Clinical Study Protocol

INCB 54828-MA-TA-208 / NCT04003623

A Phase 2, Open-Label, Single-Arm, Multicenter Study to Evaluate the Efficacy and Safety of Pemigatinib in Participants With Previously Treated Locally Advanced/Metastatic or Surgically Unresectable Solid Tumors Harboring Activating FGFR Mutations or Translocations (FIGHT-208)

Product:	**Pemigatinib (INCB054828)**
IND Number:	**124,358**
Phase of Study:	**2**
Sponsor:	**Incyte Corporation** **1801 Augustine Cut-Off** **Wilmington, DE 19803**
Original Protocol (Version 0):	**21 MAY 2019**
Amendment (Version) 1:	**14 JUN 2019**

INVESTIGATOR'S AGREEMENT

I have read the INCB 54828-MA-TA-208 Protocol Amendment 1 (Version 1 dated 14 JUN 2019) and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this Protocol.

(Printed Name of Investigator)

(Signature of Investigator) (Date)

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LIST OF ABBREVIATIONS

Abbreviations and Special Terms	Definition
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
[redacted]	[redacted]
CFR	Code of Federal Regulations
CNS	central nervous system
CR	complete response
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DCR	disease control rate
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EOT	end of treatment
[redacted]	[redacted]
FDA	Food and Drug Administration
FGFR	fibroblast growth factor receptor
FGFR1-3	fibroblast growth factor receptors 1, 2, or 3
GCP	Good Clinical Practice
HBV	hepatitis B virus
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act of 1996
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	independent ethics committee
IRB	institutional review board
IRT	interactive response technology
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
NCI	National Cancer Institute
ORR	objective response rate
OS	overall survival
PD	progressive disease

Abbreviations and Special Terms	Definition
PFS	progression-free survival
PR	partial response
PTH	parathyroid hormone
QD	once daily
[redacted]	[redacted]
RANO	Response Assessment in Neuro-Oncology
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SD	stable disease
SoA	schedule of activities
SOP	standard operating procedure
TEAE	treatment-emergent adverse event, AEs reported for the first time or worsening of a pre-existing event after first dose of study treatment
ULN	upper limit of normal

1. PROTOCOL SUMMARY

Protocol Title: A Phase 2, Open-Label, Single-Arm, Multicenter Study to Evaluate the Efficacy and Safety of Pemigatinib in Participants With Previously Treated Locally Advanced/Metastatic or Surgically Unresectable Solid Tumors Harboring Activating FGFR Mutations or Translocations (FIGHT-208)

Protocol Number: INCB 54828-MA-TA-208

Objectives and Endpoints:

Table 1 presents the objectives and endpoints.

Table 1: Objectives and Endpoints

Objectives	Endpoints
Primary	
To determine the efficacy of pemigatinib in participants with locally advanced/metastatic or surgically unresectable solid tumor malignancies with an activating FGFR mutation or translocation	• ORR: defined as the proportion of participants in each cohort who achieve a CR or PR based on RECIST v1.1
Secondary	
• To determine other clinical efficacy measurements of pemigatinib in participants with locally advanced/metastatic or surgically unresectable solid tumor malignancies with an activating FGFR mutation and/or translocation • To determine the safety and tolerability of pemigatinib	• PFS: defined as the time from first dose until PD (per RECIST v1.1 or RANO) or death (whichever is first) in each cohort • DOR: defined as the time from the date of first assessment of CR or PR until the date of the first PD (per RECIST v1.1 or RANO) or death (whichever is first) in each cohort • DCR: defined as the proportion of participants who achieved best overall response of CR, PR, or SD per RECIST v1.1 or RANO • OS: defined as the time from first dose of study drug to death of any cause in each cohort • Safety and tolerability: Occurrence of TEAEs and treatment-related AEs according to NCI CTCAE v5.0, physical exam changes, vital sign changes, laboratory evaluations, and ECG values in each cohort
[redacted]	

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	Solid tumor malignancy
Population	Male and female participants at least 18 years of age who have a solid tumor malignancy with an activating FGFR mutation or translocation who have progressed on prior therapies and have no available standard treatment options
Number of Participants	Approximately 50 participants will be enrolled
Study Design	Single-arm, open-label, multicenter
Estimated Duration of Study Participation	Up to 35 days for screening, continuous treatment in consecutive 21-day cycles as long as participants are receiving benefit and have not met any criteria for study withdrawal, and 30 (+5) days for follow-up after the last dose of study drug. It is estimated that an individual will participate for approximately 6 months

Treatment Groups and Duration:

This is an open-label, monotherapy study of pemigatinib in participants with advanced/metastatic or surgically unresectable solid tumor malignancies harboring an activating mutation or translocation. This study consists of 2 cohorts, Cohort A will enroll participants with FGFR translocations, fusions, and rearrangements, and Cohort B will enroll participants with FGFR mutations.

