Official Title:	**A Phase 2, Open-Label, Randomized, Multicenter Study to Evaluate the Efficacy and Safety of Pemigatinib Plus Pembrolizumab Versus Pemigatinib Alone Versus Standard of Care as First-Line Treatment for Metastatic or Unresectable Urothelial Carcinoma in Cisplatin-Ineligible Participants Whose Tumors Express FGFR3 Mutation or Rearrangement (FIGHT-205)**
NCT Number:	NCT04003610
Document Date:	Clinical Study Protocol Version 2: 17 April 2020

Clinical Study Protocol

INCB 54828-205

A Phase 2, Open-Label, Randomized, Multicenter Study to Evaluate the Efficacy and Safety of Pemigatinib Plus Pembrolizumab Versus Pemigatinib Alone Versus Standard of Care as First-Line Treatment for Metastatic or Unresectable Urothelial Carcinoma in Cisplatin-Ineligible Participants Whose Tumors Express FGFR3 Mutation or Rearrangement (FIGHT-205)

Product:	**INCB054828 (pemigatinib)**
IND Number:	**124,358**
EudraCT Number:	**2019-000721-50**
Phase of Study:	**2**
Sponsor:	**Incyte Corporation** **1801 Augustine Cut-Off** **Wilmington, DE 19803**
Original Protocol:	**11 JUN 2019**
Amendment 1:	**17 APR 2020**

INVESTIGATOR'S AGREEMENT

I have read the INCB 54828-205 Protocol Amendment 1 (dated 17 APR 2020) 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)

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

Abbreviations and Special Terms	Definition
5-FU	fluorouracil
AE	adverse event
AESI	adverse event of special interest
AIDS	acquired immunodeficiency syndrome
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the plasma or serum concentration-time curve
$AUC_{0-\tau}$	area under the steady-state plasma or serum concentration-time curve over 1 dose interval
BICR	blinded independent central review
CBC	complete blood count
[redacted]	[redacted]
CFR	Code of Federal Regulations
CI	confidence interval
CL_{ss}/F	apparent oral dose clearance at steady state
C_{max}	maximum observed plasma or serum concentration
C_{min}	minimum observed plasma or serum concentration over the dose interval
CNS	central nervous system
CPS	combined positive score
CR	complete response
CrCl	creatinine clearance
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DDI	drug-drug interaction
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DOR	duration of response
EAU	European Association of Urology
ECG	electrocardiogram

Abbreviations and Special Terms	Definition
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
E_{max}	maximum effect
EORTC	European Organization for the Research and Treatment of Cancer
EORTC QLQ-C30	European Organization for the Research and Treatment of Cancer Core Quality of Life Questionnaire
EOT	end of treatment
EQ-5D-5L	5-level version of EuroQol-5D
FDA	Food and Drug Administration
FFPE	formalin-fixed paraffin-embedded
FGF	fibroblast growth factor
FGFR	fibroblast growth factor receptor
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GFR	glomerular filtration rate
GI	gastrointestinal
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act of 1996
HIV	human immunodeficiency virus
HR	hazard ratio
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICR	independent central review
IEC	independent ethics committee
IgH	immunoglobulin H
IHC	immunohistochemistry
INR	international normalized ratio
irAE	immune-related adverse event
IRB	institutional review board
IRT	interactive response technology
ITT	intent-to-treat

Abbreviations and Special Terms	Definition
IV	intravenously
LN	lymph node
MedDRA	Medical Dictionary for Regulatory Activities
MIBC	muscle-invasive bladder cancer
MRI	magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NMIBC	nonmuscle-invasive bladder cancer
NNRTI	non-nucleoside reverse transcriptase inhibitor
NSAID	nonsteroidal anti-inflammatory drug
NSCLC	non–small-cell lung cancer
OCT	optical coherence tomography
OCT2	organic cation transporter 2
ORR	objective response rate
OS	overall survival
PBPK	physiologically-based pharmacokinetic
PD	progressive disease
PD-1	programmed cell death protein 1
PD-L1	programmed cell death ligand 1
PD-L2	programmed cell death ligand 2
PFS	progression-free survival
PK	pharmacokinetic
PO	orally
PP	per protocol
PR	partial response
PSA	prostate-specific antigen
PT	prothrombin time
PTT	partial thromboplastin time
QD	once daily
QXW	every X weeks
RECIST v1.1	Response Evaluation Criteria in Solid Tumors version 1.1
RNA	ribonucleic acid
RPED	retinal pigmented epithelium detachment
SAE	serious adverse event
SD	standard deviation

Abbreviations and Special Terms	Definition
SmPC	Summary of Product Characteristics
SOC	standard of care
SRD	serous retinal detachment
$t_{½}$	apparent terminal-phase disposition half-life
T1DM	type 1 diabetes mellitus
TCC	transitional cell carcinoma
TEAE	treatment-emergent adverse event
t_{max}	time to maximum concentration
TSH	thyroid-stimulating hormone
UC	urothelial carcinoma
ULN	upper limit of normal
V_z/F	apparent oral dose volume of distribution
WBC	white blood cell

1. PROTOCOL SUMMARY

Protocol Title: A Phase 2, Open-Label, Randomized, Multicenter Study to Evaluate the Efficacy and Safety of Pemigatinib Plus Pembrolizumab Versus Pemigatinib Alone Versus Standard of Care as First-Line Treatment for Metastatic or Unresectable Urothelial Carcinoma in Cisplatin-Ineligible Participants Whose Tumors Express FGFR3 Mutation or Rearrangement (FIGHT-205)

Protocol Number: INCB 54828-205

Objectives and Endpoints:

Table 1 presents the primary objective and endpoint.

Table 1: Primary Objective and Endpoint

Objective	Endpoint
Primary	
To evaluate and compare PFS in participants treated with pemigatinib in combination with pembrolizumab (Treatment Group A) and pemigatinib alone (Treatment Group B) versus SOC (Treatment Group C). Differences in PFS will be evaluated hierarchically, and the comparison between pemigatinib in combination with pembrolizumab (Treatment Group A) and SOC (Treatment Group C) will be evaluated first, and if significant difference is detected, a second comparison will be made in PFS between pemigatinib alone (Treatment Group B) and SOC (Treatment Group C). Hypothesis: The combination of pembrolizumab plus pemigatinib has superior PFS as compared with SOC. Contribution of pemigatinib alone to combination will be assessed by comparing Treatment Groups A and C and Treatment Groups B and C.	Progression-free survival, defined as the time from randomization date until the date of disease progression (as measured by BICR per RECIST v1.1) or death due to any cause, whichever occurs first.

Overall Design:

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

Table 2: Key Study Design Elements

Study Phase	Phase 2
Clinical Indication	The treatment of UC in patients who are ineligible to receive cisplatin and whose tumors have an FGFR3 mutation or rearrangement
Population	Male and female participants at least 18 years of age who have untreated metastatic or unresectable UC.
Number of Participants	Approximately 372 participants will be randomized 1:1:1 to 1 of the following 3 treatment groups (124 participants per group): • Treatment Group A: Pemigatinib + pembrolizumab • Treatment Group B: Pemigatinib • Treatment Group C: SOC (gemcitabine/carboplatin or pembrolizumab)
Study Design	Active-controlled, open-label, and randomized. Randomization will occur after the participant has completed screening. Participants will be stratified by eligible to receive carboplatin vs not eligible to receive carboplatin, PD-L1 CPS ≥ 10 vs CPS < 10, and LN-only disease versus other metastatic disease. This is an event-driven clinical study designed to ensure power to detect success of the primary endpoint of PFS. A total of 210 PFS events in the combined treatment groups of pemigatinib plus pembrolizumab and SOC are needed.
Estimated Duration of Study Participation	Up to 35 days for screening followed by continuous treatment in consecutive 21-day cycles as long as participants are receiving benefit and have not met any criteria for study withdrawal, and at least 30 days after the last dose of study treatment for follow-up. Participants who receive pembrolizumab may receive up to 35 cycles of pembrolizumab (approximately 2 years). Participants who receive pemigatinib may receive treatment until disease progression. Participants who receive carboplatin and gemcitabine may receive 4 to 6 cycles. The safety follow-up visit is 30 days after the last dose of study treatment. Report SAEs occurring within 90 days after the last dose of study treatment or within 30 days after the last dose of study treatment when starting a new anticancer therapy, whichever is earlier. It is estimated that an individual will participate for approximately 18 months.
DMC	Yes (internal and external)

Treatment Groups and Duration:

Table 3: Treatment Groups for Randomization

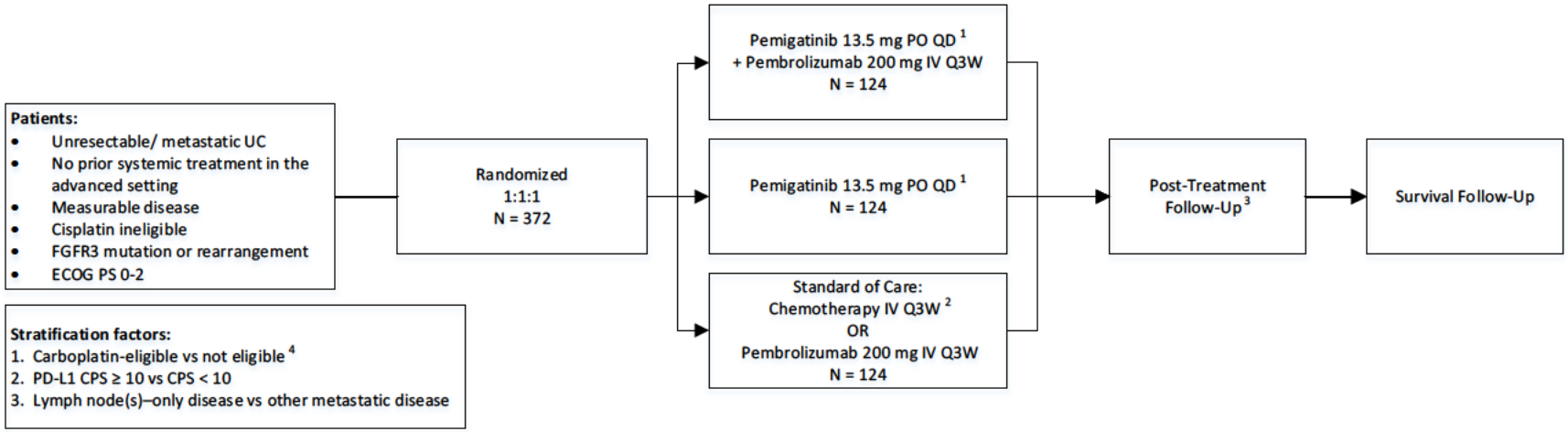
Treatment Group	Regimen
A	Pemigatinib 13.5 mg QD PO[a] until PD + pembrolizumab 200 mg Q3W IV up to 35 cycles (approximately 2 years) or PD, whichever occurs first
B	Pemigatinib 13.5 mg QD PO[a] until PD
C	One of 2 SOC treatment options: 1. Gemcitabine 1000 mg/m2 Q3W IV on Days 1 and 8 + carboplatin AUC 5 (or AUC 4.5 if required per local guidelines) Q3W on Day 1 or 2 for 4 to 6 cycles. (Participants whose tumors express PD-L1 CPS < 10 who are eligible to receive carboplatin.) OR 2. Pembrolizumab 200 mg Q3W IV up to 35 cycles (approximately 2 years). (Participants whose tumors express PD-L1 CPS ≥ 10 or participants who are not considered eligible to receive any platinum-containing chemotherapy regardless of PD-L1 expression status [only applicable in regions where pembrolizumab is used as SOC for participants who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status].)

[a] Participants not reaching the target serum phosphate during Cycle 1 will increase the daily dose to 18 mg starting at Cycle 2 as described in Section 6.6.2.1.

Figure 1 presents the study design schema.

Adherence to the study design requirements, including those specified in the schedule of activities, is essential and required for study conduct. All study assessments will be performed as indicated in the schedule of activities (see Table 4), and all laboratory assessments will be performed as indicated in Table 5. Table 15 presents a summary of clinical laboratory analytes to be assessed. The order of assessments is suggested by the order of mention within the schedule. See Section 8 for instructions on each assessment. Further details of study procedures and assessments can be found in the study reference manual.

Figure 1: Study Design Schema



ECOG PS = Eastern Cooperative Oncology Group Performance Status; IV = intravenous; PO = orally; Q3W = every 3 weeks; UC = urothelial carcinoma.
[1] Participants not reaching the target serum phosphate during Cycle 1 will increase the daily dose of pemigatinib to 18 mg.
[2] Gemcitabine 1000 mg/m^2 IV Q3W on Days 1 and 8 + carboplatin AUC 5 (or 4.5) Q3W on Day 1 or 2.
[3] Participants may receive pembrolizumab for up to 2 years, pemigatinib until disease progression, and chemotherapy for 4-6 cycles, or other criteria per protocol.
[4] Carboplatin-eligible participants if randomized to SOC will receive gemcitabine/carboplatin; if not eligible to receive carboplatin, will receive pembrolizumab.
Note: Patients not eligible for carboplatin will not be enrolled in regions where pembrolizumab is not used as SOC in this population.

Table 4: Schedule of Activities

Visit Day (Range)	Prescreening	Screening	Treatment					Post-Treatment				Notes
			Cycle 1			Cycle 2+		EOT	Safety Follow-Up	Post-Treatment Follow-Up	Survival Follow-Up	
		Days -35 to -1	Day 1 (± 3 d)	Day 8 (± 3 d)	Day 15 (± 3 d)	Day 1 (± 3 d)	Day 8 (± 3 d)	At Treatment Discon	30 d (± 5 d)	Same Disease Assessment (± 7 d)	Every 12 Weeks (± 14 d)	
Administrative Procedures												
FGFR3 tissue genomic testing	X*	X*										*Participants can be randomized based on local genomics testing if available, but confirmation via central laboratory is required. Assess in prescreening or screening only. Section 8.7
Tumor tissue testing for PD-L1 expression (CPS)	X*	X*										*Participants can be randomized based on local testing, if available, but confirmation via central laboratory is required. Assess in prescreening or screening only. Section 8.7.
Prescreening informed consent	X*											*For FGFR3 and PD-L1 testing if needed. Section 8.1.2
Main informed consent		X										Signed before any Protocol-specific screening procedures are performed. Section 8.1.1
Contact IRT	X	X	X	X		X	X	X	X			Section 8.1.3
Inclusion/exclusion criteria		X	X									Sections 5.1 and 5.2
General and disease medical history		X										Section 8.1.5
Prior/concomitant medications		X	X	X	X	X	X	X	X			Section 6.7
Dispense pemigatinib			X			X*						*Assessments for up-titration will be conducted during Cycle 1. First possibility to up-titrate a participant is at C2D1. Section 6.6.2.1

Table 4: Schedule of Activities (Continued)

Visit Day (Range)	Prescreening	Screening	Treatment					Post-Treatment				Notes
			Cycle 1			Cycle 2+		EOT	Safety Follow-Up	Post-Treatment Follow-Up	Survival Follow-Up	
		Days -35 to -1	Day 1 (± 3 d)	Day 8 (± 3 d)	Day 15 (± 3 d)	Day 1 (± 3 d)	Day 8 (± 3 d)	At Treatment Discon	30 d (± 5 d)	Same Disease Assessment (± 7 d)	Every 12 Weeks (± 14 d)	
Administer pembrolizumab			X*			X*						*Administered Q3W. Section 6.1
Administer gemcitabine			X	X		X*	X*					*Days 1 and 8 of each cycle for up to 6 cycles (minimum of 4 cycles) in the absence of progression or per institutional standards. Section 6.1
Administer carboplatin			X*			X*						*Day 1 (or 2) for up to 6 cycles (minimum of 4 cycles) in the absence of progression or per institutional standards. Section 6.1
Distribute reminder cards			X	X	X	X	X*					*Only participants scheduled to receive chemotherapy. Section 8.1.4

Table 4: Schedule of Activities (Continued)

Visit Day (Range)	Prescreening	Screening	Treatment					Post-Treatment				Notes
			Cycle 1			Cycle 2+		EOT	Safety Follow-Up	Post-Treatment Follow-Up	Survival Follow-Up	
		Days -35 to -1	Day 1 (± 3 d)	Day 8 (± 3 d)	Day 15 (± 3 d)	Day 1 (± 3 d)	Day 8 (± 3 d)	At Treatment Discon	30 d (± 5 d)	Same Disease Assessment (± 7 d)	Every 12 Weeks (± 14 d)	
Safety Assessments												
AE assessments*		X	X	X	X	X	X**	X	X	X		*Body systems with symptoms should be physically examined. **Only participants scheduled to receive chemotherapy. Section 8.5.1
Full physical examination		X				X*			X	X*		*Targeted examination. Section 8.5.2
Vital signs/body weight/height		X*	X	X	X	X	X**	X	X			*Height at screening only. **Only participants scheduled to receive chemotherapy. Section 8.5.3
12-lead ECG		X				X*		X	X			*Prior to receipt of study drugs on C2D1 and C4D1 and every 3 cycles thereafter (ie, C7, C10, C13, etc). Section 8.5.4
Slit lamp, visual acuity, funduscopy with digital imaging and optical coherence tomography		X				X*		X				*Performed every 3 cycles (± 7 days) starting with Cycle 3 and/or as clinically indicated. Treatment Groups A and B only. Section 8.5.5

Table 4: Schedule of Activities (Continued)

Visit Day (Range)	Prescreening	Screening	Treatment					Post-Treatment				Notes
			Cycle 1			Cycle 2+		EOT	Safety Follow-Up	Post-Treatment Follow-Up	Survival Follow-Up	
		Days -35 to -1	Day 1 (± 3 d)	Day 8 (± 3 d)	Day 15 (± 3 d)	Day 1 (± 3 d)	Day 8 (± 3 d)	At Treatment Discon	30 d (± 5 d)	Same Disease Assessment (± 7 d)	Every 12 Weeks (± 14 d)	
Efficacy Assessments												
CT of the chest, CT or MRI of the abdomen, and pelvis.*		X				X**		X		X**		*The same modality should be used for all scans. **Q9W (± 7 days) from date of randomization starting at the end of Cycle 3 through Week 54 and then Q12W (± 7 days; ie, Week 66, Week 78, etc) until EOT (if applicable). Follow same schedule if treatment is discontinued for reason other than disease progression. Sections 8.2 and 8.10.2
Bone scan and brain imaging		X*				X**		X**		X**		* Required at baseline within 35 days prior to randomization if participant has clinical symptoms of bone or brain metastases. **If positive at baseline, follow same schedule as CT/MRI. During follow-up, can be done per SOC. Follow same schedule if treatment is discontinued for reason other than disease progression. Section 8.2.1 and 8.10.2
ECOG		X	X			X		X	X	X		Section 8.2.3
Survival											X	Section 8.10.3
Quality of Life Assessments												
EORTC QLQ-C30 and EQ-5D-5L		X				X*			X			*Every 3 cycles on Day 1 starting on Cycle 4. Section 8.3

Table 4: Schedule of Activities (Continued)

Visit Day (Range)	Prescreening	Screening	Treatment					Post-Treatment				Notes
			Cycle 1			Cycle 2+		EOT	Safety Follow-Up	Post-Treatment Follow-Up	Survival Follow-Up	
		Days -35 to -1	Day 1 (± 3 d)	Day 8 (± 3 d)	Day 15 (± 3 d)	Day 1 (± 3 d)	Day 8 (± 3 d)	At Treatment Discon	30 d (± 5 d)	Same Disease Assessment (± 7 d)	Every 12 Weeks (± 14 d)	
Laboratory Assessments												
Blood chemistries		X	X	X	X	X*	X**	X	X			*Participants who develop hyperphosphatemia during Cycle 1 must continue to be monitored during Cycle 2 (serum phosphate only). **Only participants scheduled to receive chemotherapy. Section 8.5.6
CBC with differential		X	X	X	X	X*	X**	X	X			*Must be assessed prior to each study treatment administration for each treatment group. **Only participants scheduled to receive chemotherapy. Section 8.5.6
Coagulation		X				X*		X	X			*Every 2 cycles starting at Cycle 2. Section 8.5.6
TSH (T3, T4 if abnormal TSH)		X				X*		X	X			*Every 2 cycles starting at Cycle 2. Section 8.5.6
Parathyroid (endocrine) for pemigatinib participants only		X				X*		X				*Every 3 cycles on Day 1 starting with Cycle 3. Section 8.5.6
Pregnancy testing		X*				X**		X*				*Serum only. At screening should be performed a maximum of 7 days before administration of study drug. **Urine or serum. Positive urine test must be confirmed with a serum test. Section 8.5.6.1
Serology		X										Section 8.5.6.2
Urinalysis		X				X		X				Section 8.5.6

2. INTRODUCTION

2.1. Background

Pemigatinib is an inhibitor of the FGFR family of receptor tyrosine kinases that is proposed for the treatment of UC. Aberrant signaling through FGFR resulting from gene amplification or mutation, chromosomal translocation, and ligand-dependent activation of the receptors has been demonstrated in multiple types of human cancers. Fibroblast growth factor receptor signaling contributes to the development of malignancies by promoting tumor cell proliferation, survival, migration, and angiogenesis. In this study, the sponsor is proposing to study pemigatinib monotherapy or pemigatinib in combination with pembrolizumab for the treatment of metastatic or unresectable UC in the first-line setting in participants who are cisplatin-ineligible and whose tumors have an FGFR3 mutation or rearrangement as a monotherapy or in combination with pembrolizumab. Refer to the IB for additional background information on pemigatinib.

