [redacted]

   Description of change: Specified that only participants enrolled into Part 1 Dose Level 1 will participate in the [redacted]

   Rationale for change: Clarification.

2. **Section 4.1.1, Part 1 – Dose Finding (Table 5: Potential Dose Levels to Be Explored in Part 1)**

   Description of change: Specified the dose levels to be explored and removed ambiguity in Table 5. Added the lower and upper limit for the [redacted]% target DLT rate interval.

   Rationale for change: Clarification.

3. **Section 4.1.2, Part 2 – Dose Expansion**

   Description of change: Detailed the plan for exploration of RDE(s) in Part 2 of the study. Specifically, Part 2 will not begin until all RDE(s) have been identified, and if more than 1 RDE is selected, participants will be randomized to an assigned RDE within the applicable disease cohort.

   Rationale for change: Clarification.

4. **Section 4.1.3, Safety Monitoring**

   Description of change: Added a rule that requires a suspension in enrollment for review of safety if [redacted]% of participants (when [redacted] or more participants have been enrolled) experience a treatment-related Grade 4 or higher AE. Also added a rule that requires a suspension in enrollment for review of safety if more than [redacted] participants enrolled or if [redacted]% of participants (when [redacted] or more participants have enrolled) have an event of interstitial lung disease/pneumonitis ≥ Grade 3.

   Rationale for change: Health authority comment.

5. **Section 5.1, Inclusion Criteria (Inclusion Criteria 5, 6, and 7)**

   Description of change: Modified the inclusion criteria specifying prior treatment required for participants with NSCLC (Inclusion Criterion 6) and CRC (Inclusion Criterion 7) and modified Inclusion Criterion 5 to indicate that participants must have received at least 1 line of prior therapy.

   Rationale for change: Health authority comment.

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

   Description of change: Updated Exclusion Criterion 6 to exclude participants who received thoracic radiation exceeding 30 Gy within 6 months of the first dose of study treatment and require participants to have recovered from all radiation-related toxicities to ≤ Grade 1 and not require corticosteroids.

   Rationale for change: Health authority comment.

7. **Section 6.5.1, Definition of a Dose-Limiting Toxicity (Table 9: Definition of Dose-Limiting Toxicity); Section 10.2, Populations for Analysis (Table 21: Populations for Analysis)**

   Description of change: Modified the definition of a DLT to include all Grade ≥ 3 nonhematologic toxicities with exceptions specified, clarified the definition of a DLT for Grade 4 neutropenia, and added specific irAEs that will be considered DLTs. Clarified that participants who discontinue treatment due to a DLT or TRAE will be included in the DLT-evaluable population if they received at least 1 dose of INCB099280 and even if they did not start treatment with adagrasib.

   Rationale for change: Health authority comment.

8. **Section 8.3.4, Electrocardiograms (Table 15: Electrocardiogram Collection Schedule); Section 8.4.1, Blood Sample Collection (Table 18: Pharmacokinetic Blood Sample Timing)**

   Description of change: Included windows around the timing for electrocardiograms and the timing of blood collection for [redacted].

   Rationale for change: Clarification of timing windows.

9. **Section 10.5, Interim Analysis**

   Description of change: Added information on how suboptimal RDEs may be dropped.

   Rationale for change: Clarification.

10. **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.

Signature Page for VV-CLIN-022457 v5.0

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