Participants will receive pemigatinib 13.5 mg QD continuously (each cycle consisting of 3 weeks) as long as they are receiving benefit and have not met any criteria for study withdrawal.

Participants with local laboratory data documenting a gain-of-function FGFR1, FGFR2, or FGFR3 mutations or gene rearrangements identified in a CLIA-certified laboratory are eligible. This study excludes participants with bladder cancer and cholangiocarcinoma. Confirmatory testing through the central genomics laboratory (Tempus, Chicago, IL) will be performed for all participants; however, results from the central genomics laboratory are not required before enrollment. Participants will be assigned to 1 of the following cohorts (see Appendix C for list of alterations):

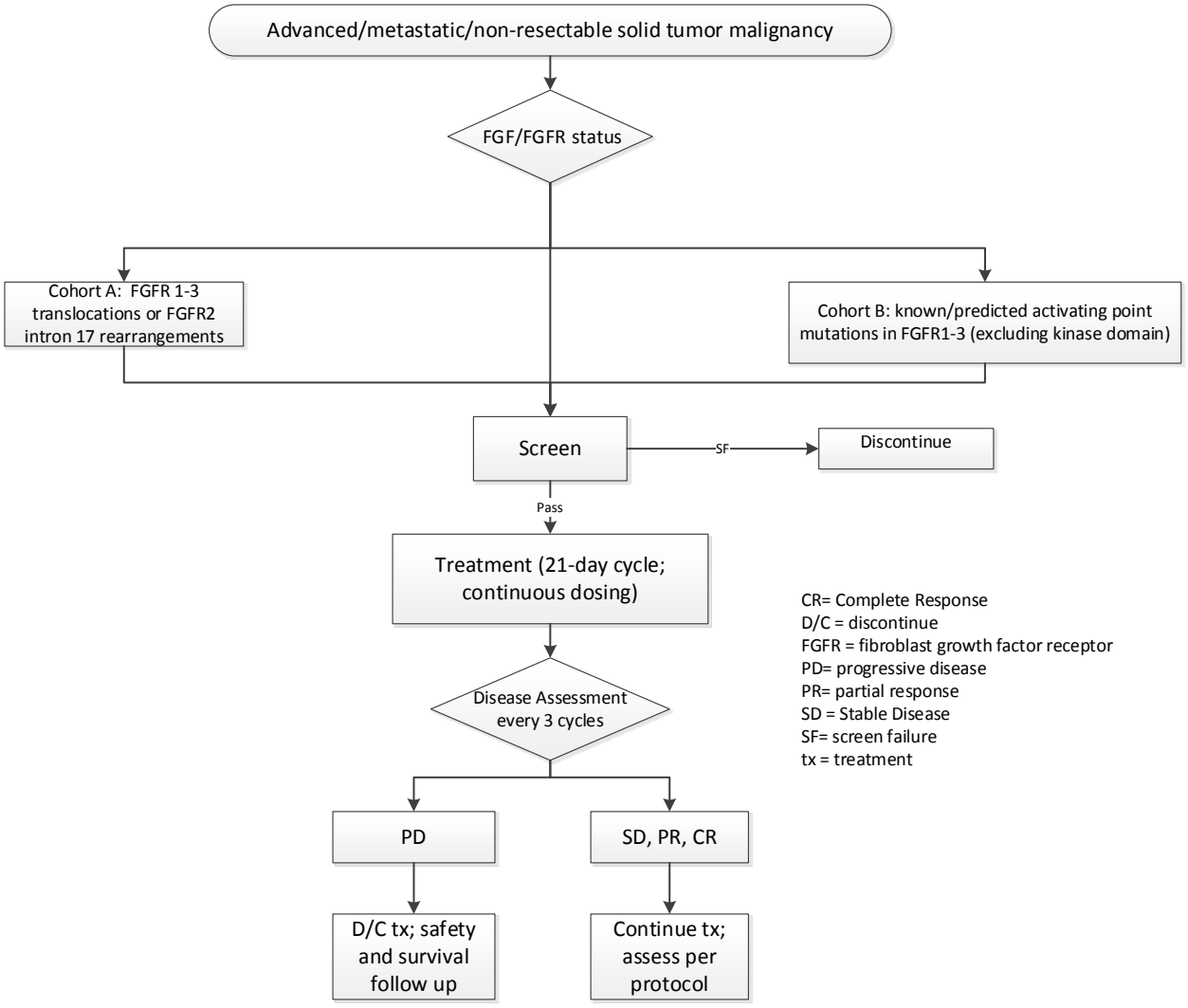
- Cohort A: FGFR1-3 in-frame fusions or FGFR2 intron 17 rearrangements
- Cohort B: Known/predicted activating point mutations in FGFGR1-3 (excluding kinase domain)