2.1.1. Fibroblast Growth Factor Receptor Inhibition in Oncology

The mammalian FGFR family is composed of 4 highly conserved receptors (FGFR1, FGFR2, FGFR3, and FGFR4) that have an extracellular ligand-binding domain, a single transmembrane domain, and an intracellular tyrosine kinase domain. Eighteen FGF ligands, divided into canonical and hormonal FGFs, bind to FGFRs, leading to receptor dimerization, activation of the kinase domain, and transphosphorylation of the receptors (Eswarakumar et al 2005). Subsequent signal transduction occurs through phosphorylation of substrate proteins, such as FGFR substrate 2, which leads to activation of the RAS mitogen–activated protein kinase and phosphoinositide 3-kinase–protein kinase B pathways and of the phospholipase Cγ that activates the protein kinase C pathway. In some cellular context, signal transducer and activator of transcription proteins are also activated by FGFRs. Signaling through the FGF-FGFR pathway is tightly controlled through feedback regulation. Mitogen activated protein kinase phosphatases and Sprouty proteins are upregulated upon FGFR stimulation and antagonize FGF-dependent activation of extracellular signal-regulated kinases. In many cases, FGFR pathway activation promotes cell proliferation, survival, and migration; however, cellular context plays an important role, and in certain tissues, FGFR signaling results in growth arrest and cellular differentiation (Dailey et al 2005).

In adults, FGF-FGFR signaling is involved in angiogenesis during wound healing. The hormonal FGF ligands contribute to regulation of metabolic pathways involving lipid, glucose, phosphate, and vitamin D (Itoh 2010). Genetic defects in the FGF23-signaling pathway lead to disordered phosphate metabolism: loss of function mutations in FGF23 or its signaling results in retention of phosphate and tissue mineralizing, while gain of function mutations in the FGF23 pathway manifests as hypophosphatemic Rickets syndrome (Farrow and White 2010).

Strong genetic and functional evidence supports that dysregulation of FGFR can lead to the establishment and progression of cancer. Genetic alterations in FGFR1, FGFR2, and FGFR3 have been described in many tumor types (Knights and Cook 2010, Turner and Grose 2010). These include activating mutations, translocations, and gene amplification resulting in ligand independent constitutive activation of the receptors or aberrant ligand-dependent signaling through FGFRs. Mutations that lead to activation of FGFR3 occur in 50% to 70% of low-grade superficial bladder cancer (Knowles and Hurst 2015). The most prevalent FGFR3 mutations are Ser to Cys changes in the extracellular domain that promote autodimerization and ligand independent activation of signaling (di Martino et al 2009). These mutations match germline mutations in FGFR3 that are described in congenital skeletal dysplasias (Greulich and Pollock 2011). In high-grade muscle invasive urothelial bladder cancer, activating mutations of FGFR3 occur in 11% of cases and increases in copy number in an additional 3% (Cancer Genome Atlas Research Network 2014).

Translocations involving FGFR3 have also been described in bladder cancer including the intrachromosomal rearrangement generating the FGFR3—transforming acidic coiled-coil–containing protein 3 fusion (Williams et al 2013). Fibroblast growth factor receptor 3 is a target of the t(4;14) translocation that affects approximately 15% of multiple myeloma patients (Chesi et al 1997). This balanced translocation adjoins the FGFR3 coding sequence to the strong IgH enhancer elements in plasma cells and drives high levels of FGFR3 expression. Finally, recent large scale tumor sequencing efforts have uncovered multiple, but rare, transforming alterations in FGFR genes across a number of tumor histologies (Liao et al 2013, Wu et al 2013). In addition to these examples where FGFR dysregulation is a primary driver of tumorigenesis, FGFR has been reported to be a mechanism for resistance to hormone therapy in breast cancer and to EGFR inhibitors in non–small cell lung cancer by providing an alternative survival pathway (Turner et al 2010, Ware et al 2010).

A substantial body of evidence supports that a genetically activated FGFR pathway sensitizes FGFR-altered cancer cells to knockdown or inhibition of these receptors (Kunii et al 2008, Lamont et al 2011, Qing et al 2009, Weiss et al 2010). A large screen of more than 500 tumor cell lines with a selective FGFR inhibitor demonstrated that only a small percentage (5.9%) of all cells are sensitive to FGFR inhibition, and growth-suppressed cell lines were highly enriched for FGFR alterations (Guagnano et al 2012). These results demonstrate that FGFR inhibitors are active in a targeted manner against cancers with activated FGFR pathway. An implication of these data is that selection based on molecular-, genetic-, or protein-based diagnostic tests for specific FGFR alterations in tumors may be important for identifying patients most likely to benefit from an FGFR inhibitor.

Results from early clinical studies of selective FGFR inhibitors, including pemigatinib, have shown a tolerable safety profile for the class and preliminary signs of clinical benefit in participants with FGF/FGFR alterations (Seikfer et al 2019).

2.1.2. Overview and Treatment of Urothelial Carcinoma

Globally, bladder cancer was the 11th most common cancer based on 2018 estimates, accounting for approximately 549,000 new cases and 200,000 deaths (Global Cancer Observatory 2019). Urothelial carcinoma is the predominant histologic type of bladder cancer in the United States and Western Europe, where it accounts for approximately 90 percent of bladder cancers. Also known as TCC, bladder cancer describes a range of tumors arising from the urothelial endothelium and includes the bladder, renal pelvis, ureter, and urethra. The majority of patients with TCC develop localized, non-invasive disease. However, approximately 25% of patients will have muscle-invasive disease and either present with or later develop metastases (von der Maase et al 2005).

A number of clinical and molecular characteristics have been shown to correlate with survival. Poor performance status and the presence of visceral (ie, pulmonary, liver, bone) metastases correlate with shortened survival in clinical studies. This was illustrated by an intergroup study that compared cisplatin alone with methotrexate, vinblastine, doxorubicin, and cisplatin in patients with metastatic disease (Loehrer et al 1992). The presence of bone or liver metastases and poor performance status were most predictive of poor response and survival. The presence of these unfavorable features was associated with median survival of 4 months, compared with 18 months in those participants without these features. No participants with liver or bone metastases and only 1 participant with a Karnofsky performance status < 80% survived beyond 6 years (Saxman et al 1997). Several subsequent reports confirmed the relationship between shortened survival and poor performance status or the presence of visceral metastases. In the second-line setting (patients with platinum-refractory TCC), multivariate analysis identified ECOG performance status > 1, hemoglobin level less than 10 g/dL, and the presence of liver metastasis as the main adverse prognostic factors for OS (Bellmunt et al 2010). These factors illustrate that since bladder cancer is more often a disease of the elderly and infirm, many patients cannot benefit from modern cisplatin-based chemotherapy regimens, and other treatment options are needed for this large population of patients.

Based on NCCN guidelines (NCCN 2019), the current SOC for the initial treatment of metastatic, locally advanced bladder cancer is systemic chemotherapy with or without a platinum-containing regimen. The median survival with combination chemotherapy is approximately 14 to 15 months (von der Maase et al 2005). While this is superior to the estimated 6-month survival with metastatic disease prior to the development of modern chemotherapy regimens, the 5-year survival rate is approximately 15% with contemporary chemotherapy regimens. Second-line chemotherapy, usually as a single agent, has had only a limited role, with a modest increase in median 2-month OS), which was at best 6.9 months as compared with best supportive care (Bellmunt et al 2009).

NCCN guidelines for recommendation of chemotherapy also highlight specific medical comorbidities, such as performance status along with cardiac function and renal dysfunction, in consideration of the appropriate treatment. A Phase 3 study comparing gemcitabine/carboplatin with methotrexate/carboplatin/vinblastine in cisplatin-ineligible participants demonstrated a median survival of only 8 to 9 months with both regimens (De Santis et al 2012). Notably, those with both poor renal function and poor performance status fared especially poorly with combination chemotherapy in this study. Thus, there remains a significant unmet medical need for well-tolerated active therapies in this population.

Treatment for bladder cancer has evolved over time to encompass not only traditional chemotherapy, but has been particularly impacted by the use of immunotherapy (Bellmunt et al 2017). The PD-1/PD-L1 inhibitors such as atezolizumab, pembrolizumab, nivolumab, and durvalumab have demonstrated activity and are currently being evaluated in randomized clinical studies in patients with UC. These include studies as first- and second-line therapy and as well as in the adjuvant setting. Pembrolizumab, atezolizumab, nivolumab, durvalumab, and avelumab recently received accelerated approval from the FDA for the treatment of advanced UC that has progressed during or after previous platinum-based chemotherapy. In addition, atezolizumab received accelerated approval from the FDA for the treatment of advanced UC who were not eligible for cisplatin-containing chemotherapy.

On 18 MAY 2017, the FDA granted accelerated approval to pembrolizumab for patients with locally advanced or metastatic UC who were not eligible for cisplatin-containing chemotherapy, based on data from a multicenter, open-label, single-arm study, KEYNOTE-052 (NCT02335424), investigating pembrolizumab in 370 participants. On that same day, the FDA granted regular approval to pembrolizumab for patients with locally advanced or metastatic UC with disease progression on or after platinum-containing chemotherapy. Approval was based on data from a multicenter, randomized, active-controlled study, KEYNOTE-045. Participants were randomized to receive either pembrolizumab 200 mg Q3W IV (N = 270) or the investigator's choice of paclitaxel, docetaxel, or vinflunine (Bellmunt et al 2017, Keytruda® 2019).

In addition to pembrolizumab, atezolizumab was also granted an accelerated approval (18 MAY 2016) for the treatment of adults with locally advanced or metastatic UC who were not eligible for cisplatin-containing chemotherapy based on data from IMvigor210, which was a single-arm, open-label study that included 310 participants. Patients received 1200 mg of atezolizumab Q3W IV (Balar et al 2017b, Tecentriq® 2019).

Subsequent to the accelerated approvals of pembrolizumab and atezolizumab, on 18 MAY 2018, the FDA initiated guidance on decreased survival associated with the use of pembrolizumab or atezolizumab as monotherapy compared to platinum-based chemotherapy in clinical studies to treat patients with metastatic UC who have not received prior therapy and who have low expression of the protein PD-L1 (FDA 2018b). For these patients, systemic chemotherapy continues to be the recommended treatment option. Based on the revised indication, Pembrolizumab is indicated for the treatment of patients with locally advanced or metastatic UC who are not eligible for cisplatin-containing therapy and whose tumors express PD-L1 (CPS $\geq$ 10) or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status. More effective and less toxic treatments are greatly needed in this patient population, and immunotherapy offers additional options for patients progressing after their initial systemic therapy.

2.2. Study Rationale

Pemigatinib is a potent selective inhibitor of FGFR1, FGFR2, and FGFR3. This compound, as monotherapy or in combination with pembrolizumab, is proposed for the first-line treatment of participants with metastatic or unresectable UC with FGFR3 mutations or rearrangements who are not eligible to receive platinum containing regimens.

2.2.1. Scientific Rationale for Study Design

The planned study will evaluate the safety of pemigatinib as a monotherapy or in combination with pembrolizumab as a first-line treatment in participants with metastatic or unresectable UC with FGFR3 mutations or rearrangements. Current practice guidelines (NCCN 2019) for metastatic or unresectable bladder cancer indicate that patients who are not eligible to receive cisplatin as the preferred regimen in combination with gemcitabine, should instead receive the combination of carboplatin and gemcitabine. In addition, patients whose tumors express PD-L1, or who are not eligible for any platinum-containing chemotherapy regardless of PD-L1, may also receive approved checkpoint inhibitors (ie, pembrolizumab or atezolizumab). Based on available data from a large Phase 2/3 study conducted in this population, the median PFS in a gemcitabine and carboplatin group is expected to be 5.8 months (De Santis et al 2012).

Pembrolizumab was approved based on efficacy results observed in KEYNOTE-052. An ORR of 29% was observed in all participants with 21% and 47% ORR in those with PD-L1 CPS < 10 and ≥ 10 respectively. Both CRs and PRs were also higher in the PD-L1 CPS ≥ 10 group (15% and 32%, respectively) as compared with those in all participants and PD-L1 CPS < 10 (Keytruda 2019). Based on data from study KEYNOTE-052, median PFS in first-line treatment of cisplatin-ineligible patients, regardless of tumor CPS score, with pembrolizumab was 2.3 months, and median OS was 11.5 months. In participants whose tumors expressed CPS ≥ 10, the median PFS was 4.9 months, and the median OS was 18.5 months.

Preliminary data from the ongoing Phase 2 study (INCB 54828-201) with pemigatinib as monotherapy in second-line or greater treatment have shown clinical activity and tolerable safety in 159 UC participants with FGFR alterations (more pronounced in FGFR3 mutations or translocations) has shown an ORR of 21.3% and a median PFS of 4.1 months. As of a data cutoff date of 25 NOV 2018, the safety and tolerability of pemigatinib administered alone or in combination with another chemotherapy/immunotherapy was being evaluated in 5 ongoing clinical studies in participants with advanced malignancies. Participants with metastatic or unresectable UC had received pemigatinib 13.5 mg QD on a 2-weeks-on/1-week-off therapy schedule or on a continuous schedule; 99 participants with FGFR3 mutations or fusions received the interval schedule, and 7 participants with FGFR3 mutations or fusions received the continuous schedule. Based on preliminary unaudited data from these ongoing studies, the most frequently occurring TEAEs (ie, incidence > 20%) were (in descending order of frequency) hyperphosphatemia, diarrhea, alopecia, fatigue, dry mouth, stomatitis, constipation, dysgeusia, nausea, decreased appetite, and anemia.

The patients with FGFR alterations, specifically FGFR3 mutations, are expected to be low expressors of PD-L1 (Sweis et al 2016), [redacted] Combination of FGFR pathway inhibitor with PD-1 and PD-L1 inhibitors may provide additional benefit to these patients.

Pembrolizumab has been studied in combination with pemigatinib in INCB 54828-101. As of a data cutoff date 25 NOV 2018, 23 participants have been treated with this combination with pemigatinib 9 mg and 13.5 mg with both the intermittent and the continuous dosing regimens. Of the 23 participants treated across various tumor types, 3 participants had a confirmed diagnosis of UC with FGF/FGFR alteration with a best response of PR in 2 out the 3 participants, one of whom was still ongoing at 21 months of treatment.

The proposed study is an open-label, multicenter, randomized, and active-controlled study of pemigatinib in combination with pembrolizumab or pemigatinib alone versus SOC for cisplatin-ineligible patients who have required the FGFR3 mutation or rearrangement. Stratification factors of carboplatin eligibility, PD-L1 CPS, and metastatic disease beyond the lymph node(s) will be used to ensure appropriate distribution of similar populations across treatment groups. PD-L1 CPS was selected due to the impact on survival in participants treated with checkpoint inhibitors (FDA 2018b). Other stratification factors may contribute to a complicated disease state in this difficult patient population.

Due to the clear pharmacodynamic impact of the study drug (pemigatinib) on the participants (elevation of serum phosphate/hyperphosphatemia), this will be an open-label study, and all participants will know which treatment they will receive after randomization.

2.2.2. Justification for Dose and Schedule

2.2.2.1. Pemigatinib

Pemigatinib will be administered at 13.5 mg QD each cycle until PD. Each cycle is 21 days. This dose and dosing schedule was selected based on clinical and safety data from the INCB 54828-101 study, where the continuous dosing regimen has been tested in 15 participants at 9, 13.5, or 20 mg QD continuous administration, respectively. In Study INCB 54828-101, the emerging safety data demonstrated that tolerability of the continuous dosing regimen of pemigatinib was comparable to that of intermittent dosing (refer to the IB).

The hypothesis with a targeted therapy is that continued inhibition of the aberrant receptor may increase the potential for benefit from the treatment. Therefore, administering pemigatinib continuously will allow that consistent inhibition of the aberrant FGFR receptor in this population. Continuous dosing would still allow for dose holds for safety reasons with criteria and procedures for dose interruptions and adjustments clearly outlined in the Protocol.

In Study INCB54828-201 (as described above), 159 participants in total with metastatic or surgically unresectable UC had received pemigatinib 13.5 mg QD on an intermittent or continuous schedule. Ninety-nine participants with FGFR3 mutations or fusions received pemigatinib on the intermittent schedule, whereas 7 participants received treatment on the continuous schedule. Both schedules appeared tolerable; efficacy data from the continuous schedule is not available yet (refer to the IB).

No change in PK parameters is expected for continuous administration, as steady-state concentrations are expected to be reached at Day 4 based on a half-life of 20.2 hours. However, at the 13.5 mg dose, the continuous dose regimen increased the average per cycle exposure of pemigatinib by 50%.

Hyperphosphatemia is an expected on-target pharmacological effect of FGFR inhibition. The magnitude and frequency of hyperphosphatemia (defined as any postbaseline phosphate level exceeding 5.5 mg/dL), which is managed with a low-phosphate diet and introduction of phosphate binders, appears to be dose-dependent as demonstrated in Parts 1 and 2 of Study INCB 54828-101 (refer to the IB). The majority of participants treated at 13.5 mg experienced hyperphosphatemia.

Although hyperphosphatemia has been observed in the majority of participants treated with pemigatinib, some participants do not achieve hyperphosphatemia where pharmacological concentrations of pemigatinib in these participants may be lower.

In a population E_{max} model, those participants treated with pemigatinib 13.5 mg who did not develop hyperphosphatemia, the AUC with pemigatinib 18 mg was estimated using a linear exposure relationship. The simulation suggested that the serum phosphate may increase above 5.5 mg/dL after treatment with pemigatinib 18 mg for the participants treated with pemigatinib 13.5 mg who did not develop hyperphosphatemia.

Any participant who does not reach the target serum phosphate level of > 5.5 mg/dL at any time during Cycle 1 and who is compliant with taking study drug and does not experience an ongoing Grade 2 or higher treatment-related AEs will increase the daily dose to 18 mg QD starting at Cycle 2 Day 1.

Refer to the IB for more information.

Dose modifications for tolerability issues are noted in Section 6.6.

2.2.2.2. Pembrolizumab

The planned dose of pembrolizumab for this study is 200 mg Q3W up to 35 cycles. Based on the totality of data generated in the KEYTRUDA development program, 200 mg Q3W is the appropriate dose of pembrolizumab for adults across all indications and regardless of tumor type. As outlined below, this dose is justified by:

- Clinical data from 8 randomized studies demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg Q2W.
- Clinical data showing meaningful improvement in benefit-risk including OS at 200 mg Q3W across multiple indications.
- Pharmacology data showing full target saturation in both systemic circulation (inferred from PK data) and tumor (inferred from PBPK analysis) at 200 mg Q3W.

Among the 8 randomized dose-comparison studies, a total of 2262 participants were enrolled with melanoma and NSCLC, covering different disease settings (ie, treatment naive, previously treated, PD-L1 enriched, and all-comers) and different treatment settings (monotherapy and in combination with chemotherapy). Five studies compared 2 mg/kg Q3W versus 10 mg/kg Q2W (KEYNOTE-001 B2, -001 D, -002, -010, and -021), and 3 studies compared 10 mg/kg Q3W versus 10 mg/kg Q2W (KEYNOTE-001 B3, -001 F2, and -006). All of these studies demonstrated flat dose- and exposure-response relationships across the doses studied representing an approximate 5- to 7.5-fold difference in exposure. The 2 mg/kg (or 200 mg fixed dose) Q3W provided similar responses to the highest doses studied. Subsequently, flat dose/exposure-response relationships were also observed in other tumor types including head and neck cancer, bladder cancer, gastric cancer and classical Hodgkin lymphoma, confirming 200 mg Q3W as the appropriate dose independent of the tumor type. These findings are consistent with the mechanism of action of pembrolizumab, which acts by interaction with immune cells, and not via direct binding to cancer cells.

Additionally, pharmacology data clearly show target saturation at 200 mg Q3W. First, PK data in KEYNOTE-001 evaluating target-mediated drug disposition conclusively demonstrated saturation of PD-1 in systemic circulation at doses much lower than 200 mg Q3W. Secondly, a PBPK analysis was conducted to predict tumor PD-1 saturation over a wide range of tumor penetration and PD-1 expression. This evaluation concluded that pembrolizumab at 200 mg Q3W achieves full PD-1 saturation in both blood and tumor.

Finally, population PK analysis of pembrolizumab, which characterized the influence of body weight and other participant covariates on exposure, has shown that the fixed-dosing provides similar control of PK variability as weight based dosing, with considerable overlap in the distribution of exposures from the 200 mg Q3W fixed dose and 2 mg/kg Q3W dose. Supported by these PK characteristics, and given that fixed-dose has advantages of reduced dosing complexity and reduced potential of dosing errors, the 200 mg Q3W fixed-dose was selected for evaluation across all pembrolizumab protocols.

A pembrolizumab monotherapy arm is added in this study in order to establish the magnitude of benefit from pemigatinib in the pembrolizumab plus pemigatinib combination regimen.

Dose modifications for tolerability issues are noted in Section 6.6.

2.2.2.3. Gemcitabine and Carboplatin

Cisplatin-based combination chemotherapy is standard first-line treatment for patients with advanced or metastatic bladder cancer based on NCCN guidelines (NCCN 2019) and EAU guidelines (EAU 2019). However, cisplatin ineligibility is common in bladder cancer patients because of renal dysfunction (CrCl < 60 mL/min), poor performance status (ECOG performance status ≥ 2), New York Heart Association Class III heart failure, or Grade 2 or higher neuropathy or hearing loss (Galsky 2015). As a result, the guidelines recommend alternative treatments that include carboplatin plus gemcitabine or pembrolizumab monotherapy.

Carboplatin is often substituted for cisplatin in cisplatin-ineligible patients, but it is associated with inferior outcomes, as demonstrated in a meta-analysis of randomized Phase 2 studies (Galsky et al 2012). The meta-analysis showed that carboplatin-based chemotherapy had an ORR of 28% to 56% versus 36% to 71% in cisplatin-based chemotherapy. In addition, EORTC Study 30986 showed that carboplatin plus gemcitabine resulted in a median PFS of 5.8 months and median OS of 9.3 months and was superior to methotrexate/carboplatin/vinblastine chemotherapy regimen (De Santis et al 2012).

Gemcitabine and carboplatin will be administered based on the treatment regimen noted in the NCCN guidelines and EORTC Study 30986 (De Santis et al 2009). Participants will receive gemcitabine 1000 mg/m^2 IV over 30 minutes on Days 1 and 8, followed by carboplatin on Day 1 or 2. Each cycle is 3 weeks. Treatment will continue for a minimum of 4 cycles with up to 6 cycles (or per institutional standards) until disease progression or intolerable toxicity. In case of CR, 2 more cycles may be given.

2.2.2.4. Combination of Pemigatinib and Pembrolizumab

Based on data published by Sweis et al (2016), the majority of the patients with FGFR alterations, specifically FGFR3 mutations, are expected to be low expressors of PD-L1. In study KEYNOTE-052, approximately 20% of participants whose tumors expressed PD-L1 CPS < 10 experienced response to pembrolizumab compared with 47% of participants whose tumors expressed PD-L1 CPS ≥ 10 (Vuky et al 2018). Additionally, it has been suggested that responses to immunotherapy vary by The Cancer Genome Atlas expression analysis; patients with UC have been classified into 4 subtypes (luminal cluster I, luminal cluster II, basal cluster III, and basal cluster IV). Among patients with luminal subtype I UC tumors, ORRs to PD-1 and PD-L1 inhibitors appear lower than those for patients with luminal subtype type II and basal subtype III tumors, corresponding with relatively lower expression of PD-1, PD-L1, and CTLA4 in luminal subtype I. FGFR3 genetic alterations are enriched in luminal subtype I UC, [redacted]. Combination of FGFR pathway inhibitor with PD-1 and PD-L1 inhibitors may provide additional benefit to these patients.

Pemigatinib will be administered at 13.5 mg QD PO continuously for a cycle until PD. Each cycle is 3 weeks. Pembrolizumab will be administered at 200 mg Q3W IV up to 35 cycles.

As of 25 NOV 2018, in Study INCB 54828-101, a total of 23 participants received pemigatinib in combination with pembrolizumab (all doses and dose regimens combined) across multiple tumor types (including bladder). Participants received the prescribed dose of pembrolizumab with either 9 mg or 13.5 mg of pemigatinib at both the intermittent and continuous dose and schedule: 14 participants received the combination at the 13.5 mg intermittent dose, 3 participants received the combination at the 9 mg intermittent dose, and 6 participants received the combination at the continuous dose. All participants (100%) who were dosed in combination with pemigatinib and pembrolizumab had TEAEs. Dose reductions of pemigatinib occurred in 5 of the participants receiving the combination. Refer to the IB for more information. No dose-limiting toxicities were observed.

The most frequently reported TEAE in combination with pembrolizumab for the intermittent dosing schedule of pemigatinib was hyperphosphatemia (14 participants [82%]; serum phosphate > 5.5 mg/dL) and for the continuous dosing schedule of pemigatinib in combination with pembrolizumab, the most frequently reported TEAE was dry mouth (4 participants [67%]). Other frequently reported TEAEs for intermittent dosing schedule included decreased appetite (6 participants at 13.5 mg [64%], anemia (8 participants at 13.5 mg [57%]), and diarrhea (7 participants at 13.5 mg [50%] and 1 participant at 9 mg [33%]). For continuous dosing pemigatinib (13.5 mg) plus pembrolizumab, additional TEAEs included dysgeusia (3 participants [50%]) and hyperphosphatemia (3 participants [50%]). Twenty participants (87%) across all doses and regimens had treatment-related AEs.

Thirteen participants (57%) had a Grade 3 event or higher across all doses and regimens in the combination. Serious AEs were reported in a total of 8 participants (35%) who received pemigatinib plus pembrolizumab (all doses and dose regimens combined). One participant (4%) had a TEAE with a fatal outcome (9 mg intermittent dosing; completed suicide). It was not considered related to study drug.

One participant (4%) discontinued treatment due to an AE (13.5 mg intermittent dosing plus pembrolizumab). One participant (4%) had a dose reduction of pemigatinib (13.5 mg continuous dosing) due to TEAE, and 11 participants (48%) had treatment interruptions due to a TEAE (across all doses and regimens). This safety data from Study INCB 54828-101 show that the continuous dosing regimen of pemigatinib at 13.5 mg in combination with pembrolizumab was tolerable.

No DDI is expected based on metabolic pathways of pembrolizumab and pemigatinib. Furthermore, PK parameters of pemigatinib are not different when it was given as monotherapy and in combination with pembrolizumab (see Table 6; refer to the IB for more information).

Table 6: Pharmacokinetic Parameters of Pemigatinib Monotherapy and in Combination With Pembrolizumab

Dose	N	C_{max} (nmol/L)	t_{max} (h)[a]	C_{min} (nmol/L)	CL_{ss}/F (L/h)	V_z/F (L)	$AUC_{0-\tau}$ (h·nmol/L)	$t_{½}$ (h)
Pemi 13.5 mg QD	53	262 ± 150 (228)	1 (0.5, 6)	68.4 ± 59.7 (51.8)	12.0 ± 5.77 (10.6)	320 ± 200 (273)	2980 ± 1910 (2600)	20.2 ± 12.9 (17.5)
Pemi 13.5 mg QD + pembro	15	258 ± 115 (232)	1 (0.5, 8)	59.8 ± 35.4 (48.1)	12.3 ± 6.32 (11.0)	322 ± 150 (296)	2740 ± 1110 (2510)	18.3 ± 8.87 (16.2)

Pemi = pemigatinib; pembro = pembrolizumab.
[a] Values are presented in the format of "Mean ± SD (Geometric Mean) except t_{max}, which is presented in the format of "Median (Min, Max)."

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected AEs of pemigatinib, pembrolizumab, gemcitabine and carboplatin may be found in the IB or package insert for each compound.

2.3.1. Benefit/Risk of Pemigatinib

Pemigatinib is under investigation for the treatment of patients with advanced or metastatic UC. In addition to treatment with immunotherapy, there is an unmet need for safe and efficacious treatments with targeted agents as well as immunotherapies whose tumors express FGFR3 regardless of PD-L1 status. The most frequently reported TEAE in Study INCB 54828-101 was hyperphosphatemia (serum phosphate > 5.5 mg/dL), an on-target pharmacological effect of FGFR inhibition, in 69.8% of participants on pemigatinib monotherapy (all doses and dose regimens combined). Likewise, hyperphosphatemia was among the most frequently occurring TEAEs in Studies INCB 54828 102, INCB 54828-201, INCB 54828-202, and INCB 54828-203, and it was also among the most frequently occurring events for each of the combination therapy groups. Other frequently occurring TEAEs (> 20%) in participants who received at least 1 dose of study drug included diarrhea, alopecia, fatigue, dry mouth, stomatitis, constipation, dysgeusia, nausea, decreased appetite, and anemia. Current data in the Phase 2 study INCB 54828-201 (NCT02872714) with pemigatinib as a monotherapy suggest that targeted inhibition of FGFR may provide therapeutic benefit and the benefit/risk assessment for participants in this study is considered to be favorable (Necchi et al 2018).

2.3.2. Benefit/Risk of Pembrolizumab

Pembrolizumab has been approved for first-line treatment of patients with locally advanced or metastatic bladder cancer who are not eligible for cisplatin-containing therapy and whose tumors express PD-L1 (CPS ≥10), or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status. It is also approved for the treatment of patients with locally advanced or metastatic UC who have disease progression during or following any platinum-containing chemotherapy, or within 12 months of neo-adjuvant or adjuvant treatment. There is an unmet medical need for safe and efficacious first-line therapy in patients with locally advanced or metastatic UC who are ineligible for any platinum-containing chemotherapy and harbor a FGFR3 mutation/rearrangement. As such, there is a continual need for novel therapies in this setting. [redacted] Additional details regarding specific benefits and risks for participants in this study are in the IB, product inserts for each compound, and informed consent documents.

2.3.3. Benefit/Risk of Combination of Pemigatinib and Pembrolizumab

The recommended Phase 2 dose of pemigatinib in monotherapy and in combination with pembrolizumab has been selected based on the INCB 54828-101 study, which is the first clinical study being conducted with pemigatinib. Doses ranging from 1 to 20 mg QD have been evaluated to date, along with different combination treatments with pemigatinib and no compounding effects of AEs have been observed in the combinations. Pharmacokinetics and pharmacodynamics have been evaluated in each of these cohorts to assess the extent of target inhibition, which in turn was used along with the safety data to select a dose for Phase 2. The dose of 13.5 mg continuous dosing has been selected for this study. More detailed information about the known and expected risks and reasonably expected AEs of pemigatinib is explained in the IB.

3. OBJECTIVES AND ENDPOINTS

The objectives and endpoints apply to a study population of male or female participants at least 18 years of age with a histologically confirmed diagnosis of metastatic or unresectable UC, whose tumors have an FGFR3 mutation or rearrangement and who are medically ineligible to receive cisplatin-based chemotherapy and have not received prior treatment.

This study will be considered to have met its primary objective if pembrolizumab plus pemigatinib or pemigatinib alone is superior to SOC for the primary endpoint.

Table 7 presents the objectives and endpoints.

Table 7: Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate and compare PFS in participants treated with pemigatinib in combination with pembrolizumab (Treatment Group A) and pemigatinib alone (Treatment Group B) versus SOC (Treatment Group C). Differences in PFS will be evaluated hierarchically, and the comparison between pemigatinib in combination with pembrolizumab (Treatment Group A) and SOC (Treatment Group C) will be evaluated first, and if significant difference is detected, a second comparison will be made in PFS between pemigatinib alone (Treatment Group B) and SOC (Treatment Group C). Hypothesis: The combination of pembrolizumab plus pemigatinib has superior PFS as compared with SOC. Contribution of pemigatinib alone to combination will be assessed by comparing Treatment Groups A and C and Treatment Groups B and C.	Progression-free survival, defined as the time from randomization date until the date of disease progression (as measured by BICR per RECIST v1.1) or death due to any cause, whichever occurs first.
Secondary	
To evaluate and compare the efficacy of the 3 treatment groups with respect to OS.	Overall survival, defined the time from the date of randomization until death due to any cause.
To evaluate and compare the efficacy of the 3 treatment groups with respect to overall tumor response and DOR.	• Objective response rate, defined as the proportion of participants with best overall response of CR or PR determined by BICR per RECIST v1.1. • Duration of response, defined as the time from the date of the first assessment of CR or PR until the date of the first disease progression per BICR per RECIST v1.1 or death, whichever occurs first.
To evaluate the safety of the 3 treatment groups.	Safety and tolerability of pemigatinib with or without pembrolizumab and SOC will be assessed by evaluating the frequency and severity of AEs, physical examination findings, vital sign changes, and clinical laboratory assessments.
To evaluate changes from baseline in patient-reported outcomes.	Patient-reported outcome scales (ie, EORTC QLQ-C30, EQ-5D-5L) at each timepoint and change from baseline to each timepoint.

Table 7: Objectives and Endpoints (Continued)

[redacted]

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 2, open-label, randomized and active-controlled study of pemigatinib plus pembrolizumab or pemigatinib alone versus the SOC for participants with metastatic or unresectable UC not eligible to receive cisplatin and harboring FGFR3 mutation or rearrangement and who have not received prior treatment. Randomization will occur after the participant has completed screening. Participants will be stratified by eligible to receive carboplatin versus not eligible to receive carboplatin, PD-L1 CPS ≥ 10 versus CPS < 10, and LN-only disease versus other metastatic disease. This is an event-driven clinical study designed to ensure power to detect success of the primary endpoint of PFS. A total of 210 PFS events in the combined treatment groups of pemigatinib plus pembrolizumab and SOC are needed to support the primary objective, where PFS is defined as the time from randomization date until the date of disease progression or death due to any cause, whichever occurs first.

Participants who are screened and found to have the FGFR3 mutation or rearrangement) will be randomized 1:1:1 into 1 of the 3 treatment groups indicated in Table 8.

Table 8: Treatment Groups for Randomization

Treatment Group	Regimen
A	Pemigatinib 13.5 mg QD PO[a] until PD + pembrolizumab 200 mg Q3W IV up to 35 cycles (approximately 2 years) or PD, whichever occurs first
B	Pemigatinib 13.5 mg QD PO[a] until PD
C	One of 2 SOC treatment options: 1. Gemcitabine 1000 mg/m2 Q3W IV on Days 1 and 8 + carboplatin AUC 5 (or AUC 4.5 if required per local guidelines) Q3W on Day 1 or 2 for 4 to 6 cycles. (Participants whose tumors express PD-L1 CPS < 10 who are eligible to receive carboplatin.) OR 2. Pembrolizumab 200 mg Q3W IV up to 35 cycles (approximately 2 years). (Participants whose tumors express PD-L1 CPS ≥ 10 or participants who are not considered eligible to receive any platinum-containing chemotherapy regardless of PD-L1 expression status [only applicable in regions where pembrolizumab is used as standard of care for participants who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status].)

[a] Participants not reaching the target serum phosphate during Cycle 1 will increase the daily dose to 18 mg starting at Cycle 2 as described in Section 6.6.2.1.

Participant eligibility will be based on genomic testing for FGFR3. Participants can be randomized based on local results, if available, and results will be retrospectively confirmed by the sponsor's central laboratory. Previous therapies may include only neo-adjuvant or adjuvant treatment with platinum-containing chemotherapy if completed at least 12 months before the start of treatment for this study; otherwise, participants should be treatment naive before screening and according criteria outlined in Section 5.

Treatment will start on Cycle 1 Day 1. Participants will undergo regular safety assessments during treatment, as well as regular efficacy assessments. Participants will be allowed to continue administration in 3-week cycles, as per protocol for each treatment, until disease progression per RECIST v1.1 as assessed by BICR or unacceptable toxicity is reported.

A futility analysis will be performed as described in Section 10.5.

See Figure 1 for the study design.

Full study drug administration information can be found in Section 6.

4.2. Overall Study Duration

The study begins when the first participant signs the ICF and enters into the screening period. The end of the study is defined as the date of the last scheduled procedure shown in the schedule of activities for the last participant in the study globally.

A participant is considered to have completed the study if he/she has completed all phases of the study including the last scheduled procedure shown in the schedule of activities (see Table 4), or the participant has died, and the date of death is available.

If approximately 210 PFS events have been reported, a database lock of the study may occur to allow the analysis of the study data. Any remaining participants may continue to receive study treatment and be seen by the investigator as per institutional guidelines or standard clinical practice. The investigator will be expected to monitor for AEs and report any SAEs, and pregnancies, as detailed in Section 9, and continue to follow procedures for drug accountability. The remaining participants are considered to be on study until a discontinuation criterion is met and written notification is provided to the sponsor.

4.3. Study Termination

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

The sponsor may terminate the study electively, if required by regulatory decision or upon advice of the DMC (see Section 10.6). If the study is terminated prematurely, the sponsor will notify the investigators/head of study site (Japan), the IRBs and IECs, and regulatory bodies of the decision and reason for termination of the study.

For Japan, the head of study sites will notify the investigators and the IRBs of the decision and reason for termination of the study.

5. STUDY POPULATION

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

5.1. Inclusion Criteria

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

1. Male or female participants aged 18 years and older at the time of signing the informed consent; a legally minor participant from Japan needs written parental or legal guardian's consent.
2. Histologically documented metastatic or unresectable UC; may include primary site from bladder, ureters, upper tract, renal pelvis, urethra, or urachus. Both transitional cell and mixed transitional cell histologies are allowed, provided urothelial component is ≥ 50%.

   Note: Participants with non-UC of the urinary tract are not allowed.
3. Have at least 1 measurable target lesion per RECIST v1.1 as assessed by the local site investigator/radiologist.

Eligibility for chemotherapy is defined as meeting either criterion #4 **OR** #5 as described below.
4. Cisplatin ineligibility, defined by the presence of one of the following criteria: a. Creatinine clearance of < 60 mL/min but ≥ 30 mL/min (measured by the Cockcroft-Gault formula or 24-hour urine). b. ECOG performance status 2 (within 7 days prior to randomization). c. ≥ Grade 2 audiometric hearing loss (25 db in 2 consecutive wave ranges; CTCAE v5.0). d. New York Heart Association Class III heart failure. e. ≥ Grade 2 peripheral neuropathy (CTCAE v5.0).
OR
5. Ineligibility to receive any platinum-based chemotherapy (ie, ineligible for cisplatin and carboplatin), defined as ECOG performance status 2 (within 7 days prior to randomization) AND at least one of the following: a. Documented visceral metastatic disease (due to poor prognosis and lack of benefit). b. Creatinine clearance of < 60 mL/min but ≥ 30 mL/min (measured by the Cockcroft-Gault formula or 24-hour urine). c. ≥ Grade 2 audiometric hearing loss (25 db in 2 consecutive wave ranges; CTCAE v5.0). d. ≥ Grade 2 peripheral neuropathy (CTCAE v5.0). e. Other reason, identified on the eCRF, for the participant being unable to receive carboplatin safely. Additional criteria for platinum ineligibility will be considered and allowed on a case-by-case basis, following consultation with the sponsor.
Note: The reason(s) for ineligibility for cisplatin or any platinum-based chemotherapy must be documented in the participant's medical record and on the eCRF. *Note:* Only applicable in regions where pembrolizumab is used as SOC for participants who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status.

6. Must have known FGFR3 mutation or rearrangement (participant can be randomized based on a local report, but this will need to be retrospectively confirmed by the sponsor's central laboratory; see Appendix E). See Section 8.7.1 for details on tumor tissue requirements.

   Note: Participants with gene amplifications only are excluded.

7. Local or central laboratory test result of PD-L1 is mandatory at screening. Participants can be randomized based on a local genomics report, but this will need to be retrospectively confirmed by the sponsor's central laboratory. If local result is not available, formalin-fixed, paraffin-embedded tissue blocks or slides must be sent to the sponsor's central laboratory. Formalin-fixed, paraffin-embedded tissue blocks are preferred to slides. If submitting unstained cut slides, newly cut slides should be submitted to the testing laboratory within 30 days from the date slides are cut (see Section 8.7.1 for details on tumor tissue requirements).

   Note: In the event the participant does not have local PD-L1 results or the sample is not evaluable for PD-L1, the participant will not be eligible. If a local result is available and the participant is randomized, but the sample fails or the local result is not confirmed by the central laboratory, the site should contact the medical monitor.

8. Have received no prior systemic chemotherapy for metastatic or unresectable UC except:

   a. Adjuvant platinum-based chemotherapy, following radical cystectomy, with recurrence > 12 months from completion of therapy.
   b. Neo-adjuvant platinum-based chemotherapy, with recurrence > 12 months since completion of therapy.
      Note: Low-dose chemotherapy (eg, low-dose cisplatin, cisplatin + 5-FU, mitomycin + 5-FU, or cisplatin + paclitaxel) given concurrently with radiation to the primary tumor site is not considered as systemic therapy. A washout period of 3 weeks before the first dose of study treatment is required. In the clinical setting, chemotherapy is given with the sole purpose of sensitizing the tumor to local radiation. It is not administered at doses with any systemic efficacy. Surgery is not considered first-line therapy following diagnosis of advanced/metastatic disease.