Note that there is no difference in the treatment regimen between the cohorts.

The sponsor may choose to cap enrollment of any one tumor type and/or FGFR alteration for lack of response based on predefined futility boundaries.

A fresh biopsy at baseline (or archival tissue that was collected within 12 months from date of screening) will be required for enrollment for participants whose tumors were not previously profiled at the reference lab. Additional biopsies on-treatment and/or at time of progression though not mandatory are encouraged for safely accessible lesions. Treatment will start on Day 1. Participants will undergo regular safety assessments during treatment as well as regular efficacy assessments.

Figure 1: Study Design Schema



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

Table 3: Schedule of Activities

Visit Day (Range)	Screening	Treatment				EOT	Follow-Up		Survival	Notes
		Cycle 1			Cycles 2+		Safety	Disease		
	Days -35 to -1	Day 1	Day 8 (± 3 d)	Day 15 (± 3 d)	Day 1 (± 3 d)		(EOT + 30-35 d)	Every 9 Weeks (± 7 d)	Every 12 Weeks	
Administrative procedures										
Informed consent	X									Section 8.1.1
Contact IRT	X	X			X	X				
Inclusion/exclusion criteria	X									
Prior treatments, procedures, surgery for disease	X									
General and disease medical history	X									
Prior/concomitant medications	X	X	X	X	X	X	X			
Dispense/administer pemigatinib		X			X*					*Assess for up-titration.
Collect study drug and review diary cards			X	X	X	X				Study drug collected only at Cycles 2+ and EOT.
Safety assessments										
Slit lamp, visual acuity, fundoscopy with digital imaging (eye)	X				X*	X				*Once every 3 cycles starting at Cycle 3.
Optical coherence tomography	X*				X*	X*				*Only if clinically indicated.
AE assessments	X	X	X	X	X	X	X			
Physical examination	X	X	X	X	X	X	X			Height at screening only.
Vital signs/body weight	X	X	X	X	X	X	X			Weight on Day 1 of each cycle.
12-lead ECG	X	X			X	X	X			
Efficacy assessments										
CT or MRI	X				X*	X**		X		*Once every 3 cycles starting at the end of Cycle 3. Participants achieving PR or CR will have a confirmatory CT or MRI ≥ 4 weeks (per RECIST v1.1). **Perform at EOT if not done within 1 month prior to EOT.
ECOG	X	X			X	X	X			
[redacted]										
Survival									X	

Table 4: Schedule of Laboratory Assessments

Procedure	Screening	Treatment					Follow-Up		Survival	Notes
		Cycle 1			Cycles 2+		Safety	Disease		
	Days -35 to -1	Day 1	Day 8 (± 3 d)	Day 15 (± 3 d)	Day 1 (± 3 d)	EOT	(EOT + 30-35 d)	Every 9 Weeks (± 7 d)	Every 12 Weeks	
Clinical laboratory assessments										
Blood chemistries	X	X*	X	X	X**	X	X			*May be performed within 3 days of first dose (cannot be same as screening results). **Hyperphosphatemia in Cycle 1 requires Day 8 testing of serum phosphate in Cycle 2+.
Hematology	X	X*			X	X				*May be performed within 3 days of first dose (cannot be same as screening results).
Endocrine (PTH only)	X				X*	X				*Every 3 cycles on Day 1 starting with Cycle 3.
HBV/HCV testing	X									
Urinalysis	X					X				
Pregnancy testing	X*	X			X	X*				*Serum
[redacted]										
Genomic testing										
Tumor tissue sampling	X*				X**	X***				*Mandatory tissue at baseline; archival tissue allowed if less than 12 months from date of screening. **Optional on-treatment biopsies (preferably Cycle 2 between Days 7-14). ***Optional biopsy at time of progression.
Blood or Saliva	X									Tumor/normal matched sample.