9. ECOG performance status 0 to 2.

10. Willingness to avoid pregnancy or fathering children based on the criteria below (excluding participants in Japan).

    a. Men must agree to take appropriate precautions to avoid fathering children (defined as the use of an effective method [barrier method] in combination with a highly effective method in preventing pregnancy [see Appendix A]) from screening through 120 days after the last dose of pemigatinib and/or pembrolizumab or 180 days after the last dose of chemotherapy, and must refrain from donating sperm during this period. Permitted methods that are highly effective (at least 99% effective) and effective in preventing pregnancy (see Appendix A) should be communicated to the participants and their understanding confirmed.
       Note: Men being treated with gemcitabine must be advised to seek further advice regarding cryoconservation of sperm before treatment because of the possibility of infertility due to therapy with gemcitabine.

b. Women of childbearing potential must have a negative serum pregnancy test at screening (a maximum of 7 days before the first dose on Day 1) and must agree to take appropriate precautions to avoid pregnancy (defined as the use of an effective method [barrier method] in combination with a highly effective method in preventing pregnancy [see Appendix A]) from screening through 120 days after the last dose of pemigatinib and/or pembrolizumab or 180 days after the last dose of chemotherapy. Permitted methods that are highly effective (at least 99% effective) and effective in preventing pregnancy (see Appendix A) should be communicated to the participants and their understanding confirmed.
c. Women of nonchildbearing potential (ie, surgically sterile with a hysterectomy and/or bilateral oophorectomy OR ≥ 12 months of amenorrhea) are eligible.

11. For Japanese participants only, willingness to avoid pregnancy or fathering children based on the criteria below.

a. Female participants should agree to use medically acceptable contraceptive measures (see Appendix A), should not be breastfeeding, and must have a negative pregnancy test before the start of study treatment administration if of childbearing potential. All female participants of childbearing potential must understand and accept that pregnancy must be avoided during participation in the study from screening through 120 days after the last dose of pemigatinib and/or pembrolizumab (based on menstrual cycle) and 180 days after last dose of chemotherapy.

OR

Female participants must have evidence of nonchildbearing potential by fulfilling one of the following criteria at screening:

– Postmenopausal, defined as aged > 50 years and amenorrheic for at least 12 months after cessation of all exogenous hormonal treatments.

Note: Female participants who have been amenorrheic for ≥12 months resulting from chemotherapy/radiotherapy are considered of childbearing potential and should agree to use adequate contraceptive measures.

– Documentation of irreversible surgical sterilization by hysterectomy, bilateral oophorectomy, or bilateral salpingectomy but not tubal ligation.

b. Male participants should avoid unprotected sex with women of childbearing potential during the study and for a washout period of 120 days after the last dose of pemigatinib and/or pembrolizumab or 180 days after the last dose of chemotherapy. Participants should refrain from donating sperm from the start of the study treatment administration until 180 days after discontinuing study treatment.

5.2. Exclusion Criteria

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

1. Prior receipt of a selective FGFR inhibitor (eg, erdafitinib, rogaratinib, infigratinib, dovitinib, vofatamab) for any indication or reason.
2. Completion of prior therapy with an anti–PD-1, anti–PD-L1, or anti–PD-L2 agent, or with an agent directed to another co-inhibitory T-cell receptor, ≤ 18 months prior to the start of treatment for this study.
3. Receipt of anticancer medications or investigational drugs for unresectable and/or metastatic disease (not including adjuvant/neo-adjuvant treatment with platinum-containing chemotherapy completed ≥ 12 months prior to the start of treatment for this study).
4. Concurrent anticancer therapy (eg, chemotherapy, radiation therapy, surgery, immunotherapy, biologic therapy, hormonal therapy, investigational therapy, tumor embolization), except for treatment allowed per protocol.
5. Has disease that is suitable for local therapy administered with curative intent.
6. Has tumor with any neuroendocrine or small cell component.
7. Current evidence of clinically significant corneal (including but not limited to bullous/band keratopathy, corneal abrasion, inflammation/ulceration, and keratoconjunctivitis, etc) or retinal disorder (including but not limited to macular/retinal degeneration, diabetic retinopathy, retinal detachment, etc) as confirmed by ophthalmologic examination.
8. Has received prior radiotherapy to a metastatic site within 3 weeks of the first dose of study treatment, with the exception of palliative radiotherapy to bone lesions, which is allowed if completed 2 weeks before the start of study treatment. Participants must have recovered from all radiation-related toxicities and must not require corticosteroids.
9. Has CNS metastases, unless the participant has completed local therapy (eg, whole brain radiation therapy, surgery, radiosurgery) and has discontinued use of corticosteroids for this indication for at least 4 weeks before starting treatment in this study. Any signs (eg, radiologic) or symptoms of CNS metastases must be stable for at least 4 weeks before starting study treatment.
10. Known additional malignancy that is progressing or required active treatment within the past 3 years.
    a. Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ (eg, breast carcinoma, cervical cancer in situ) that have undergone potentially curative therapy are not excluded.

b. A history of prostate cancer (T2NXMX or lower with Gleason score ≤ 7) treated with definitive intent (surgically or with radiation therapy) at least 1 year prior to study entry is acceptable, provided that the participant is considered prostate cancer-free and the following criteria are met:

   – Participants who have undergone radical prostatectomy must have undetectable PSA for > 1 year and at screening.

   – Participants who have had radiation must have a PSA doubling time > 1 year (based on at least 3 values determined > 1 month apart) and a total PSA value that does not meet Phoenix criteria for biochemical recurrence (ie, < 2.0 ng/mL above nadir).

c. Participants with untreated low-risk prostate cancer (Gleason score ≤ 6) on active surveillance with PSA doubling time > 1 year (based on at least 3 values determined > 1 month apart) are also eligible.

11. Participants with laboratory values at screening defined in Table 9.

Table 9: Exclusionary Laboratory Values

Laboratory Parameter		Exclusion Criterion
Hematology		
a	Platelets	≤ 100,000 (transfusion allowed with 2-week washout period)
b	Hemoglobin	≤ 9.0 g/dL (transfusion allowed within 2-week washout period)
c	ANC	≤ 1.5×10^9/L
Hepatic		
d	ALT and AST	≥ 2.5 × ULN (5 × ULN for liver mets)
e	Total bilirubin	≥ 1.5 × ULN (Note: Participants excluded based on total bilirubin may be enrolled if direct bilirubin ≤ ULN; 2.5 × ULN if Gilbert's syndrome or liver mets)
Renal		
f	Measured or calculated CrCl (GFR can be used in place of CrCl)	≤30mL/min
	CrCl = [[140 - age(yr)]*weight(kg)]/[72*serum Cr(mg/dL)] (multiply by 0.85 for women)	
Chemistry		
g	Serum phosphate	> institutional ULN
h	Serum calcium	Outside of normal range or serum albumin-corrected calcium outside of the normal range when serum albumin is outside of the normal range
Coagulation		
i	INR or PT, aPTT or PTT	≥ 1.5 × ULN unless the participant is receiving anticoagulation therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants

12. History of calcium and phosphate hemostasis disorder or systemic mineral imbalance with ectopic calcification of soft tissues (exceptions: commonly observed calcifications in soft tissues such as the skin, kidney tendon or vessels due to injury, disease, or aging in the absence of systemic mineral imbalance).
13. Inability to swallow and retain oral medication.
14. Clinically significant or uncontrolled cardiac disease, including unstable angina, acute myocardial infarction within 6 months from Day 1 of study treatment administration, New York Heart Association Class IV congestive heart failure, and uncontrolled arrhythmia (participants with pacemakers or with atrial fibrillation and well-controlled hear rates are allowed).
15. History or presence of an abnormal ECG that, in the investigator's opinion, is clinically meaningful. A screening QTcF interval > 480 ms is excluded. For participants with an intraventricular conduction delay (QRS interval ≥ 120 ms), the JTc interval may be used in place of the QTc with sponsor approval. The JTc must be ≤ 340 ms if JTc is used in place of the QTc.
16. Active chronic or current infectious disease requiring systemic antibiotic, antifungal, or antiviral treatment within 2 weeks prior to the first dose of study treatment (participants with asymptomatic chronic infections on prophylactic treatment are allowed).
17. Has a known history of HBV (defined as HBsAg reactive) or known active HCV (defined as HCV RNA [qualitative] is detected) infection.
18. Known HIV infection.

    Note: HIV screening test is optional for participants enrolled in the United States, but participants with known HIV infection in the United States will be excluded.
19. Use of any potent CYP3A4 inhibitors or inducers or moderate CYP3A4 inducers within 14 days or five half-lives (whichever is longer) before the first dose of study treatment (see Appendix D).
20. Known hypersensitivity or severe reaction to pemigatinib or excipients of pemigatinib (refer to the IB).
21. Inability or unlikeliness of the participant to comply with the dose schedule and study evaluations, in the opinion of the investigator.
22. Inadequate recovery from toxicity and/or complications from a major surgery before starting therapy.
23. Women who are pregnant or breastfeeding.
24. Any condition that would, in the investigator's judgment, interfere with full participation in the study, including administration of study treatment and attending required study visits; pose a significant risk to the participant; or interfere with interpretation of study data.
25. Inability of the participant (or parent, guardian, or legally authorized representative) to comprehend the ICF or unwillingness to sign the ICF.

26. History of autoimmune disease that has required systemic treatment in past 2 years (ie, with use of disease modifying agents, corticosteroids, or immunosuppressive drugs).
    a. Replacement therapy (eg, thyroxine, insulin, physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment and is allowed.
    b. Brief (< 7 days) use of systemic corticosteroids is allowed when use is considered SOC.
    c. Participants with vitiligo, psoriasis, type 1 diabetes mellitus, hypothyroidism, or resolved childhood asthma/atopy will not be excluded.
    d. Participants requiring intermittent use of bronchodilators, inhaled steroids, or local steroid injections will not be excluded.
    e. Participants with hypothyroidism that is stable with hormone replacement or Sjögren's syndrome will not be excluded.
27. Has a history of (noninfectious) pneumonitis that required steroids or has current pneumonitis or evidence of interstitial lung disease.
28. Has received therapy with hematopoietic growth factor such as granulocyte colony-stimulating factor or granulocyte-macrophage colony-stimulating factor in the 14 days prior to the start of study treatment.
29. Has received a live vaccine within 30 days prior to the first dose of study drug. Examples of live vaccines include, but are not limited to: measles, mumps, rubella, varicella/zoster (chicken pox), Bacillus Calmette-Guerin. Seasonal influenza vaccines for injection are allowed; however, intranasal influenza vaccine (eg, FluMist®) are not allowed.
30. Has hypersensitivity to monoclonal antibodies (including pembrolizumab) and/or any of their excipients.
31. Has severe hypersensitivity (≥ Grade 3) to carboplatin and/or gemcitabine and any of their excipients.
32. Has a known psychiatric or substance abuse disorder that would interfere with the participant's ability to cooperate with the requirements of the study.
33. Has had an allogenic tissue/solid organ transplant.
34. Has a known history of active tuberculosis (Bacillus tuberculosis).
35. Is receiving hemodialysis.
36. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy (at a dose exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to randomization.
37. History of hypovitaminosis D requiring supraphysiologic doses (eg, 50,000 UI/weekly) to replenish the deficiency. Participants receiving vitamin D supplements are allowed.
38. Any contraindication to pembrolizumab, gemcitabine, or carboplatin as per each package insert or SmPC.

5.3. Lifestyle Considerations

5.3.1. Meals and Dietary Restrictions

Based on the preliminary results from food-effect cohort in Study INCB 54828-101, no significant food effect was observed. Pemigatinib may be administrated with or without food.

Refrain from consumption of red wine, Seville oranges, and grapefruit or grapefruit juice (pomelos, exotic citrus fruits, grapefruit hybrids, or fruit juices) for 7 days before the start of study treatment until after the final dose since these can impact the bioavailability of pemigatinib.

5.4. Screen Failures

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

Tests with results that fail eligibility requirements may be repeated during screening if the investigator believes the result to be in error. Additionally, a participant who fails screening may repeat the screening process 1 time if the investigator believes that there has been a change in eligibility status. A participant who is rescreened is not required to sign another ICF if the rescreening occurs within 35 days from the previous ICF signature date.

5.5. Replacement of Participants

No participants will be replaced at any time during this study.

6. STUDY TREATMENT

6.1. Study Treatments Administered

Please see Table 10 for the list of possible treatments that will be tested in this study.

Table 10: Study Treatment Information

	Study Treatment			
Study treatment name:	Pemigatinib	Pembrolizumab	Gemcitabine[a]	Carboplatin[a]
Dosage formulation:	Tablet	Solution, vial	Sterile, lyophilized powder, liquid solution, or concentrate solution	Sterile, lyophilized powder, liquid solution, or concentrate solution
Unit dose strength(s) /dosage level(s):	4.5, 9, 13.5, and 18 mg tablets[b] Dose: 13.5 mg daily dose	100 mg/4 mL vial Dose: 200 mg daily	200 mg/single-use vial or 1 g/single-use vial Dose: 1000 mg/m^2 per administration	Dose: AUC 5 mg/mL/min (or AUC 4.5 mg/mL/min if required per local guidelines)
Route of administration:	PO	IV	IV	IV
Administration instructions:	Administered PO QD every day for each 21-day cycle until disease progression.	Administered IV on Day 1 of each 21-day cycle for up to 35 cycles	Administered IV over 30 minutes on Days 1 and 8 of each 3-week cycle for up to 6 cycles (minimum of 4 cycles) in absence of progression or per institutional standard.	Administered IV on Day 1 or 2 of each 21-day cycle for up to 6 cycles (minimum of 4 cycles) in absence of progression or per institutional standard
Packaging and labeling:	Provided in 14-count bottles. Each bottle will be labeled as required per country requirement.	Provided in 25 mg/mL solution for infusion.	Gemcitabine will be obtained from each site's pharmacy stock.[c]	Carboplatin will be obtained from each site's pharmacy stock.[c]
Storage:	Room temperature 15°C-30°C (59°F-86°F)	Refrigerated 2°C-8°C (36°F-46°F)	Room temperature (refer to the applicable package insert)	Room temperature, protect from light (refer to the applicable package insert)

[a] Clinical supply concentration and formulation of chemotherapy may vary by local sourcing.
[b] 18 mg tablets only administered if Protocol criteria are met for up-titration from 13.5 mg as described in Section 6.6.2.1.
[c] The sponsor may provide certain reference therapies, such as gemcitabine or carboplatin, where required by applicable law or regulation, or under other limited circumstances when a participant may not otherwise have access to the therapies.

6.2. Phosphate Binders in Japan

Details on phosphate binders in Japan only are provided in Table 11. The phosphate binders are provided by the sponsor. These binders should only be used for management of hyperphosphatemia during the study according to the recommendations described in Section 6.6.2.

Table 11: Study Treatment 2 (Phosphate Binders for Japan)

Study treatment name:	Bixalomer	Lanthanum carbonate hydrate
Dosage formulation:	Capsule	Tablet
Unit dose strength(s) /dosage level(s):	250 mg	250 mg
Route of administration:	Oral	Oral
Administration instructions:	The usual starting dose of bixalomer for adults is 500 mg 3 times daily just before meals. The dose can be adjusted based on symptoms and serum phosphorus concentration. The maximum daily dose should not exceed 7500 mg.	The usual starting dose of lanthanum carbonate hydrate for adults is 750 mg 3 times daily immediately after meals. The dose can be adjusted based on symptoms and serum phosphorus concentration. The maximum daily dose should not exceed 2250 mg.
Packaging and labeling:	Bixalomer will be labeled as required per country requirement.	Lanthanum carbonate hydrate will be labeled as required per country requirement.
Storage:	Per JP pharmacopeia, room temperature (1°C-30°C).	Per JP pharmacopeia, room temperature (1°C-30°C).

6.3. Preparation, Handling, and Accountability

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

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

The investigator, investigational drug storage manager, 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, investigational drug storage manager, or designee must maintain records that document:

- Delivery of study drug(s) to the study site.
- Inventory of study drug(s) at the site.

- Participant use of the study drug(s) including pill and vial counts from each supply dispensed.
- Lot numbers and/or vial numbers (as applicable) of study drug used to prepare the infusion solution.
- Return of study drug(s) to the investigator, investigational drug storage manager, or designee by participants.

  Note: Returned study treatment should not be redispensed to the participants.

The investigational product must be used only in accordance with the Protocol (see Appendix C). The investigator or investigational drug storage manager 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, investigational drug storage manager, 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, investigational drug storage manager, or designee will oversee shipment of any remaining study drug back to the sponsor or its designee for destruction according to institutional standard operating procedures. If local procedures mandate on-site destruction of investigational supply, the site should (where local procedures allow) maintain the investigational supply until the study monitor inspects the accountability records in order to evaluate compliance and accuracy of accountability by the investigative site. At sites where the study drug is destroyed before monitor inspection, the monitors rely on documentation of destruction per the site's standard operating procedure.

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

For Japan, phosphate binders are provided by the sponsor. Requirements for the accountability, reconciliation, and record maintenance of the binders is the same as for study drug as described above. Further guidance and information are provided in the Japan-specific Pharmacy Manual.

6.4. Measures to Minimize Bias: Randomization and Blinding

The study will be open-label due to the clear pharmacodynamic impact of pemigatinib on the participant (elevation of serum phosphate/hyperphosphatemia). It is difficult to effectively blind the study, even with a double-dummy, due to serum phosphate elevation that occurs in most participants treated with pemigatinib.

An ICR committee that is blinded to the assigned treatment will be used to evaluate radiographic tumor response to support the primary and secondary endpoints to minimize bias. 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 Study Reference Manual.

Study treatment will be dispensed at the study visits summarized in the schedule of activities (see Table 4). See Table 8 for study treatment groups to be randomized.

6.4.1. Stratification

The stratification factors were selected to ensure that baseline characteristics known to have prognostic impact are distributed equally among the three treatment groups.

Participants will be stratified by:

- Carboplatin-eligible versus not eligible
- PD-L1 CPS ≥ 10 versus PD-L1 CPS < 10
- LN-only disease versus other metastatic disease

6.4.1.1. PD-L1 CPS Results

Recently acquired or archived tumor tissue (obtained since most recent therapy) from an unresectable or metastatic site must be analyzed and be evaluable for PD-L1 status during screening in order for a participant to be randomized. PD-L1 status can be evaluated locally or centrally prior to randomization.

For participants who have PD-L1 status evaluated centrally, investigators will be blinded to the central vendor's PD-L1 CPS results and will be alerted to completion of a participant's PD-L1 evaluation, as well as to instances where the tumor tissue sample is inadequate for PD-L1 evaluation (not evaluable). PD-L1 CPS will influence stratification of patients prior to randomization into treatment groups.

Note: In the event the participant does not have local PD-L1 results or the sample is not evaluable for PD-L1, the participant will not be eligible. If a local result is available and the participant is randomized but the sample fails or the local result is not confirmed by the central laboratory, the site should contact the medical monitor.

Treatment Group C

- For **carboplatin-eligible participants**, all participants with PD-L1 CPS ≥ 10 will be assigned to pembrolizumab if randomized to Treatment Group C.
- For **carboplatin-ineligible participants**, all participants who are carboplatin ineligible will be assigned to pembrolizumab regardless of their PD-L1 status, if randomized to Treatment Group C.

Note: Only applicable in regions where pembrolizumab is used as standard of care for participants who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status.

6.5. Study Treatment Compliance

Compliance with all study-related treatments should be emphasized to the participant by the site personnel, and appropriate steps should be taken to optimize compliance during the study. Compliance with pemigatinib will be monitored/calculated by the sponsor based on the drug

accountability documented by the site staff and monitored by the sponsor/designee (bottle/pill/vial counts).

Participants will be instructed to bring all pemigatinib bottles/pills with them to the study visits in order for site personnel to conduct bottle/pill counts to assess study drug accountability. The drug accountability documentation will be used by the sponsor to calculate treatment compliance.

Compliance with study drug administration of pembrolizumab, gemcitabine, and carboplatin will be calculated by the sponsor based on study drug accountability and infusion records documented by the site staff and monitored by the sponsor/designee.

Refer to Section 9.10 for additional information on overdose.

6.6. Dose Modifications

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

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

6.6.1. Criteria and Procedures for Dose Interruptions and Adjustments of Pemigatinib

Treatment with pemigatinib may be delayed up to 2 weeks (14 days) to allow for resolution of toxicity. Participants may resume treatment if no medical condition or other circumstance exists that, in the opinion of the investigator, would make the participant unsuitable for further participation in the study. The treating investigator should contact the sponsor to discuss the case of any participant whose treatment may be delayed for more than 14 days before restarting treatment with pemigatinib.

For participants who present with possible or confirmed serous retinal detachment/retinal pigmented epithelium detachment (SRD/RPED) based on OCT, the guidelines in Table 12 should be followed. It is recommended to discuss the findings with the Incyte medical monitor before making changes to the participant's treatment.

For participants randomized to receive pemigatinib in combination with pembrolizumab (Treatment Group A), participants may continue to receive pemigatinib or pembrolizumab as a monotherapy if criteria are met for dose interruption or discontinuation of either component.