Note: 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 drug administration on Cycle 1 Day 1.

2. INTRODUCTION

2.1. Background

Pemigatinib is an inhibitor of the FGFR family of receptor tyrosine kinases that is proposed for the treatment of solid tumor malignancies with an activating FGFR mutation or translocation. Aberrant signaling through FGFR resulting from gene mutations or chromosomal translocations 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. Incyte is proposing to study pemigatinib for the treatment of solid tumor malignancies harboring an activating FGFR mutation or translocation.

2.1.1. Fibroblast Growth Factor Receptor Inhibitor 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 contexts, 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 FGF-23 signaling pathway lead to disordered phosphate metabolism: loss of function mutations in FGF-23 or its signaling results in retention of phosphate and tissue mineralizing, while gain of function mutations in the FGF-23 pathway manifests as hypophosphatemic Rickets syndrome (Farrow and White 2010).

Strong genetic and functional evidence support 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.

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, Nakamura et al 2015, Qing et al 2009, Sia et al 2015, 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.

2.1.2. Solid Tumor Malignancies With Activating FGFR Mutations and Translocations

Activation of the FGFR pathway by mutation or rearrangement is well recognized as an oncogenic event in cancer. A recent survey of 4853 solid tumors identified FGFR1-3 mutations or rearrangements in 2.25% of all tumors tested (Helsten et al 2016). Analysis of FGFR1-3 mutations and rearrangements in the NCI Genomic Data Commons Data Portal (2019), demonstrate that FGFR alterations are not restricted to 1 tumor type but rather broadly distributed across a diverse range of tumors (see Table 5). Importantly, preclinical and clinical data support the use of FGFR inhibitors in FGFR altered cell lines and tumors derived from a variety of cancer types, including bladder cancer, cholangiocarcinoma, endometrial cancer, glioma, and squamous lung cancer (Porta et al 2017).

Table 5: Tumors With Frequency > 1% for FGFR1-3 Mutations and Rearrangements in TCGA

Tumor Type	FGFR1		FGFR2		FGFR3		Total (%)
	Mutation (%)	Fusion (%)	Mutation (%)	Fusion (%)	Mutation (%)	Fusion (%)	
Urothelial carcinoma	0	0	0.75	0	12.64	3.15	**16.54**
Cholangiocarcinoma	0	0	0	13.9	0	0	**13.9**
Endometrial carcinoma	0	0	9.68	0.18	0	0	**9.86**
Glioblastoma multiforme	0.48	0	0	0	0.48	8.62	**9.58**
Lung squamous cell carcinoma	0.21	0.2	1.45	0.2	1.45	1.4	**4.91**
Cervical carcinoma	0	0	0.51	0	0	1.97	**2.48**
Renal papillary cell carcinoma	0	0	0	0	1.41	0.68	**2.09**
Rectal adenocarcinoma	0	0	2.01	0	0	0	**2.01**
Head and neck squamous cell carcinoma	0	0	0	0	1.14	0.76	**1.9**
Low grade glioma	0.19	0	0	0	0	1.71	**1.9**
Uterine carcinosarcoma	0	0	1.75	0	0	0	**1.75**
Esophageal adenocarcinoma	0	0.54	0	0	0	1.08	**1.62**
Stomach adenocarcinoma	0.25	0	0.5	0.48	0.25	0	**1.48**
Prostate adenocarcinoma	0	0	0	1.2	0	0.2	**1.4**
Breast (invasive) carcinoma	0	0.36	0. 6	0.36	0	0	**1.32**
Adrenocortical carcinoma	0	0	1.1	0	0	0	**1.1**
Pheochromocytoma and paraganglioma	1.09	0	0	0	0	0	**1.09**
Colorectal adenocarcinoma	0.27	0	0.54	0	0.27	0	**1.08**
Skin cutaneous melanoma	0.21	0	0.84	0	0	0	**1.05**

Based on these observations, an FGFR inhibitor may be active across a variety of tumor types with activating point mutations and gene fusions of FGFR1-3.