Guidelines for interrupting/restarting pemigatinib are provided in Table 12.

Table 12: Guidelines for Interruption and Restarting Pemigatinib

ADVERSE EVENT	ACTION TAKEN
Chemistry	
• AST and/or ALT is > 5.0 × ULN. Note: In participants with liver metastasis-related elevations at baseline, contact sponsor to discuss clinical management and possible dose reductions.	**Step 1:** Interrupt pemigatinib up to 2 weeks (14 days) until the toxicity has resolved to ≤ Grade 1 except by approval of the medical monitor. **Step 2:** Restart pemigatinib at same dose. If assessed as related to pemigatinib, restart pemigatinib at next lower dose; monitor as clinically indicated.
Other Toxicities, including SRD/RPED	
Any Grade 1 or Grade 2 toxicity.	Continue pemigatinib treatment and treat the toxicity; monitor as clinically indicated.
Any Grade 3 toxicity, if clinically significant and not manageable by supportive care.	**Step 1:** Interrupt pemigatinib up to 2 weeks (14 days) until the toxicity resolves to ≤ Grade 1. **Step 2:** Restart pemigatinib at same dose. If assessed as related to pemigatinib, restart pemigatinib at next lower dose; monitor as clinically indicated.
Any recurrent Grade 3 toxicity after 2 dose reductions.	Discontinue pemigatinib administration and follow-up per Protocol. (Exceptions require approval of sponsor.)
• Any other Grade 4 toxicity. • QT/QTcF to > 500 ms or to > 60 ms over baseline.	Discontinue pemigatinib administration and follow-up per Protocol.

For pemigatinib dose adjustments, the following dose reductions are permitted:

- Participants dosed at 13.5 mg can reduce a maximum of 2 dose levels down; they can decrease to 9 mg, and, if additional dose reduction is required, participants can decrease to 4.5 mg.
- Participants who are up-titrated to 18 mg as described in Section 6.6.2.1 can reduce a maximum of 3 dose levels down (13.5 mg then 9 mg) to 4.5 mg if indicated.

Dose reductions below 4.5 mg are not allowed for any treatment group receiving pemigatinib. The frequency of dosing remains the same (QD) as well as the schedule (continuous dosing).

6.6.2. Management of Hyperphosphatemia

Hyperphosphatemia is an expected on-target pharmacologic effect of FGFR inhibition. Hyperphosphatemia should be managed with diet modifications, phosphate binders and diuretics, or a dose reduction per the recommendations in Table 13.

If binders are used to manage hyperphosphatemia during treatment, it is recommended to stop binders at the same time pemigatinib is stopped to reduce risk of hypophosphatemia.

For Japanese participants, the phosphate binders bixalomer or lanthanum carbonate hydrate will be provided by the sponsor for treatment of hyperphosphatemia, when required (see Table 11).

Table 13: Recommended Approach for Hyperphosphatemia Management

Serum Phosphate Level	Supportive Care	Guidance for Interruption/Discontinuation of Pemigatinib	Guidance for Restarting Pemigatinib
> 5.5 mg/dL and ≤ 7 mg/dL	Initiate a low-phosphate diet.	No action.	Not applicable.
> 7 mg/dL and ≤ 10 mg/dL	Initiate/continue a low-phosphate diet and initiate phosphate-binding therapy once serum phosphate level is > 7 mg/dL. Monitor serum phosphate at least twice a week and adjust the dose of binders as needed; continue to monitor serum phosphate at least twice a week until return to normal range.	If serum phosphate level continues to be > 7 mg/dL and ≤ 10 mg/dL with concomitant phosphate-binding therapy for 2 weeks, or if there is recurrence of serum phosphate level in this range, *interrupt* pemigatinib for up to 2 weeks (not including the planned dose interruption per treatment cycle).	Restart at the same dose when serum phosphate is < 7 mg/dL. If serum phosphate level recurs at > 7 mg/dL, restart pemigatinib with dose reduction.
> 10 mg/dL	Continue to maintain a low-phosphate diet, adjust phosphate-binding therapy, and start/continue phosphaturic agent. Continue to monitor serum phosphate at least twice a week until return to normal range.	If serum phosphate level is > 10 mg/dL for 1 week following phosphate-binding therapy and low phosphate diet, *interrupt* pemigatinib. If there is recurrence of serum phosphate level in this range following 2 dose reductions, *permanently discontinue* pemigatinib.	Restart pemigatinib at reduced dose with phosphate binders when serum phosphate is < 7 mg/dL.

6.6.2.1. Up-Titration

Any participant who does not reach the target serum phosphate level of > 5.5 mg/dL at any time during Cycle 1 and who is compliant with taking study drug and does not experience an ongoing Grade 2 or higher treatment-related AE will increase the daily dose to 18 mg starting at Cycle 2 Day 1.

Participants who are titrated up to 18 mg QD must begin the next cycle at the new dose level and must agree to all Cycle 1 assessments ([redacted] safety assessments [hematology and blood chemistry]). Up-titration may not occur earlier than on Day 1 of Cycle 2 so that participants are observed for phosphate level and AEs at least for 1 cycle.

See Section 6.6.1 for maximum dose adjustments allowed for participants who are up-titrated.

6.6.3. Criteria for Permanent Discontinuation of Pemigatinib

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

- Occurrence of an AE that is related to pemigatinib that, in the judgment of the investigator or the sponsor's medical monitor, compromises the participant's ability to continue study-specific procedures or is considered to not be in the participant's best interest.
- An AE requiring more than the maximum amount of dose reductions.
- Persistent AE requiring a delay of therapy for more than 3 weeks (21 days) unless a greater delay has been approved by the sponsor.
- Increase in QT/QTcF to > 500 ms or to > 60 ms over baseline. In case of a QTcF > 500 ms, the participant must be hospitalized, and a continuous ECG monitoring must be set up until the measure of the QTcF interval decreases below 500 ms and until acceptable in the opinion of a local cardiologist.

See Section 7 for discontinuation procedures.

6.6.4. Criteria for Procedures for Doses Interruptions or Adjustments of Pembrolizumab, Gemcitabine, and Carboplatin

These agents are approved therapies and have specific participant safety management guidelines within the prescribing information; the treating investigator should refer to and follow the labeled guidances. See Appendix B for criteria specific for pembrolizumab.

6.7. Concomitant Medications and Procedures

All concomitant medications and treatments (including over-the-counter or prescription medicines, vitamins, vaccines, and/or herbal supplements) must be recorded in the eCRF. Any prior medication received up to 28 days before the first dose of study treatment and 30 days after the last dose of study treatment, or until the participant begins a new anticancer therapy, whichever occurs first, will be recorded in the eCRF. Any addition, deletion, or change in the dose of these medications will also be recorded.

Concomitant medications administered 90 days after the last dose of study treatment should be recorded for SAEs as defined in Section 9. Concomitant treatments/procedures that are required to manage a participant's medical condition during the study will also be recorded in the eCRF.

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

6.7.1. Restricted Medications and Procedures

Pemigatinib is predominantly metabolized by CYP3A4. There is a sufficient safety margin, with doses greater than the recommended Phase 2 dose of 13.5 mg QD having been tested, and up to 20 mg QD is tolerable. The expected 50% increase in exposure in participants who concomitantly use CYP3A4 moderate inhibitors is covered by the safety margin. Therefore, the use of moderate CYP3A4 inhibitors should involve careful monitoring, especially in relation to

safety, while moderate CYP3A4 inducers and potent CYP3A4 inhibitors and inducers are prohibited (see Appendix D).

Careful monitoring is required when pemigatinib is concomitantly administered with OCT2 substrates such as dofetilide and metformin.

Calcium-based phosphate binding medications should not be used due to a concern for soft tissue mineralization. However, if other types of phosphate binders (eg, calcium-free sevelamer or lanthanum) are not available in certain regions, calcium-based binders may be used with appropriate clinical monitoring.

6.7.2. Prohibited Medications and Procedures

6.7.2.1. Prohibited Medications and Procedures for Pemigatinib

A CYP3A4-mediated DDI study (INCB 54828-104) indicated there is evidence of a clinically significant effect on pemigatinib exposure when coadministered with a potent CYP3A4 inhibitor, itraconazole (increased pemigatinib AUC by 88%) or potent CYP3A4 inducer, rifampin (decreased pemigatinib AUC by 85%). A PBPK model was developed and validated using in vitro and clinical DDI data. PBPK model-simulated pemigatinib AUCs were increased by approximately 50% for moderate CYP3A4 inhibitors and decreased by more than 50% for moderate CYP3A4 inducers. In addition, PBPK modeling showed no DDI effect when pemigatinib was coadministered with a weak CYP3A4 inhibitor or inducer.

The following medications and measures are prohibited for pemigatinib.

- The concomitant administration of potent CYP3A4 inhibitors and inducers and moderate CYP3A4 inducers (see Appendix D). Based on the low overall bioavailability of topical ketoconazole, there are no restrictions on topical ketoconazole.
- Any concomitant use of a selective FGFR inhibitor (other than pemigatinib).
- Investigational study drug for any indication.
- Use of any anticancer medications other than the study medications being tested in this Protocol.
- Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing study.

Refer to the IB for more information on DDIs.

Dose modifications for tolerability issues are noted in Section 6.6.

6.7.2.2. Prohibited Medications and Procedures for Pembrolizumab, Gemcitabine, and Carboplatin

Refer to the package inserts and SmPCs for restricted medications and procedures for gemcitabine and carboplatin.

Listed below are prohibited concomitant medications or vaccinations during the course of the study for pembrolizumab:

- Antineoplastic systemic chemotherapy or biological therapy.
- Immunotherapy not specified in this Protocol.
- Chemotherapy not specified in this Protocol.
- Investigational agents other than pembrolizumab.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an AE that is suspected to have immunologic etiology. Physiologic doses of corticosteroids not exceeding 10 mg daily of prednisone equivalent may be used during the study.

  Note: Inhaled steroids are allowed for management of asthma or seasonal allergies.
- Radiation therapy: Palliative radiotherapy is permitted to a single lesion or to the brain (after discussion with the sponsor) if considered medically necessary by the treating physician, as long as the lesion is NOT a RECIST v1.1-defined target lesion and radiotherapy is NOT administered for tumor control.
- Live vaccines within 30 days prior to the first dose of study intervention and while participating in the study. Examples of live vaccines include, but are not limited to the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist) are live attenuated vaccines and are not allowed.

For participants who, in an assessment by the investigator, require the use of any of the aforementioned treatments for clinical management, continuation of study treatment and further participation in the study must be discussed and agreed upon with the sponsor. If participants receive additional anticancer therapies, this will be judged to represent evidence of PD, and study treatment will be discontinued. These participants should complete all end-of- treatment assessments and continue to be followed for survival in the follow-up period.

6.7.3. Permitted Medications and Procedures

6.7.3.1. Rescue Medications and Supportive Care for Pembrolizumab

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines in Appendix B. Where appropriate, these guidelines include the use of oral or IV treatment with corticosteroids, as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab.

Note: If after the evaluation of the event, it is determined not to be related to pembrolizumab, the investigator does not need to follow the treatment guidance. It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

6.8. Treatment After the End of the Study

There is no treatment for the participant once criteria have been met for study discontinuation as described in Section 7.

7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Treatment

7.1.1. Reasons for Discontinuation

Participants **must** be withdrawn from study treatment for the following reasons. Please note that if a participant discontinues study treatment for reasons other than disease progression or withdraw of consent, the participant should be followed until disease progression is documented.

- The participant or participant's legally acceptable representative requests to discontinue study intervention.
- The participant interrupts pemigatinib administration for more than 21 days (unless Sponsor has given approval to continue).
- The participant interrupts pembrolizumab administration for more than 12 weeks (unless Sponsor has given approval to continue).
- The participant has a confirmed positive serum pregnancy test.
- Disease progression has been reported per RECIST v1.1.
- Other anticancer treatment is initiated.
- Consent is withdrawn.

  Note: Consent withdrawn means that the participant has explicitly indicated that they do not want to be followed any longer; in this case no further data, except data in public domain, may be solicited from or collected on the participant. Participants may choose to discontinue study treatment and remain in the study to be followed for progression and survival.
- Further participation would be injurious to the participant's health or well-being, in the investigator's medical judgment.
- Unacceptable toxicity as noted in Section 6.6.1.
- The study is terminated by the sponsor, local health authority, IRB, or IEC.

- Completion of 35 treatment cycles (approximately 2 years) with pembrolizumab plus pemigatinib or pembrolizumab monotherapy. Note: Participants in Treatment Group A (pembrolizumab + pemigatinib) must discontinue pembrolizumab after 35 treatment cycles but can continue pemigatinib until PD.
- Intercurrent illness other than another malignancy as noted above that prevents further administration of treatment
- Recurrent Grade 3 colitis/diarrhea.
- Any progression or recurrence of any malignancy, or any occurrence of another malignancy that requires active treatment.
- Recurrent Grade 2 pneumonitis.

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

- If, during the course of the study, a participant is found not to have met eligibility criteria, the medical monitor, in collaboration with the investigator, will determine whether the participant should be withdrawn from study treatment.
- If a participant is noncompliant with study procedures or study treatment administration in the investigator's opinion, the sponsor should be consulted for instruction on handling the participant.

7.1.2. Discontinuation Procedures

In the event that the decision is made to permanently discontinue the study treatment, the EOT visit should be conducted. Reasonable efforts should be made to have the participant return for a follow-up visit. These visits are described in the schedule of activities (see Table 4). 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 immediately.
- The reason(s) for withdrawal must be documented in the participant's medical record, and the primary reason for withdrawal must be included in the eCRF.
- The EOT visit should be performed.
- The date of the EOT visit should be recorded in the IRT.
- Participants must be followed for safety until the time of the follow-up visit or until study treatment–related toxicities resolve, return to baseline, or are deemed irreversible, whichever is longest.

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

7.2. Participant Withdrawal From the Study

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

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

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

See Table 4 and Table 5 for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

7.3. Lost to Follow-Up

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

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

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

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Administrative and General Procedures

8.1.1. Informed Consent Process

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

A participant who is rescreened is not required to sign another ICF if the rescreening occurs within 35 days from the previous ICF signature date.

[redacted]

8.1.2. Prescreening and Screening Procedures

Prescreening through the sponsor's central laboratory is available for participants without a genomic testing report for FGFR3 and PD-L1 status (local results and archival tumor sample within approximately 2 years of screening are valid for this study to allow participants to start screening) and with metastatic or unresectable UC. Prescreening allows genomic testing to be performed outside of the 35-day screening window and prior to signing the main consent form for the study. Participants will be required to sign a specific prescreening consent form; however, no other protocol assessments will be performed under the prescreening consent.

Screening is the interval between signing the ICF and the day the participant is randomized in the study. Screening may not exceed 35 days. Assessments that are required to demonstrate eligibility may be performed over the course of 1 or more days during the screening process.

Procedures conducted as part of the participant's routine clinical management (eg, blood count, imaging study) and obtained before signing of informed consent may be used for screening or baseline purposes provided the procedure meets the Protocol-defined criteria and has been performed in the timeframe of the study (ie, within 14 days of Cycle 1 Day 1). For participants who are randomized 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 by the investigator to confirm eligibility before randomization. Tests with results that fail eligibility requirements may be repeated once during screening if the investigator believes the results to be in error. For screening assessments that are repeated, the most recent available result before randomization will be used to determine eligibility. Treatment should start as soon as possible, but within 5 days after the date of randomization.

See Section 5.4 for information regarding screen failures.

8.1.3. Interactive Response Technology Procedure

Each participant will be identified in the study by a participant ID number, which is a combination of the site ID and participant number. Site staff should contact the IRT to obtain the participant ID number during prescreening and screening. Upon determining that the participant is eligible for randomization, the IRT will be contacted to obtain the treatment assignment. Additionally, the IRT will be contacted at the study visits indicated in Table 4 to update the study drug supply.

Additional details are provided in the IRT Manual.

8.1.4. Distribution of Reminder Cards

Participants will be provided with a reminder card at the study visits indicated in Table 4. The reminder card will indicate the date/time of the next visit. [redacted]

8.1.5. Demography and Medical History

8.1.5.1. Demographics and General Medical History

Demographic data and general medical history will be collected at screening by the investigator or qualified designee and will include year of birth/age, race, ethnicity, medical and surgical history, and current illnesses. Medical history will include relevant medical or surgical treatment within the last 10 years that are considered to be clinically significant by the investigator.

8.1.5.2. Disease Characteristics and Treatment History

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

8.2. Efficacy Assessments

8.2.1. Tumor Imaging

The process for image collection and transmission to the central imaging vendor and the scanning options can be found in the ICR Reference Manual. Objective assessment of tumor status is required using appropriate disease-specific techniques, and a central radiologic facility will be used to determine responses in a blinded manner and will be logged in to the eCRF. RECIST v1.1 (Eisenhauer et al 2009) will be used, and the recommended method for measuring and following tumor burden will be CT scan to include the chest, abdomen, and pelvis; the neck can be included if needed. Alternative modalities (eg, MRI) may be substituted for a CT scan at the discretion of the investigator, provided that the same modality is used throughout the study and that the methodology is consistent with RECIST v1.1.

The schedule for efficacy assessments will be at screening (this will be considered the baseline scan), every 9 weeks (every 3 cycles) from date of randomization until 1 year, then every 12 weeks (every 4 cycles) thereafter, and then at EOT (if applicable). The schedule should be followed regardless of treatment delays. If imaging was obtained within 4 weeks before EOT, a scan at EOT is not mandatory. Follow-up visits may be scheduled to coincide with the imaging schedule. For participants showing a response, a confirmatory scan may be performed a minimum of 4 weeks (per RECIST v1.1) from the previous scan. For participants showing a progression based on local radiologic review, treatment should not be discontinued until progression of disease has been determined by BICR, unless the principal investigator believes it is in the best interest of the participant to discontinuation treatment before receiving confirmation.

Bone scans and brain imaging will be performed at baseline for all participants with clinical symptoms of bone or brain metastases. Bone scans at baseline must be sent to central imaging vendor for review with initial tumor imaging. Participants with positive bone scans at baseline will be followed with additional scans performed every 9 weeks (± 7 days) from date of randomization, or more frequently if clinically indicated. For participants with new symptoms suggestive of osseous metastasis, a bone scan should be obtained. Additionally, plain X-ray evaluation should be obtained for symptomatic sites with negative bone scan evaluations.

When the investigator identifies radiographic progression per RECIST v1.1, the central imaging vendor will perform expedited verification of radiologic PD, and communicate the results to the study site and sponsor. Treatment should continue until PD has been verified.

For participants who discontinue study treatment for reasons other than disease progression, every effort should be made to continue monitoring their disease status by radiographic imaging until the start of new anticancer treatment, disease progression, pregnancy, death, withdrawal of consent, or the end of the study, whichever occurs first.

8.2.1.1. Initial Tumor Imaging

Initial tumor imaging at screening must be performed within 35 days prior to the date of randomization. Any imaging obtained after Cycle 1 Day 1 cannot be included in the screening assessment. The site study team must review screening images to confirm that the participant has measurable disease per RECIST v1.1.

Screening images must be submitted to the BICR committee for retrospective review.

Tumor imaging performed as part of routine clinical management is acceptable as screening imaging if it is of diagnostic quality and performed within 35 days prior to the date of randomization and can be assessed by BICR.

Tumor imaging required at baseline includes the following:

- CT (preferred) or MRI of the abdomen and pelvis
- CT of the chest
- Bone scan (whole body) and brain imaging only if participant has clinical symptoms of brain or bone metastases

If brain imaging is performed to document the stability of existing metastases, MRI should be used if possible. If MRI is medically contraindicated, CT with contrast is an acceptable alternative.

8.2.2. Tumor Imaging During the Study

The first on-study imaging assessment should be performed at 9 weeks (63 days + 7 days) from the date of randomization. Subsequent tumor imaging should be performed every 9 weeks (63 days ± 7 days) or more frequently if clinically indicated. After 54 weeks (378 days ± 7 days), participants who continue receiving study intervention will have imaging every 12 weeks (84 days ± 7 days). Imaging timing should follow calendar days and not be adjusted for delays in cycle starts. Imaging should continue to be performed until disease progression is identified by the investigator and verified by BICR, the start of new anticancer treatment,

withdrawal of consent, or death. All supplemental imaging must be submitted to the imaging central vendor as soon as possible. Brain imaging and bone scans must be repeated at the same frequency as other imaging assessments if positive at baseline or if participants exhibit symptoms indicative of bone or brain metastases.

Objective response should be confirmed by a repeat imaging assessment. Tumor imaging to confirm PR or CR should be performed at least 4 weeks after the first indication of a response. Participants will then return to regular scheduled imaging, starting with the next scheduled imaging time point. Participants who have additional imaging for confirmation do not need to undergo the next scheduled tumor imaging if it is less than 4 weeks later; tumor imaging may resume at the subsequent scheduled imaging timepoint.

Note: Response does not typically need to be verified in real time by BICR.