2.2. Study Rationale

Pemigatinib is a potent selective inhibitor of FGFR1-3. This compound is proposed for the treatment of participants with advanced/metastatic or surgically unresectable solid tumor malignancies harboring activating FGFR mutations or translocations.

2.2.1. Scientific Rationale for Study Design

The planned study will evaluate the efficacy and safety of pemigatinib as treatment in participants with advanced/metastatic or unresectable solid tumor malignancies with an activating FGFR mutation or translocation. Preliminary data from the ongoing Phase 1/2 study (INCB 54828-101) in second-line or greater treatment in all tumor types have shown interesting efficacy signals (ORR, PFS) and tolerable safety in participants with FGFR alterations.

The proposed study design is a single arm, open-label study of pemigatinib. Individual investigators will evaluate tumor responses to support the primary and secondary endpoints.

2.2.2. Justification for Dose and Regimen

Pemigatinib will be administered at 13.5 mg QD, continuously, during a cycle. Each cycle is 3 weeks. This dose and dosing schedule was selected based on emerging clinical and safety data from the INCB 54828-101 study, where the continuous dosing regimen has been tested in 8 and 16 participants at 9 mg and 13.5 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.

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.

Hyperphosphatemia is an expected on-target pharmacological effect of FGFR inhibition. The incidence of hyperphosphatemia, defined as any postbaseline phosphate level exceeding 5.5 mg/dL, has been observed in the majority of participants treated with pemigatinib (refer to the IB for complete data). Some participants do not achieve hyperphosphatemia, and it is estimated that pharmacological concentration of pemigatinib in these participants is lower (see Figure 2). Therefore, up-titration of pemigatinib will be used to increase the exposure of pemigatinib in participants who do not achieve hyperphosphatemia when treated with 13.5 mg QD. The goal is to increase the serum concentration of pemigatinib.

[redacted]

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 starting at Cycle 2 Day 1.

Dose modifications for tolerability issues are noted in Section 6.5.

2.3. Benefit/Risk Assessment of Pemigatinib

Targeted therapies with a manageable safety profile that can provide a durable response or significant disease control in a molecularly defined population would provide a meaningful clinical benefit.

The comprehensive safety data that are included in the IB (v5) utilized a data cut of 25 NOV 2018. As of the cutoff date, a total of 562 participants (78 healthy participants and 484 participants with advanced malignancies) were enrolled in ongoing clinical studies and received at least 1 dose of pemigatinib. 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. Additional details are provided in the following section.

2.3.1. Study INCB 54828-101

Of the 150 participants with advanced malignancies who have been enrolled in Study INCB 54828-101 as of the data cutoff date, 43 participants have been administered pemigatinib in Part 1(monotherapy dose escalation), 63 participants in Part 2 (monotherapy dose expansion), and 44 participants in Part 3 (pemigatinib combined with gemcitabine and cisplatin [8 participants], docetaxel [7 participants], pembrolizumab [23 participants], and trastuzumab [6 participants]).

Dose limiting toxicities informed dose escalation procedures during Part 1 of the study. Among participants in Part 1, 28 received pemigatinib at doses of 1 to 20 mg QD on a 2-weeks-on/1-week-off therapy schedule (ie, interval dose regimen), and 15 participants received pemigatinib at doses of 9, 13.5, or 20 mg QD on a continuous schedule (ie, continuous dose regimen). There were no DLTs for the monotherapy dose regimens, and the monotherapy MTD was not reached. The recommended Part 2 dose for pemigatinib was determined to be 13.5 mg based on PD and clinical effect, and the recommended Phase 2 dose regimens for pemigatinib based on safety and pharmacokinetic data and preliminary signals of clinical benefit were 13.5 mg QD following the interval schedule and 13.5 mg QD following the continuous schedule.