8.2.2.1. End of Treatment and Follow-Up Tumor Imaging

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

For participants who discontinue study treatment without documented disease progression, every effort should be made to continue monitoring disease status by tumor imaging with the same imaging schedule used during treatment, calculated from the date of randomization until the start of new anticancer treatment, disease progression, pregnancy, death, withdrawal of consent, or the end of the study, whichever occurs first.

8.2.3. ECOG Performance Status

ECOG performance status (see Table 14) will be assessed at the visits specified in the schedule of activities (see Table 4).

Table 14: ECOG Performance Status

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

Source: Oken et al 1982.

8.3. Quality of Life Assessments

The EORTC QLQ-C30 and EQ-5D-5L are not pure efficacy or safety endpoints because they are affected by both disease progression and treatment tolerability. Participants will be asked to complete the EORTC QLQ-C30 and EQ-5D-5L. Questionnaires must be completed at each interval prior to receiving study treatment as indicated in the schedule of activities (see Table 4).

8.3.1. EORTC QLQ-C30

The EORTC QLQ-C30 is the most widely used cancer specific health-related quality of life instrument, which contains 30 items and measures 5 functional dimensions (ie, physical, role, emotional, cognitive, and social), 3 symptom items (ie, fatigue, nausea/vomiting, and pain), 6 single items (ie, dyspnea, sleep disturbance, appetite loss, constipation, diarrhea, and financial impact), and a global health and quality of life scale (Aaronson et al 1993). The reliability, validity, and practicality of these instruments have been reported. This instrument is translated and validated into more than 80 languages. For each scale and single item, a linear transformation will be applied to standardize the scores between 0 (worst) and 100 (best) as described in the EORTC QLQ-C30 Scoring Manual.

8.3.2. EQ-5D-5L

The EQ-5D-5L is a standardized instrument for use as a measure of health outcome (Rabin and de Charro 2001). The EQ-5D-5L will provide data for use in economic models and analyses including developing health utilities or quality adjusted life years. The 5 health state dimensions in this instrument include the following: mobility, self -care, usual activities, pain/discomfort, and anxiety/depression. Each dimension is rated on a three point scale from 1 (extreme problem) to 3 (no problem). The EQ-5D-5L also includes a graded (0 to 100) vertical visual analog scale on which the participant rates his or her general state of health at the time of the assessment. The EQ-5D-5L will always be completed by participants first before completing the EORTC QLQ-C30.

8.5. Safety Assessments

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

8.5.1. Adverse Events

Adverse events (CTCAE v5.0) will be monitored from the time the participant signs the ICF until at least 30 days for after the last dose of study treatment. SAEs must be reported up until 90 days after the last dose of study treatment or 30 days if participant starts a new anticancer therapy, whichever is earlier. Adverse events that begin or worsen after informed consent should be recorded on the Adverse Events Form in the eCRF regardless of the assumption of a causal relationship with the study treatments. Conditions that were already present at the time of informed consent should be recorded on the Medical History Form in the eCRF. Adverse events (including laboratory abnormalities that constitute AEs) should be described using a diagnosis whenever possible rather than by individual underlying signs and symptoms.

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

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

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

For Japanese participants, the relationship to phosphate binders should also be collected on the Adverse Events Form in the eCRF.

8.5.2. Physical Examinations

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

At the screening visit, a comprehensive physical examination should be conducted. The comprehensive physical examination will include height and body weight, and assessment(s) of

the following organ or body systems: skin; head, eyes, ears, nose, and throat; thyroid; lungs; cardiovascular system; abdomen (liver, spleen); extremities; and lymph nodes; as well as a brief neurological examination.

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

8.5.3. Vital Signs

Vital sign measurements (to be taken before blood collection for laboratory tests), include blood pressure, pulse, respiratory rate, and body temperature. If vital signs cannot be taken before blood collection for laboratory tests, there must be a minimum of 30 minutes from the completion of the blood collection procedures to the beginning of the vital signs collection. Blood pressure and pulse will be taken with the participant in the recumbent, semirecumbent, or sitting position after 5 minutes of rest. Weight will also be assessed at each study visit. Abnormal vital sign results identified after the first dose of study treatment constitute an AE if they are considered clinically meaningful, induce clinical signs or symptoms, require concomitant therapy, or require changes in study treatment.

8.5.4. Electrocardiograms

A single 12-lead ECG will be obtained at the study visits noted in the schedule of activities (see Table 4). The ECGs will be performed with the participant in a supine or semisupine position after approximately 5 to 10 minutes of rest. Sites should use an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. If the screening ECG renders abnormal but not clinically significant results, the investigator should use clinical judgement to perform additional monitoring during study treatment. Clinically notable abnormalities that are considered clinically significant in the judgment of the investigator are to be reported as AEs. In the event that a single QTc is > 480 ms at screening, the participant may enroll if the average QTc for the 3 ECGs is ≤ 480 ms or with approval from the medical monitor. For participants with an intraventricular conduction delay (QRS interval > 120 ms) at screening, the JTc interval may be used in place of the QTc with medical monitor approval. The JTc must be ≤ 340 ms if JTc is used in place of the QTc. In addition, the JTc interval should be used for all subsequent assessments.

8.5.5. Comprehensive Eye Examination

A comprehensive eye examination should be performed by a qualified ophthalmologist at screening on all participants, once every 3 cycles (± 7 days starting with Cycle 3) for participants randomized to Treatment Groups A and B only, at EOT for all participants, and as clinically indicated. The eye examination should include a visual acuity test, slit-lamp examination, funduscopy with digital imaging, and OCT. Every effort should be made to ensure that all subsequent examinations are performed by the same ophthalmologist.

8.5.6. Laboratory Assessments

See Table 15 for the list of clinical laboratory tests to be performed and the schedule of activities for the timing and frequency (see Table 4). The site's local laboratory will perform all clinical

laboratory assessments for safety (ie, blood chemistries, hematology assessments, coagulation tests, endocrine function, and urinalysis). [redacted] Additional testing may be required by the sponsor based on emerging safety data. All Protocol-required laboratory assessments must be conducted in accordance with the Laboratory Manual and the schedule of activities (see Table 4). Information regarding collection, processing, and shipping of laboratory assessments is provided in the Laboratory Manual.

Serum phosphate testing is required on a more frequent basis if a participant develops hyperphosphatemia during Cycle 1 and is up-titrated (see Section 6.6.2.1). Parathyroid hormone (endocrine) testing will be required at baseline and every 3 cycles starting with Cycle 3 (only for participants who are randomized to receive a regimen that includes pemigatinib) as parathyroid hormone plays a role in calcium and phosphate hemostasis (Khundmiri et al 2016).

Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the last dose of study treatment should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

Screening laboratory assessments must be performed within 14 days of Cycle 1 Day 1. If performed more than 14 days before Cycle 1 Day 1, then the tests must be repeated and eligibility confirmed before study treatment administration on Cycle 1 Day 1. Laboratory samples collected on study Day 1 must be performed before study treatment administration. After Cycle 1, predose laboratory procedures can be conducted up to 72 hours before study treatment administration (within the 3-day study window), and results should be reviewed by the investigator or qualified designee and found to be acceptable before a new cycle of treatment is initiated.

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

Table 15: Required Laboratory Analytes

Blood Chemistries	Hematology	Urinalysis With Microscopic Examination	Serology	Coagulation
Albumin ALP ALT AST Amylase Bicarbonate or CO_2 [a] Blood urea nitrogen or urea Calcium Chloride Creatinine Glucose Lactate dehydrogenase Lipase Phosphate Potassium Sodium Total bilirubin Direct bilirubin (if total bilirubin is elevated above ULN) Total protein Uric acid Vitamin D (25-hydroxyvitamin D and 1,25-dihydrosyvitamin D)	CBC, including: • Hemoglobin • Hematocrit • Platelet count • Red blood cell count • WBC count Differential count, including: • Basophils • Eosinophils • Lymphocytes • Monocytes • Neutrophils Absolute values must be provided for: • WBC differential laboratory results	Color and appearance pH and specific gravity Bilirubin Glucose Ketones Leukocytes Nitrite Occult blood Protein	HBsAg HBsAg antibody Hepatitis B core antibody HCV antibody Note: If any of the above are positive, HBV DNA, HCV RNA to assess risk of reactivation. HIV (if applicable)	INR PT aPTT or PTT
			Endocrine Function	**Pregnancy Testing**
			Parathyroid hormone TSH (T3, T4 if TSH abnormal)	Women of childbearing potential only require a serum test at screening (maximum 7 days before study drug administration) and EOT, and a urine pregnancy test for all other assessments. Pregnancy tests (serum or urine) should be repeated on Day 1 of each cycle, 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 as required by local regulations.
[a] Not required in Japan.

8.5.6.1. Pregnancy Testing

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

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

If a pregnancy is confirmed by a serum pregnancy test, see Section 9.7 for reporting requirements.

8.5.6.2. Serology

Hepatitis screening assessments will be performed at the screening visit to rule out hepatitis infection; required analytes are shown in Table 15. 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.

8.7. Pharmacodynamic and Translational Assessments

Refer to Table 4, Table 5, Table 17, and Figure 2 for additional information on timing of assessments.

8.7.1. Tumor Tissue Collection and Requirements

All potential participants must have documented FGFR3 mutation or rearrangement and PD-L1 status **prior to randomization**; screening and randomization may be based on local genomics and PD-L1 results, but confirmatory testing through the sponsor's central laboratory will be performed on all participants during the study. Participants who have a Dako PD-L1 IHC 22C3 pharmDx report will not need to have their PD-L1 status confirmed centrally. Participants who have a documented FGFR3 mutation or rearrangement confirmed by Foundation Medicine do not need the FGFR status reconfirmed centrally if the report is within 24 months. Since confirmation via central laboratory is required, a pathologist review/quality check of samples should be performed prior to shipment. Based on data from study INCB 54828-201, the concordance rate for FGFR testing was about 90% for approximately 20 participants.

Requirement of biopsies for FGFR3 genomic alteration (see Section 8.7.1.1) and PD-L1 test (see Section 8.7.1.2): a tumor tissue sample from < 24 months prior to screening from the primary or metastatic lesion or newly obtained core or excisional biopsy from the primary or metastatic lesion that were not previously irradiated must be provided to the central laboratory for testing. Formalin fixed, paraffin-embedded tissue blocks are preferred to slides. If providing slides, the requirement is 15 to 25 unstained consecutive FFPE slides (see Figure 2). Newly obtained biopsies are preferred to archived tissue. Tissue from a metastatic lesion or advanced bladder cancer is preferred to NMIBC or MIBC. Detailed instructions for tissue collection, handling, processing, and shipment are provided in the Laboratory Manual.

8.7.1.1. Tumor For Genomics Testing for FGFR Genetic Alterations and Gene Expression

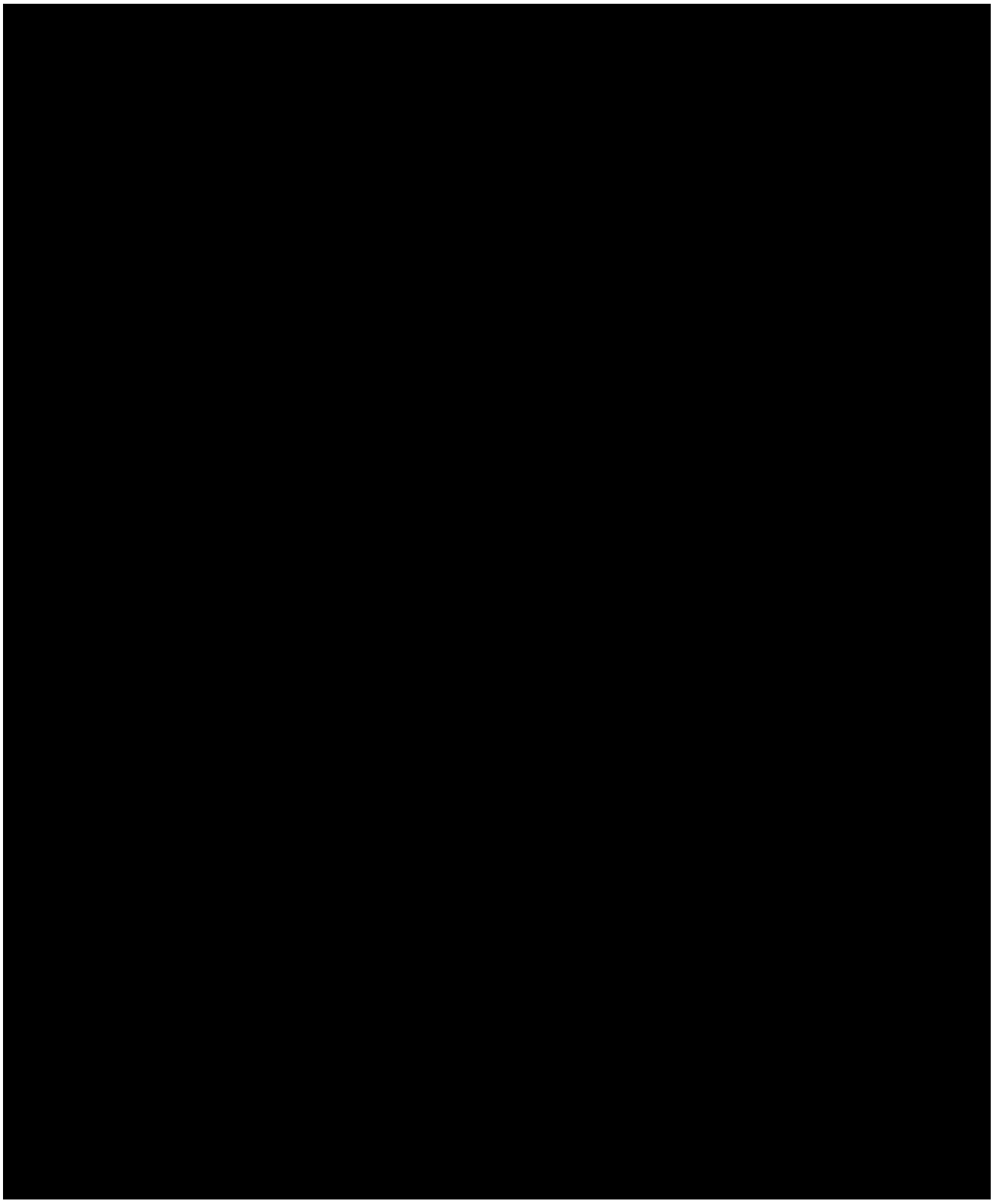
If submitting unstained cut slides, 10 unstained, consecutive FFPE, newly cut slides should be submitted to the testing laboratory (Foundation Medicine) within 30 days from the date they are cut (details pertaining to tumor submission are in the Procedures Manual). Details for sample collection, processing, and shipping will be provided in the Laboratory Manual. Participants who have a documented FGFR3 mutation or rearrangement confirmed by Foundation Medicine do not need the FGFR status reconfirmed centrally if the report is within 24 months.

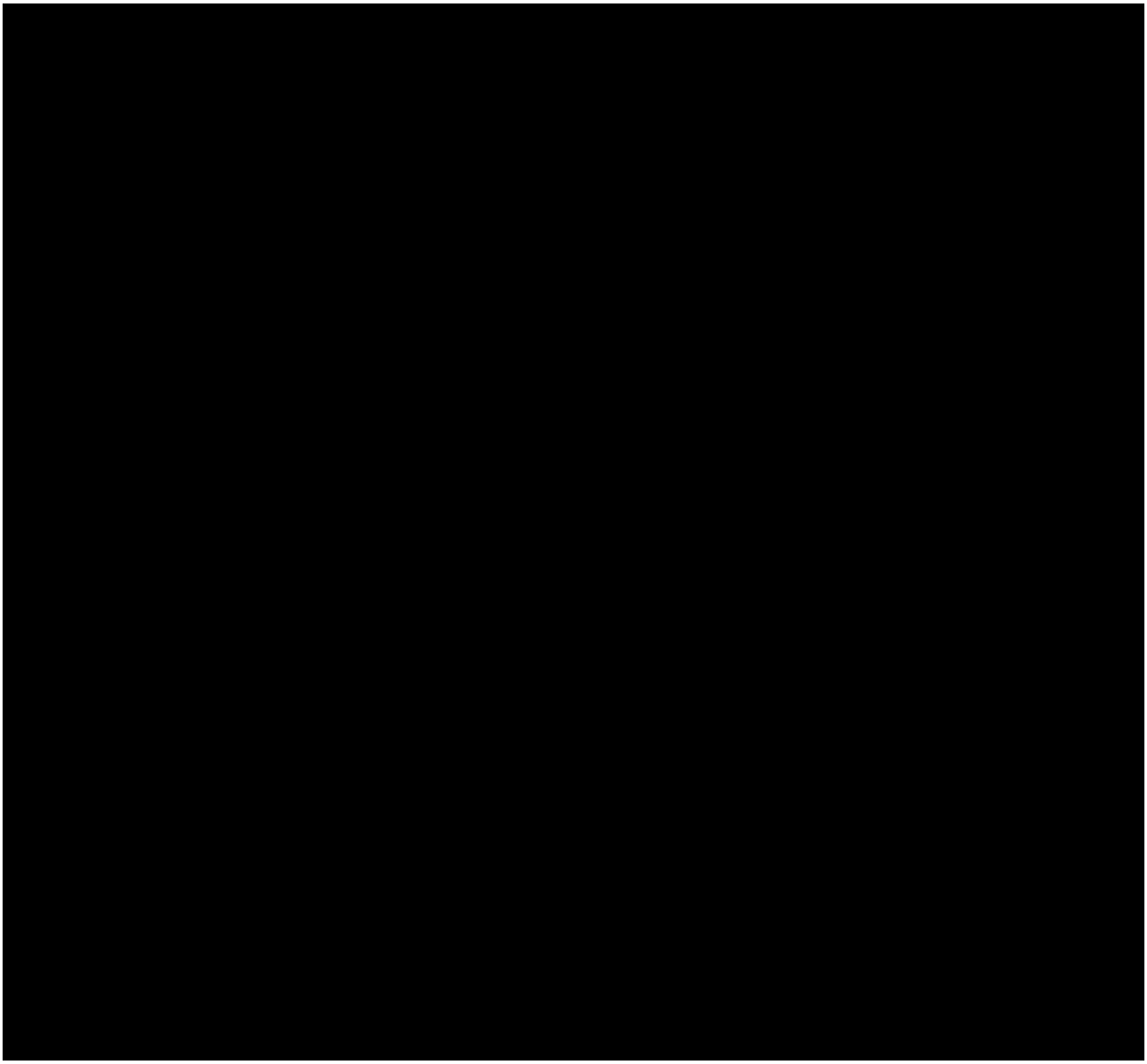
Refer to Appendix E for a list of known FGFR3 alterations. Novel alterations may be discovered in which case the Sponsor must be contacted to review eligibility.

8.7.1.2. Tumor Tissue Collection for Testing PD-L1 Expression

PD-L1 expression must be tested by a local or central laboratory as part of the prescreening or screening process using an approved IHC companion diagnostic (ie, Dako PD-L1 IHC 22C3 pharmDx). A participant can be randomized using a local report but this will need to be retrospectively confirmed by the sponsor's central lab. Patients who have a Dako PD-L1 IHC 22C3 pharmDx report will not need to have their PD-L1 status confirmed centrally. PD-L1 status (CPS ≥10 or CPS < 10) must be determined during the screening period prior to randomization. If submitting unstained cut slides, 3 unstained, consecutive FFPE, newly cut slides should be

submitted to the testing laboratory within 30 days from the date they are cut (details pertaining to tumor submission are in the Procedures Manual). Details for sample collection, processing, and shipping will be provided in the Laboratory Manual.





8.8. Unscheduled Visits

Unscheduled visits may occur as clinically indicated. They can be used for visits that occur outside of visit windows and should be noted in the eCRF as an unscheduled visit.

8.9. End of Treatment and/or Early Termination

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

8.10. Follow-Up

8.10.1. Safety Follow-Up

The safety follow-up period is the interval between the EOT visit and the scheduled follow-up visit, which should occur no later than 30 days after the EOT visit (or after the last dose of study treatment if the EOT visit was not performed). Adverse events and SAEs must be reported up until 1) at least 30 days after the last dose of study treatment, the date of the follow-up visit, or the start of a new anticancer therapy or 2) until toxicities resolve, return to baseline, or are deemed irreversible, whichever is longer. Reasonable efforts should be made to have the participant return for the follow-up visit and report any AEs that may occur during this period. If the participant cannot return to the site for the safety follow-up visit (eg, lives far away), the participant should be contacted by telephone for assessment of AEs and SAEs. Sites should document this contact in the source.

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

8.10.2. Post-Treatment Disease Follow-Up

Participants who discontinue study treatment for a reason other than disease progression will move into the disease status follow-up period and should continue to be assessed by radiologic imaging to monitor disease status at the same schedule as if continuing on treatment per the schedule of activities (see Table 4). Every effort should be made to collect information regarding disease status until:

- The start of new anticancer therapy.
- Disease progression (confirmed by BICR).
- Pregnancy.
- Death.
- Withdrawal of consent.
- The end of the study.