Overall 105 participants (99.1%) who received pemigatinib monotherapy (all doses and dose regimens combined) in Study INCB 54828-101 had TEAEs. Treatment-emergent AEs occurring in ≥ 10% of participants who received pemigatinib monotherapy (Parts 1 and 2 combined) are presented by dose and dose regimen and overall in Table 6. Consistent with the expected pharmacological effect of FGFR inhibition on serum phosphate levels, the most frequently occurring TEAE was hyperphosphatemia (74 participants [69.8%]; serum phosphate > 5.5 mg/dL). Other frequent TEAEs (> 30%) included fatigue in 43 participants (40.6%), dry mouth in 39 participants (36.8%), and alopecia in 35 participants (33.0%). Comparison of the most frequently occurring TEAEs for the continuous and interval dose regimens suggests higher incidences of hyperphosphatemia (76.7% vs 67.1%), stomatitis (46.7% vs 22.4%), dry mouth (43.3% vs 34.2%), diarrhea (43.3% vs 22.4%), constipation (40.0% vs 25.0%), alopecia (40.0% vs 30.3%), and nausea (33.3% vs 22.4%) with continuous dosing. Other TEAEs that occurred more frequently with continuous dosing included dry eye, pain in extremity, hypercalcemia, onycholysis, and paronychia.

Forty-five participants (42.5%) who received pemigatinib monotherapy had at least 1 SAE; the overall incidence of SAEs for the continuous dose regimen (56.7%) was higher than was seen for the interval dose regimen (36.8%). Pneumonia in 7 participants (6.6%) was the most frequently occurring SAE. Other SAEs occurring in more than 1 participant included back pain and disease progression in 4 participants (3.8%) each; abdominal pain, dehydration, fatigue, hyponatremia, and acute renal failure in 3 participants (2.8%) each; and blood bilirubin increased, cerebrovascular accident, constipation, hypotension, pain in extremity, pleural effusion, and pyrexia in 2 participants (1.9%) each. Within the eye disorders, a single participant had an SAE of ocular hyperemia (Grade 2), which was considered unrelated to pemigatinib by the investigator.

A total of 11 participants (10.4%), 7 participants (9.2%) on an interval dose regimen and 4 participants (13.3%) on a continuous dose regimen, had SAEs with a fatal outcome: disease progression in 4 participants (3.8%) and pneumonia, malignant neoplasm progression (ie, disease progression), cerebrovascular accident, intracranial hemorrhage, multiorgan failure, esophageal varices hemorrhage, pneumonia, respiratory failure, and acute respiratory failure secondary to acute anemia (verbatim term) in 1 participant (0.9%) each. None of these fatal events were assessed as related to pemigatinib by the investigator.

Eleven participants (10.4%) discontinued pemigatinib monotherapy due to TEAEs; pneumonia in 3 participants (2.8%) and dehydration and small intestinal obstruction in 2 participants (1.9%) each were the only TEAEs leading to discontinuation of pemigatinib that occurred in more than 1 participant.

More detailed information about the known and expected benefits and risks (clinical safety and nonclinical toxicology) and reasonably expected AEs of pemigatinib are provided in the IB.

Table 6: Summary of Treatment-Emergent Adverse Events Occurring in ≥ 10% of Participants on Pemigatinib Monotherapy in Study INCB 54828-101 (Parts 1 and 2 Combined) in Decreasing Order of Frequency

	Pemigatinib Interval Dose Regimen[a]						Pemigatinib Continuous Dose Regimen[b]				
MedDRA Preferred Term, n (%)	1/2/4 mg (N = 3)	6 mg (N = 4)	9 mg (N = 13)	13.5 mg (N = 50)	20 mg (N = 6)	Subtotal (N = 76)	9 mg (N = 8)	13.5 mg (N = 16)	20 mg (N = 6)	Subtotal (N = 30)	Total (N = 106)
Hyperphosphataemia	0	1 (25.0)	8 (61.5)	38 (76.0)	4 (66.7)	51 (67.1)	4 (50.0)	14 (87.5)	5 (83.3)	23 (76.7)	74 (69.8)
Fatigue	1 (33.3)	1 (25.0)	7 (53.8)	19 (38.0)	2 (33.3)	30 (39.5)	5 (62.5)	5 (31.3)	3 (50.0)	13 (43.3)	43 (40.6)
Dry mouth	0	1 (25.0)	6 (46.2)	17 (34.0)	2 (33.3)	26 (34.2)	2 (25.0)	7 (43.8)	4 (66.7)	13 (43.3)	39 (36.8)
Alopecia	0	0	7 (53.8)	15 (30.0)	1 (16.7)	23 (30.3)	2 (25.0)	7 (43.8)	3 (50.0)	12 (40.0)	35 (33.0)
Constipation	0	0	3 (23.1)	14 (28.0)	2 (33.3)	19 (25.0)	3 (37.5)	5 (31.3)	4 (66.7)	12 (40.0)	31 (29.2)
Stomatitis	0	0	3 (23.1)	11 (22.0)	3 (50.0)	17 (22.4)	4 (50.0)	7 (43.8)	3 (50.0)	14 (46.7)	31 (29.2)
Diarrhoea	0	1 (25.0)	2 (15.4)	12 (24.0)	2 (33.3)	17 (22.4)	1 (12.5)	8 (50.0)	4 (66.7)	13 (43.3)	30 (28.3)
Nausea	1 (33.3)	1 (25.0)	5 (38.5)	8 (16.0)	2 (33.3)	17 (22.4)	2 (25.0)	7 (43.8)	1 (16.7)	10 (33.3)	27 (25.5)
Decreased appetite	0	2 (50.0)	2 (15.4)	12 (24.0)	1 (16.7)	17 (22.4)	0	4 (25.0)	2 (33.3)	6 (20.0)	23 (21.7)
Dysgeusia	1 (33.3)	0	5 (38.5)	8 (16.0)	2 (33.3)	16 (21.1)	1 (12.5)	3 (18.8)	3 (50.0)	7 (23.3)	23 (21.7)
Anaemia	1 (33.3)	0	3 (23.1)	10 (20.0)	2 (33.3)	16 (21.1)	3 (37.5)	2 (12.5)	1 (16.7)	6 (20.0)	22 (20.8)
Abdominal pain	0	0	3 (23.1)	11 (22.0)	1 (16.7)	15 (19.7)	1 (12.5)	4 (25.0)	1 (16.7)	6 (20.0)	21 (19.8)
Vomiting	1 (33.3)	0	4 (30.8)	8 (16.0)	1 (16.7)	14 (18.4)	1 (12.5)	2 (12.5)	2 (33.3)	5 (16.7)	19 (17.9)
Aspartate aminotransferase increased	1 (33.3)	0	4 (30.8)	7 (14.0)	0	12 (15.8)	2 (25.0)	4 (25.0)	0	6 (20.0)	18 (17.0)
Hypophosphataemia	0	0	2 (15.4)	10 (20.0)	1 (16.7)	13 (17.1)	0	4 (25.0)	1 (16.7)	5 (16.7)	18 (17.0)
Dehydration	1 (33.3)	1 (25.0)	0	7 (14.0)	1 (16.7)	10 (13.2)	2 (25.0)	2 (12.5)	1 (16.7)	5 (16.7)	15 (14.2)
Dry eye	0	0	1 (7.7)	7 (14.0)	1 (16.7)	9 (11.8)	0	5 (31.3)	1 (16.7)	6 (20.0)	15 (14.2)
Pain in extremity	0	1 (25.0)	3 (23.1)	3 (6.0)	1 (16.7)	8 (10.5)	1 (12.5)	5 (31.3)	1 (16.7)	7 (23.3)	15 (14.2)
Alanine aminotransferase increased	1 (33.3)	0	4 (30.8)	4 (8.0)	0	9 (11.8)	2 (25.0)	3 (18.8)	0	5 (16.7)	14 (13.2)
Cough	1 (33.3)	0	1 (7.7)	6 (12.0)	2 (33.3)	10 (13.2)	1 (12.5)	3 (18.8)	0	4 (13.3)	14 (13.2)
Vision blurred	1 (33.3)	1 (25.0)	2 (15.4)	4 (8.0)	2 (33.3)	10 (13.2)	0	3 (18.8)	1 (16.7)	4 (13.3)	14 (13.2)
Weight decreased	2 (66.7)	0	2 (15.4)	5 (10.0)	2 (33.3)	11 (14.5)	1 (12.5)	0	2 (33.3)	3 (10.0)	14 (13.2)
Blood alkaline phosphatase increased	1 (33.3)	0	3 (23.1)	6 (12.0)	0	10 (13.2)	2 (25.0)	1 (6.3)	0	3 (10.0)	13 (12.3)
Hypercalcaemia	1 (33.3)	0	1 (7.7)	5 (10.0)	0	7 (9.2)	2 (25.0)	3 (18.8)	1 (16.7)	6 (20.0)	13 (12.3)
Back pain	1 (33.3)	0	4 (30.8)	4 (8.0)	0	9 (11.8)	1 (12.5)	2 (12.5)	0	3 (10.0)	12 (11.3)
Onycholysis	0	0	1 (7.7)	5 (10.0)	0	6 (7.9)	1 (12.5)	5 (31.3)	0	6 (20.0)	12 (11.3)
Paronychia	0	0	1 (7.7)	2 (4.0)	2 (33.3)	5 (6.6)	1 (12.5)	4 (25.0)	2 (33.3)	7 (23.3)	12 (11.3)
Arthralgia	0	1 (25.0)	3 (23.1)	2 (4.0)	2 (33.3)	8 (10.5)	0	2 (12.5)	1 (16.7)	3 (10.0)	11 (10.4)
Hyponatraemia	0	0	1 (7.7)	5 (10.0)	1 (16.7)	7 (9.2)	0	3 (18.8)	1 (16.7)	4 (13.3)	11 (10.4)
Nail discolouration	0	0	2 (15.4)	5 (10.0)	0	7 (9.2)	1 (12.5)	2 (12.5)	1 (16.7)	4 (13.3)	11 (10.4)