8.10.3. Survival Follow-Up

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

For participants having entered the survival follow-up period of the study, the site will use continuing participant records to supply data on subsequent treatment regimens, tumor assessments (if discontinued treatment for a reason other than progression), and OS in the eCRF. For participants who do not intend to return to the study investigator for their ongoing care, follow-up should be maintained by phone contact, participant records, and public

records/databases at intervals of no longer than 6 weeks. After the final primary analysis is performed, the follow-up interval for subsequent anticancer treatments and survival may be reduced to every 12 weeks.

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

9.1. Definition of Adverse Event

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

Events NOT Meeting the Adverse Event Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition or considered to be treatment-related by the investigator. • Efficacy endpoints as outlined in Section 3 will not be reported as AE/SAEs, specifically, any event that is related to disease progression of the cancer under study. Unblinded aggregated efficacy endpoint events and safety data will be monitored to ensure the safety of the participants in the study. Any suspected endpoint that upon review is not progression of the cancer under study will be forwarded to Incyte Pharmacovigilance as a SAE within 24 hours of determination that the event is not progression of the cancer under study. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE if it occurred after signing informed consent. If present before entering the study, the condition should be captured as medical history. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

9.2. Definition of Serious Adverse Event

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

A Serious Adverse Event is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an adverse drug experience that places the participant, in the opinion of the initial reporter, at immediate risk of death from the adverse experience as it occurred. This does not include an adverse drug experience that, had it occurred in a more severe form, might have caused death.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent or significant disability/incapacity

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

e. Is a congenital anomaly/birth defect

f. Other situations (Important Medical Event)

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

g. May lead to disability (for Japanese participants)

An event that exposes a participant to a risk of dysfunction to the extent that it interferes with daily life when the adverse drug reaction occurred. It does not mean that the adverse drug reaction could have caused disability if the reaction were more severe.

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

Adverse Event and Serious Adverse Event Recording

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

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

- The severity grade (CTCAE Grade 1 to 5). See below for further instructions on the assessment of intensity.
- Whether there is at least a reasonable possibility that the AE is related to the study treatments (including study drug(s) and/or reference therapy): suspected (yes) or not suspected (no). See below for further instructions on the assessment of causality.

- The start and end dates, unless unresolved at final follow-up.
- The action taken with regard to study drug as a result of the AE/SAE(s).
- The event outcome (eg, not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown).
- The seriousness, as per the SAE definition provided in Section 9.2.
- The action taken with regard to the event. Note: If an AE is treated with a concomitant medication or nondrug therapy, this action should be recorded on Adverse Event Form and the treatment should be specified on the appropriate eCRF (eg, Prior/Concomitant Medications, Procedures and Non-Drug Therapy).

Assessment of Intensity

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

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

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

Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE. If reference therapy is used in combination with an Incyte study drug or multiple Incyte study drugs are used, the relationship to each study drug/reference therapy must be assessed (ie, for the Incyte product(s) and for the other product(s) that is used in combination with the Incyte product). If appropriate, the relationship to the combination may be assessed as well.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than that a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- The investigator will also consult the reference safety information in the IB and/or Product Information, for marketed products, in his/her assessment.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration, will be considered and investigated.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- With regard to assessing causality of SAEs:
  - There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report. However, the causality assessment is one of the criteria used when determining regulatory reporting requirements. **Therefore, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE.**

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

9.4. Reporting of Serious Adverse Events

Regardless of suspected causality (eg, relationship to study drugs, reference therapies, or study procedure[s]), all SAEs occurring after the participant has signed the ICF through 90 days after the last dose of study treatment ***or*** 30 days after the last dose of study treatment when starting a new anticancer therapy, whichever occurs earlier must be reported to the sponsor (or designee) in English within **24 hours** of learning of its occurrence, unless otherwise specified by the Protocol. The investigator will submit any updated SAE data to the sponsor (or designee) within 24 hours of it being available. For Japan, this information must also be reported immediately to the head of the study site.

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

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

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

If the SAE is not documented in the IB for the study drug (new occurrence) and is thought to be related to the sponsor's study drug, the sponsor or its designee may urgently require further information from the investigator for reporting to health authorities. The sponsor or its designee may need to issue an Investigator Notification to inform all investigators involved in any study

with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions will be collected and reported to the competent authorities and relevant ethics committees in accordance with national regulatory requirements in participating countries.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators. For Japan, suspected expected deaths and life-threatening events will also be reported to the PMDA as per local regulatory requirements.

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

An investigator who receives an investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

Serious Adverse Event Reporting

- Information about all SAEs is collected and recorded on the Adverse Event Form in the eCRF.
- The investigator must also complete the Incyte Serious Adverse Event Report Form, in English. Refer to the Incyte Reference Guide for Completing the Serious Adverse Event Report Form.
  - Facsimile or email transmission of the Serious Adverse Event Report Form is the preferred method to transmit this information to the Incyte Pharmacovigilance Department at SafetyReporting@incyte.com. The contact information of the sponsor's study-specific representatives is listed in the Study Reference Manual provided to each site. The original copy of the Serious Adverse Event Report Form and the confirmation sheet must be kept at the study site.
- Follow-up information is recorded on an amended or new Serious Adverse Event Report Form, with an indication that it is follow-up to the previously reported SAE and the date of the original report. The follow-up report should include information that was not provided on the previous Serious Adverse Event Report Form, such as the outcome of the event (eg, resolved or ongoing), treatment provided, action taken with study drug because of the SAE (eg, dose reduced, interrupted, or discontinued), or participant disposition (eg, continued or withdrew from study participation). Each recurrence, complication, or progression of the original event should be reported as follow-up to that event, regardless of when it occurs.
- In rare circumstances and in the absence of facsimile or computer equipment, notification by telephone is acceptable with a copy of the Incyte Serious Adverse Event Report Form sent by overnight mail or courier service. Initial notification via telephone does not replace the need for the investigator to complete and sign the Serious Adverse Event Report Form within the designated reporting time frames.
- Contacts for SAE reporting can be found in the Investigator Manual.
- For Japan, any SAE relating to phosphate binders that were used for treatment of hyperphosphatemia should also be reported in the same manner.

9.5. Adverse Events of Special Interest

Dose modification guidelines for select AESIs for pembrolizumab are presented in Appendix B. A comprehensive summary of AESIs for pembrolizumab is presented in the pembrolizumab IB. There are no AESIs for pemigatinib.

9.6. Emergency Unblinding of Treatment Assignment

Not applicable.

9.7. Pregnancy

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

- The study drug must be discontinued immediately (female participants only; see Section 6.6 for the maximum permitted duration of study drug interruption).
- The investigator must complete and submit the Incyte Clinical Trial Pregnancy Form to the sponsor or its designee within **24 hours** of learning of the pregnancy.

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

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

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

9.8. Warnings and Precautions

Special warnings or precautions for the study treatments, 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.

9.9. Product Complaints

The sponsor collects product complaints on study drugs, medical devices (Japan), 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, and for Japan, complaints associated with unapproved medical devices will be reported to the sponsor with a Medical Device Defect Report Form. For Japan, the sponsor will report medical device defects to the PMDA as per local regulatory requirements. All product complaints associated with other study material will be reported directly to the respective manufacturer.

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

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

9.10. Treatment of Overdose

No specific information is available on the treatment of overdose of pemigatinib or pembrolizumab.

For this study, any dose of pemigatinib greater than 20 mg and any dose higher than ≥ 1000 mg (5 times the dose) of pembrolizumab within a 24-hour time period [± 4 hours] will be considered an overdose. In the event of an overdose, the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

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.

10. STATISTICS

10.1. Sample Size Determination

The sample size calculation is based on the primary endpoint PFS.

The SOC treatment group in this study consists of participants who will receive pembrolizumab or chemotherapy depending on the participant carboplatin eligibility and PD-L1 CPS. In KEYNOTE-052, a large single arm, Phase 2 study with pembrolizumab conducted in cisplatin-ineligible patients who had not been previously treated with systemic chemotherapy, the median PFS was 2.1 months (95% CI: 2, 3; Balar et al 2017a). In EORTC 30968, a randomized Phase 2/3 study comparing gemcitabine and carboplatin versus methotrexate/carboplatin/vinblastine, the median PFS was 5.8 months in the gemcitabine/carboplatin group as compared with 4.2 months in the other group(s) (De Santis et al 2012). Based on available data from KEYNOTE-052 and EORTC Study 30968 and participants' distribution percentages (see Table 18), it is estimated that the median PFS in the SOC treatment group (pembrolizumab or gemcitabine/carboplatin) is expected to be 5 months based on simulation.

Table 18: Median Progression-Free Survival Assumptions for Standard of Care Treatments

Patient Population	Total (%) (N = 132)	Median PFS Assumption
Carboplatin-ineligible participants who will receive pembrolizumab	26 (20%)	2.1 months
Carboplatin-eligible participants who will receive pembrolizumab (CPS ≥ 10)	16 (12%)	4.9 months
Carboplatin-eligible participants who will receive gemcitabine/carboplatin (CPS < 10)	90 (68%)	5.8 months

It is expected that treatment with pemigatinib plus pembrolizumab will result in an HR of 0.68 for PFS compared to SOC, which corresponds to an increase in median PFS of 2.4 months under the exponential model assumption. It is calculated that a total of 210 PFS events in the combined treatment groups of pemigatinib plus pembrolizumab and SOC need to be observed to ensure 80% power to test the null hypothesis: PFS HR = 1, versus the specific alternative hypothesis: PFS HR = 0.68 for pemigatinib plus pembrolizumab versus SOC. This calculation assumes analysis using a 1-sided log-rank test at a 0.025 overall significance level and participants are randomized to the treatment groups in a 1:1 ratio.

To keep a minimum meaningful hazard ratio of 0.68 for PFS in participants with pemigatinib alone versus SOC, a total of 210 PFS events in the combine treatment groups of pemigatinib alone and SOC need to be observed to achieve 80% power to test the null hypothesis: PFS HR = 1, versus the specific alterative hypothesis: PFS HR = 0.68 for pemigatinib alone versus SOC. This calculation assumes analysis using a 1-sided log-rank test at a 0.025 overall significance level and participants are randomized to the treatment groups in a 1:1 ratio.

Assuming uniform accrual of the participants over a 36-month period, an 8-month follow-up after the last participant is randomized, and a 5% lost to follow-up rate, a total of approximately 372 participants will needed to be randomized to observe the targeted PFS events at approximately 44 months after first participant is randomized.

The median OS for the SOC group is about 10 months based on EORTC Study 30968 and KEYNOTE-052. It is calculated that a total of 194 deaths in the combined treatment groups of pemigatinib plus pembrolizumab and SOC need to have been observed to achieve 76% power to detect an HR of 0.68 using a 1-sided log-rank test at a 0.025 overall significant level. Final OS analysis is expected to occur at approximately 52 months after first participant is randomized.

At the time when final PFS analysis is conducted, it is expected that about 169 deaths will be observed in the combined treatment groups of pemigatinib plus pembrolizumab and SOC. Overall survival comparison for pemigatinib plus pembrolizumab versus SOC will be conducted at nominal 1-sided alpha of 0.0147 according to the O'Brien-Fleming spending function. Final OS analysis comparing pemigatinib plus pembrolizumab versus SOC will be conducted at nominal 1-sided alpha of 0.0103 when approximately 194 deaths are observed in the combined treatment groups of pemigatinib plus pembrolizumab and SOC. The actual boundaries will be re-calculated from the actual number of deaths at the time when final PFS analysis is conducted using the alpha- and beta-spending functions.

10.2. Populations for Analysis

Table 19 presents the populations for analysis.

Table 19: Populations for Analysis

Population	Description
ITT	The ITT population includes all participants who are randomized into the study. Treatment groups for this population will be determined according to the treatment assignment at the time of randomization. All efficacy analyses will be conducted using the ITT population.
PP	Participants in the ITT who are considered to be sufficiently compliant with the Protocol comprise the PP population. This population includes all ITT participants who meet all major inclusion and no major exclusion criteria based on blinded review of clinical data. Specific criteria and review of this population will be defined in the statistical analysis plan. The primary endpoint will be analyzed using the PP population as a sensitivity analysis.
Safety	The safety population includes all randomized participants who received at least one dose of study treatment. 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.

10.3. Level of Significance

The overall level of significance is strongly controlled for primary and key secondary objectives at 1-sided 0.025 using a fixed sequential testing procedure. The primary and key secondary efficacy endpoints at final analysis will be tested in the following order:

1. PFS comparison for pemigatinib plus pembrolizumab versus SOC at 1-sided 0.025.
2. OS comparison for pemigatinib plus pembrolizumab versus SOC at 1-sided 0.0147 at the time when primary analysis of PFS is conducted; OS comparison for pemigatinib plus pembrolizumab versus SOC at 1-sided 0.0103 at final OS analysis.
3. PFS comparison for pemigatinib only versus SOC at 1-sided 0.025. If the pemigatinib group is discontinued early after futility analysis (see Section 10.5), this analysis will not be performed.
4. OS comparison for pemigatinib only versus SOC at 1-sided 0.0147 at the time when primary analysis of PFS is conducted; OS comparison for pemigatinib only-versus SOC at 1-sided 0.0103 at final OS analysis. If the pemigatinib group is discontinued early after futility analysis (see Section 10.5), this analysis will not be performed.

10.4. Statistical Analyses

10.4.1. Primary Analysis

Progression-free survival is defined as the time from the date of randomization to the date of the first documented progression or death due to any cause, whichever occurs first. Progression-free survival will be assessed via BICR according to RECIST v1.1 criteria. Participants without a PFS event at the time of analysis will be censored. Censoring for PFS will follow the FDA Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (FDA 2018a). The primary analysis of PFS will be based on ITT population and will compare PFS difference between treatment groups (pemigatinib plus pembrolizumab vs SOC, pemigatinib alone vs SOC) using a log-rank test stratified by eligibility to receive carboplatin, primary disease location, and PD-L1 CPS. The stratification will be based on the randomization stratification factors. Kaplan-Meier curves, medians, and 95% CIs of the medians will be presented for each treatment group. The HR for PFS will be calculated, along with its 95% CI, from a stratified Cox model using the same stratification factors as for the log-rank test with Efron's likelihood approximation to account for ties in event times. Progression-free survival analysis for the comparison of pemigatinib plus pembrolizumab versus SOC as well as the comparison of pemigatinib alone versus SOC will be conducted separately.

As sensitivity analyses, difference in PFS between pemigatinib plus pembrolizumab and SOC will be analyzed using log-rank test stratified by eligibility to receive carboplatin, primary disease location, and PD-L1 CPS in the PP population; difference in PFS between pemigatinib alone and SOC will be analyzed using log-rank test stratified by same stratification factors in the PP population. Difference in PFS between pemigatinib plus pembrolizumab and SOC as well as the difference between pemigatinib alone and SOC will also be analyzed using a log-rank test stratified by the same stratification factors in the randomized subjects who have known FGFR3 mutation or rearrangement confirmed by the central laboratory.

10.4.2. Secondary Analysis

Secondary efficacy analyses will be conducted for the ITT population. All the secondary analyses for pemigatinib plus pembrolizumab versus SOC and for pemigatinib alone versus SOC will be conducted separately.

Overall survival is defined as the time from date of randomization until death due to any cause. Participants without death observed at the time of analysis will be censored at last date known to be alive. The log-rank test stratified by eligibility to receive carboplatin, primary disease location, and PD-L1 CPS will be used to analyze the OS differences between treatment groups. Kaplan-Meier curves, medians, and 95% CIs of the medians will be presented for each treatment group. The HR for OS will be calculated, along with its 95% CI, from a stratified Cox model using the same stratification factors as for the log-rank test with Efron's likelihood approximation to account for ties in event times.

Objective response rate is defined as the proportion of participants with best overall response of CR or PR per RECIST v1.1 by BICR. Objective response rate will be presented by treatment groups along with 95% CIs. Objective response rates between treatment groups will be compared using Cochran–Mantel–Haenszel test stratified by eligibility to receive carboplatin, primary disease location, and PD-L1 CPS.

Duration of response is defined as the time from the date of the first assessment of CR or PR until the date of the first progressive disease per RECIST v1.1 or death. For participants who achieve a response, Kaplan-Meier curves, medians, and 95% CIs of the medians will be presented for each treatment group. Participants who are still responding at the time of analysis will be censored. Censoring of DOR will follow the same algorithm as the censoring of PFS.

EORTC QLQ-C30 and EQ-5D-5L scales as well as change and percent change from baseline will be summarized with descriptive statistics by visit.

10.4.3. Safety Analyses

Safety analyses will be conducted for the safety population.

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

The clinical laboratory data will be analyzed using summary statistics; no formal treatment group comparisons are planned. In addition, distributions of key laboratory parameters may be plotted over time; these values will also be classified into CTCAE v5.0 toxicity grades and tabulated. Descriptive statistics and mean change from baseline will be determined for vital signs at each assessment time. Vital sign results will be reviewed for clinically notable abnormalities.

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

Measures of exposure to study drug will be summarized by means of summary statistics.

10.5. Futility Analysis

A futility analysis will be performed when a total of approximately 150 participants across all 3 treatment groups have been randomized and have had at least 1 tumor assessment or have permanently discontinued from study. Enrollment will not be held while the futility analysis is being conducted. The study can be stopped for futility if the ORR difference between pemigatinib plus pembrolizumab group versus SOC group is less than 5%. In addition, if ORR in the pemigatinib monotherapy group is inferior to SOC group (ie, ORR observed in Treatment Group B is less than ORR observed in Treatment Group C), the monotherapy group may discontinue further enrollment. This rule is just a guidance and nonbinding.

10.6. Data Monitoring Committee

An independent DMC will be formed. The DMC will consist of qualified individuals who are not involved with the conduct of the study. The establishment, composition, roles, duties, and responsibilities of the DMC are addressed in the DMC Charter. Final decision regarding the study will be made by the sponsor internal team in discussion with the DMC.

11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

11.1. Investigator Responsibilities

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

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

- For Japan: The record retainer at the study site will retain the J-GCP–defined essential documentation until the regulatory approval of pemigatinib or at least 3 years after the discontinuation or completion of the study conduct, whichever is later. If the sponsor requires retention of these documents for a longer period of time, the duration and method of retention will be decided upon through discussion between the sponsor and the study site. It is the responsibility of the sponsor to inform the head of the study site as to when the documents no longer need to be retained.

11.2. Data Management

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

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

The sponsor (or designee) will be responsible for:

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

The investigator will be responsible for:

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

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

11.3. Data Privacy and Confidentiality of Study Records

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

collection, use and disclosure and/or transfer (if applicable) of personal information must be obtained in accordance with local data protection laws.

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

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

11.4. Financial Disclosure

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

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

11.5. Publication Policy

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

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

The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

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

11.6. Study and Site Closure

The sponsor 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.

For Japan: When the study is completed, the investigator should inform the head of the study site of the completion in writing and submit a written summary of the study's outcome, then the head of the study site should promptly inform the IRB and sponsor or designee of the completion in writing.

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

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

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

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APPENDIX A. INFORMATION REGARDING EFFECTIVENESS OF CONTRACEPTIVE METHODS

For male participants in the study:

Male participants must agree to take appropriate precautions to avoid fathering children (defined as the use of an effective method [barrier method] in combination with a highly effective method in preventing pregnancy). Male participants should use a condom from screening through 120 days after the last dose of pemigatinib and/or pembrolizumab or 180 days after the last dose of chemotherapy. If the male participant has a partner that is of childbearing potential, the partner should also use contraception during the study and through 120 days after the last dose of pemigatinib and/or pembrolizumab or 180 days after the last dose of chemotherapy. In addition, male participants must refrain from donating sperm from screening through 120 days after the last dose of pemigatinib and/or pembrolizumab or 180 days after the last dose of chemotherapy. Males who have had a vasectomy qualify as having met the requirement for a highly effective birth control method.

For female participants in the study:

Female participants must agree to take appropriate precautions to avoid pregnancy (defined as the use of an effective method [barrier method] in combination with a highly effective method in preventing pregnancy) from screening through 120 days after the last dose of pemigatinib and/or pembrolizumab or 180 days after the last dose of chemotherapy.

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

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[a]
  - oral
  - intravaginal (not applicable in Japan)
  - transdermal (not applicable in Japan)
- Progestogen-only hormonal contraception associated with inhibition of ovulation[a]
  - oral
  - injectable
  - implantable[b]
- Intrauterine device[b]
- Intrauterine hormone-releasing system[b]
- Bilateral tubal occlusion[b]
- Vasectomized partner[bc]
- Sexual abstinence (not applicable in Japan)[d]

Acceptable birth control methods that result in a failure rate of more than 1% per year include:

- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
- Male or female condom with or without spermicide[e]
- Cap, diaphragm, or sponge with spermicide[e]
- Tubal ligation

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

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

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

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

[e] A combination of male condom with either cap, diaphragm, or sponge with spermicide (double barrier methods) are also considered acceptable, but not highly effective, birth control methods.

Source: Clinical Trial Facilitation Group 2014.

APPENDIX B. PEMBROLIZUMAB DOSE MODIFICATIONS

Dose Modifications and Toxicity Management for Immune-Related Adverse Events Associated With Pembrolizumab

AEs associated with pembrolizumab exposure may represent an immunologic etiology. These irAEs may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than 1 body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided.

Table B1: Dose Modification and Toxicity Management Guidelines for Immune-Related Adverse Events Associated With Pembrolizumab

General instructions:

- Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.
- For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab must be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks.
- For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.

irAE	Toxicity Grade or Conditions (CTCAE v5.0)	Action Taken to Pembrolizumab	irAE Management With Corticosteroid and/or Other Therapies	Monitor and Follow-Up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		

Table B1: Dose Modification and Toxicity Management Guidelines for Immune-Related Adverse Events Associated With Pembrolizumab (Continued)

irAE	Toxicity Grade or Conditions (CTCAE v5.0)	Action Taken to Pembrolizumab	irAE Management With Corticosteroid and/or Other Therapies	Monitor and Follow-Up
Diarrhea/Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus) • Participants with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
	Grade 4 or recurrent Grade 3 (colitis)	Permanently discontinue		
AST/ALT elevation or Increased Bilirubin	Grade 2	Withhold	• Administer corticosteroids (initial dose of 0.5-1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)
	Grade 3 or 4	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[a]		

Table B1: Dose Modification and Toxicity Management Guidelines for Immune-Related Adverse Events Associated With Pembrolizumab (Continued)

irAE	Toxicity Grade or Conditions (CTCAE v5.0)	Action Taken to Pembrolizumab	irAE Management With Corticosteroid and/or Other Therapies	Monitor and Follow-Up
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or permanently discontinue[a]		
Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per SOC	• Monitor for signs and symptoms of thyroid disorders
Skin reactions	Grade 3 or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	Withhold	• Based on severity of AE administer topical and IV corticosteroids, topical emollients, oral antihistamines and immune suppression if needed.	• Withhold until adverse reaction recovers to Grade 0-1
	Grade 4 or confirmed SJS or TEN	Permanently discontinue		
Nephritis and renal dysfunction	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
All other irAEs	Intolerable/ persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Guillain-Barre Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		

[a] Decision to withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician.

Note: For participants with Grade 3 or 4 immune-related endocrinopathy where withhold of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).

Note: For nephritis and renal failure: the guideline for pembrolizumab renal failure or nephritis modification should only be followed if the etiology is determined to be immune-mediated with supporting biopsy

Dose Modification and Toxicity Management of Infusion Reactions Related to Pembrolizumab

Pembrolizumab may cause severe or life-threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided.

Table B2: Pembrolizumab Infusion Reaction Dose Modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated.	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.	None.
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hours.	Stop Infusion. Additional appropriate medical therapy may include but is not limited to: • IV fluids • Antihistamines • NSAIDs • Acetaminophen • Narcotics Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (eg, from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug intervention.	Participant may be premedicated 1.5 h (± 30 min) prior to infusion of pembrolizumab with: • Diphenhydramine 50 mg PO (or equivalent dose of antihistamine) • Acetaminophen 500-1000 mg PO (or equivalent dose of analgesic)

Grades 3 or 4 Grade 3: Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates). Grade 4: Life-threatening; pressor or ventilatory support indicated.	Stop Infusion. Additional appropriate medical therapy may include but is not limited to: • Epinephrine** • IV fluids • Antihistamines • NSAIDs • Acetaminophen • Narcotics • Oxygen • Pressors • Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. Participant is permanently discontinued from further study drug intervention.	No subsequent dosing.

Note: Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration.
Note: For further information, please refer to the CTCAE v5.0 at http://ctep.cancer.gov.

Other Allowed Dose Interruptions for Pembrolizumab

Pembrolizumab may be interrupted for situations other than treatment-related AEs such as medical/surgical events or logistical reasons not related to study therapy. Participants should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the sponsor. The reason for interruption should be documented in the participant's study record.

APPENDIX C. INSTRUCTION TO PARTICIPANTS FOR HANDLING STUDY DRUG (PEMIGATINIB)

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

- Store the study drug at room temperature.
- Only remove the number of tablets needed at the time of administration.
- Do not remove doses in advance of the next scheduled administration.
- Make every effort to take doses on schedule.
- Report any missed doses/lost tablets/capsules.
- Take study drug with a full glass of water.
- Do not take another dose if vomiting after taking study drug occurs.
- Keep study drug in a safe place and out of reach of children.
- Bring all used and unused study drug bottles to the site at each visit.
- If a dose of pemigatinib is missed by more than 4 hours, that dose should be skipped and the next scheduled dose should be administered at the usual time.

APPENDIX D. CYP3A4 INHIBITORS AND INDUCERS

Refer to FDA for Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers for the most current list (FDA 2016).

CYP3A Inducers

Inducers	Therapeutic class
Potent CYP3A Inducers	
Rifampin	Antibiotics
Mitotane	Other Antineoplastics
Avasimibe	Other Antilipemics
Rifapentine	Antibiotics
Apalutamide	Antiandrogens
Phenytoin	Anticonvulsants
Carbamazepine	Anticonvulsants
Enzalutamide	Antiandrogens
St John's Wort extract	Herbal medications
Lumacaftor	Cystic fibrosis treatments
Rifabutin	Antibiotics
Phenobarbital	Anticonvulsants
Moderate CYP3A Inducers	
Ritonavir and St. John's wort	None
Semagacestat	Alzheimer's treatments
Efavirenz	NNRTIs
Tipranavir and ritonavir	Protease inhibitors
Dabrafenib	Kinase inhibitors
Lesinurad	Antigout and uricosuric agents
Bosentan	Endothelin receptor antagonists
Genistein	Food products
Thioridazine	Antipsychotics
Nafcillin	Antibiotics
Talviraline	NNRTIs
Lopinavir	Protease inhibitors
Modafinil	Psychostimulants
Pf-06282999	Myeloperoxidase inactivators
Etravirine	NNRTIs
Lersivirine	NNRTIs
Telotristat ethyl	Antidiarrheals

CYP3A Inhibitors

Inhibitor	Therapeutic Class
Potent CYP3A Inhibitors	
VIEKIRA PAK	Antivirals
Indinavir/RIT	Protease inhibitors
Tipranavir/RIT	Protease inhibitors
Ritonavir	Protease inhibitors
Cobicistat (GS-9350)	None
Ketoconazole	Antifungals
Indinavir	Protease inhibitors
Troleandomycin	Antibiotics
Telaprevir	Antivirals
Danoprevir/RIT	Antivirals
Elvitegravir/RIT	Treatments of AIDS
Saquinavir/RIT	Protease inhibitors
Lopinavir/RIT	Protease inhibitors
Itraconazole	Antifungals
Voriconazole	Antifungals
Mibefradil	Calcium channel blockers
LCL161	Cancer treatments
Clarithromycin	Antibiotics
Posaconazole	Antifungals
Telithromycin	Antibiotics
Grapefruit juice DS	Food products
Conivaptan	Diuretics
Nefazodone	Antidepressants
Nelfinavir	Protease inhibitors
Saquinavir	Protease inhibitors
Ribociclib	Kinase inhibitors
Idelalisib	Kinase inhibitors
Boceprevir	Antivirals

Inhibitor	Therapeutic Class
Moderate CYP3A Inhibitors	
Erythromycin	Antibiotics
Fluconazole	Antifungals
Atazanavir/RIT	Protease inhibitors
Darunavir	Protease inhibitors
Diltiazem	Calcium channel blockers
Darunavir/RIT	Protease inhibitors
Dronedarone	Antiarrhythmics
Crizotinib	Kinase inhibitors
Atazanavir	Protease inhibitors
Letermovir	Antivirals
GSK2647544	Alzheimer's disease & dementia treatments
Aprepitant	Antiemetics
Casopitant	Antiemetics
Amprenavir	Protease inhibitors
Faldaprevir	Antivirals
Imatinib	Antineoplastic agents
Verapamil	Calcium channel blockers
Netupitant	Antiemetics
Nilotinib	Kinase inhibitors
Grapefruit juice	Food products
Tofisopam	Benzodiazepines
Cyclosporine	Immunosuppressants
ACT-178882	Renin inhibitors
Ciprofloxacin	Antibiotics
Magnolia vine (Schisandra sphenanthera)	Herbal medications
Isavuconazole	Antifungals
Cimetidine	H-2 receptor antagonists
FK1706	Central nervous system agents

APPENDIX E. FGFR3 GENE ALTERATIONS

Please follow instructions outlined in the Investigator Site Files for screening/enrolling participants. This list contains recurrent FGFR3 alterations that have been previously described or are present in somatic mutation databases and is not inclusive of all possible alterations. For FGFR3 alterations not present on this list, please consult with the study sponsor.

Alteration	
R248C	K650M
S249C	K650E
G370C	K650Q
S371C	K650T
Y373C	K650N
G380R	Novel FGFR3 fusion (with partner specified)
G380E	FGFR3-BAIAP2L1
A391E	FGFR3-IGH
R399C	FGFR3-TACC3
S433C	FGFR3-WHSC1
D641N	

APPENDIX F. PROTOCOL AMENDMENT SUMMARY OF CHANGES

Document	Date
Amendment 1	17 APR 2020

Amendment 1 (17 APR 2020)

Overall Rationale for the Amendment: Requests by Health Authorities for certain changes as well as feedback from Scientific Steering Committee to help with enrollment of participants.

1. **Section 1, Protocol Summary (Table 2: Key Study Design Elements; Table 3: Treatment Groups for Randomization); Section 2.2.2, Justification for Dose and Schedule; Section 4.1, Overall Design (Table 8: Treatment Groups for Randomization); Section 6.1, Study Treatments Administered (Table 10: Study Treatment Information)**

   Description of change: Added duration of treatments for the study groups.

   Rationale for change: Clarification requested by investigators.

2. **Section 1, Protocol Summary (Table 4: Schedule of Activities)**

   The following updates were made:

   a. **Description of change:** Revised QLQ-C30 and EQ-5D-5L assessments during the treatment period to every 3 cycles on Day 1 starting on Cycle 4.

      Rationale for change: In order to eliminate the requirement that a participant be seen in the clinic to complete the QLQ-C30 and EQ-5D on the same days as imaging assessments, the schedule for collection of quality-of-life assessments has been updated and will be associated/completed at the time of already planned visits to the clinic. This revision will ensure that the questionnaires are completed by participants at the required timepoints.

   b. **Description of change:** Clarified that assessments for up-titration will be completed during Cycle 1 but the first opportunity to up-titrate a participant is at Cycle 2 Day 1.

      Rationale for change: Requested by the Italian Health Authority.

   c. **Description of change:** Added that IRT should be contacted during the patient prescreening and Cycle 1 Day 8.

      Rationale for change: Administrative errors.

3. **Section 1, Protocol Summary (Table 4: Schedule of Activities); Section 4.1, Overall Design; Section 5.1, Inclusion Criteria (Criteria 6 and 7); Section 6.4.1.1, PD-L1 CPS Results; [redacted]**

   Description of change: Updated to indicate that participants can be randomized based on local genomics testing results for FGFR3 mutation or rearrangement and PD-L1 status, but tissue will need to be sent for central laboratory confirmation. Participants who have a documented FGFR3 mutation or rearrangement confirmed by Foundation Medicine do not need the FGFR status reconfirmed centrally if the report is within

24 months In addition, participants whose PD-L1 status is not evaluable will not be eligible.

Rationale for change: Concordance rates with local genomics assay compared to the central laboratory have been very high on other studies in the program. The Scientific Steering Committee and numerous sites have voiced their concerns about the turnaround time for the central testing as a barrier to recruitment. MHRA recommended that if a PD-L1 sample is not evaluable, it is not acceptable to assign an arbitrary positive score.

4. **Section 1, Protocol Summary (Table 3: Treatment Groups for Randomization; Figure 1, Study Design Schema); Section 4.1, Overall Design (Table 8: Treatment Groups for Randomization); Section 5.1, Inclusion Criteria (Criterion 5); Section 6.4.1.1, PD-L1 CPS Results**

   Description of change: Note added to indicate that in certain regions, pembrolizumab monotherapy will be administered only to participants who are not eligible for cisplatin-containing chemotherapy regardless of PD-L1 status.

   Rationale for change: MHRA recommended as this wording is consistent with the licensed indication included in the pembrolizumab SmPC. The pembrolizumab SmPC does not contain any indication for treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible to receive any platinum-containing chemotherapy regardless of PD-L1 expression status.

5. **Section 1, Protocol Summary (Table 4: Schedule of Activities); Section 8.2.1, Tumor Imaging; Section 8.2.1.1, Initial Tumor Imaging; Section 8.2.2, Tumor Imaging During the Study**

   Description of change: Updated to indicate that brain imaging and bone scans only need to be done at baseline if participants are symptomatic. Removed notes requiring that bone scans and brain imaging need to be completed to confirm CR if positive at baseline. Clarified that bone scans and brain imaging need to be repeated with other imaging assessments while a participant is on study if they were positive at baseline. Added that all imaging must be sent to central vendor as soon as possible after completion.

   Rationale for change: For clarification. The notes regarding imaging requirements to confirm CR were removed as all imaging requirements are noted in Table 4.

6. **Section 1, Protocol Summary (Table 4: Schedule of Activities); Section 8.5.5, Comprehensive Eye Examination; Section 6.6.1, Criteria and Procedures for Dose Interruptions and Adjustments of Pemigatinib**

   Description of change: Updated to indicate that OCT is mandatory at baseline, every 3 cycles, and at EOT as part of the comprehensive eye examination and to include guidelines for treatment associated with SRD/RPED.

   Rationale for change: For consistency with other protocols in the INCB054828 program.

7. **Section 1, Protocol Summary (Table 4: Schedule of Activities); Section 5.1, Inclusion Criteria (Criterion 10b); Section 8.5.6.1, Pregnancy Testing; Section 8.5.6, Laboratory Assessments (Table 15: Required Laboratory Analytes)**

   Description of change: Added specification that serum pregnancy testing at screening should be performed a maximum of 7 days before administration of study drug.

   Rationale for change: MHRA requirement.

[redacted]

9. **Section 4.3, Study Termination**

   Description of change: Added language to describe the notification process for study termination in Japan.

   Rationale for change: To clarify the process of study termination in Japan per J-GCP.

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

    Description of change: Added language to indicate age criteria for Japanese participants (criterion 1) and revised language regarding willingness to avoid pregnancy or fathering children for Japanese participants (criterion 11). Appendix A modified to indicate information that is not applicable in Japan.

    Rationale for change: Recommended standard practices in Japan.

11. **Section 5.1, Inclusion Criteria**

    Description of change: In inclusion criterion 5, added clarification that ineligibility for chemotherapy means either not eligible due to comorbidities or due to lack of benefit as previously demonstrated in clinical studies and therefore not used as SOC.

    Rationale for change: Clarification requested by Italian Health Authority.

12. **Section 5.1, Inclusion Criteria; Section 12, References; Appendix A, Information Regarding Effectiveness of Contraceptive Methods**

    Description of change: Inclusion criteria 10a and 10b were modified to require the use of a highly effective method of contraception in combination with an effective method (barrier method) of preventing pregnancy. Appendix A was modified to reflect this change.

    Rationale for change: Recommendation from Health Canada.

13. **Section 5.2, Exclusion Criteria**

    The following updates were made:

    a. **Description of change:** Exclusion criterion 2 updated to indicate that prior receipt of an anti–PD-1, anti–PD-L1, or anti–PD-L2 agent, or an agent directed to another co-inhibitory T-cell receptor, is allowed , but the last treatment must have been completed at least 18 months before enrollment in this study.

       Rationale for change: After discussion with numerous investigators and the Scientific Steering Committee, it was determined that a large number of patients are now being treated with checkpoint inhibitors for urothelial carcinoma in early-stage disease. Excluding these patients will further limit the number of participants eligible for this study.

    b. **Description of change:** Exclusion criterion 8 was updated to specify radiation to the primary tumor site for the sole purpose of sensitizing the tumor to local radiation can be done if there is a 3-week washout period prior to the first dose of study drug.

       Rationale for change: For consistency between inclusion criterion 8 and exclusion criterion 8.

    c. **Description of change:** In exclusion criterion 17, removed the note stating that no testing for HBV or HCV is required unless mandated by local health authority.

       Rationale for change: The ICF and Protocol Section 8.5.6.2 state that HBV and HCV testing will be done at screening.

    d. Description of change: In exclusion criterion 11 (Table 9: Exclusionary Laboratory Values), the hemoglobin units corrected to g/dL. Direct bilirubin value corrected to ≤ ULN.

       Rationale for change: Administrative error/incorrect unit of measure.

14. **Section 6.1, Study Treatments Administered (Table 10: Study Treatment Information)**

    Description of change: Added temperature range and language for room temperature.

    Rationale for change: Japanese requirement.

15. **Section 6.2, Phosphate Binders in Japan (Table 11: Study Treatment 2 [Phosphate Binders for Japan]); Section 6.3, Preparation, Handling, and Accountability; Section 6.6.2, Management of Hyperphosphatemia**

    Description of change: Added phosphate binder information for Japan and clarification that phosphate binders for treatment of hyperphosphatemia for Japanese participants are provided by the sponsor and that the required documentation for binders is the same as for study drug.

    Rationale for change: To clarify the tested binders in Japan for the management of hyperphosphatemia, which the sponsor provided with study-specific label, and to meet Japanese requirements.

16. **Section 6.7.1, Restricted Medications and Procedures**

    Description of change: Updated to state that calcium-based phosphate binders may be used with appropriate clinical monitoring if other types of phosphate binders are not available in certain regions.

    Rationale for change: Clarification that calcium-based phosphate binders can be used with appropriate clinical monitoring if this is the only option in certain regions.

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

    Description of change: Clarified that participants in Treatment Group A (pemigatinib + pembrolizumab) need to discontinue pembrolizumab after 35 cycles of treatment but can continue pemigatinib until progression.

    Rationale for change: For clarification.

18. **Section 8.5.1, Adverse Events**

    Description of change: Language was added to indicate that, for Japanese participants, the relationship with phosphate binders should also be collected on the Adverse Events Form in the eCRF.

    Rationale for change: Japanese requirement.

19. **Section 8.5.4, Electrocardiograms**

    Description of change: Clarified that in the event that a single QTc is > 480 ms at screening, the participant may enroll if three ECGs are completed and the average QTc for the 3 ECGs is < 480 ms or with approval from the medical monitor.

    Rationale for change: To avoid artifact measurements of a single ECG.

20. **Section 8.5.6, Laboratory Assessments**

    Description of change: Updated to indicate that the site's local laboratory will complete all safety assessments but will not analyze [redacted]. The site's laboratory will draw the blood for these tests, but the analyses will be conducted by Incyte.

    Rationale for change: Administrative error.

21. **Section 8.7.1.3, Assessment on Tumor Samples**

    Description of change: Figure 2 was updated to indicate that an archival tumor tissue sample is required from < 24 months prior to screening as stated in Section 8.7.1.

    Rationale for change: Administrative error/incorrect unit of time.

22. **Section 9.2, Definition of Serious Adverse Event**

    Description of change: Added language about AEs that may lead to disability.

    Rationale for change: Japanese requirement.

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

    Description of change: Language was added to indicate that in Japan, SAEs must be reported to the head of the study site; suspected expected deaths and life-threatening events will be reported to the PMDA; and events related to phosphate binder use for the treatment of hyperphosphatemia will be reported as SAEs.

    Rationale for change: Japanese requirement.

24. **Section 9.9, Product Complaints**

    Description of change: Language added for medical devices.

    Rationale for change: Japanese requirement.

25. **Section 10.4.1, Primary Analysis**

    Description of change: Clarified that patients with FGFR3 mutation or rearrangement confirmed by the central laboratory will be included in the primary analysis.

    Rationale for change: The introduction of local testing for FGFR3 in this amendment required that the primary analysis population be defined in this way.

26. **Section 11.1, Investigator Responsibilities**

    Description of change: Added record retention requirements for Japan.

    Rationale for change: Japanese requirement.

27. **Section 11.6, Study and Site Closure**

    Description of change: Language was added to reflect the responsibility of investigator and head of study site (Japan) upon study completion.

    Rationale for change: Japanese requirement.

28. **Appendix A, Information Regarding the Effectiveness of Contraceptive Methods**

    Description of change: Updated to indicate that partners of male participants should use contraception during the study and through 120 days after the last dose of pemigatinib and/or pembrolizumab or 180 days after the last dose of chemotherapy.

    Rationale for change: Requested by the Belgian Health Authority.

29. **Appendix B, Pembrolizumab Dose Modifications (Table B1: Dose Modification and Toxicity Management Guidelines for Immune-Related Adverse Events Associated With Pembrolizumab)**

    Description of change: Description of change: Added irAEs of skin reactions to the table.

    Rationale for change: Italian requirement.

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