Note: Participants were counted once under each MedDRA preferred term. Adverse events are ordered by the descending frequency in the total column.
Note: Treatment-emergent AEs are any AEs either reported for the first time or worsening of a pre-existing event after first dose of study drug.
[a] Pemigatinib was administered QD on a 2-weeks-on/1-week-off therapy schedule.
[b] Pemigatinib was administered QD.

3. OBJECTIVES AND ENDPOINTS

Table 7 presents the objectives and endpoints.

Table 7: Objectives and Endpoints

Objectives	Endpoints
Primary	
To determine the efficacy of pemigatinib in participants with locally advanced/metastatic or surgically unresectable solid tumor malignancies with an activating FGFR mutation or translocation	• ORR: defined as the proportion of participants in each cohort who achieve a CR or PR based on RECIST v1.1
Secondary	
• To determine other clinical efficacy measurements of pemigatinib in participants with locally advanced/metastatic or surgically unresectable solid tumor malignancies with an activating FGFR mutation and/or translocation • To determine the safety and tolerability of pemigatinib	• PFS: defined as the time from first dose until PD (per RECIST v1.1 or RANO) or death (whichever is first) in each cohort • DOR: defined as the time from the date of first assessment of CR or PR until the date of the first PD (per RECIST v1.1 or RANO) or death (whichever is first) in each cohort • DCR: defined as the proportion of participants who achieved best overall response of CR, PR, or SD per RECIST v1.1 or RANO • OS: defined as the time from first dose of study drug to death of any cause in each cohort • Safety and tolerability: Occurrence of TEAEs and treatment-related AEs according to NCI CTCAE v5.0, physical exam changes, vital sign changes, laboratory evaluations, and ECG values in each cohort
[redacted]	

4. STUDY DESIGN

4.1. Overall Design

This is an open-label, monotherapy study of pemigatinib in participants with advanced/metastatic or surgically unresectable solid tumor malignancies harboring an activating FGFR mutation or translocation. This study consists of 2 cohorts; Cohort A will enroll participants with FGFR translocations, fusions, and rearrangements, and Cohort B will enroll participants with FGFR mutations. This study will enroll approximately 50 participants. Participants will receive pemigatinib 13.5 mg QD continuously as long as they are receiving benefit and have not met any criteria for study withdrawal. Participants with local laboratory data documenting a gain-of-function FGFR1, FGFR2, or FGFR3 mutation gene rearrangement, or other mutation identified in a CLIA-certified laboratory are eligible. Confirmatory testing through the central genomics laboratory (Tempus, Chicago, IL) will be performed for all participants; however, results from the central genomics laboratory are not required before enrollment. Centralized genomic testing results will allow participants to be assigned to 1 of the following cohorts (see Appendix C for list of alterations):

- Cohort A: FGFR1-3 in-frame fusions or FGFR2 intron 17 rearrangements
- Cohort B: Known/predicted activating point mutations in FGFR1-3 (excluding kinase domain)

Note that there is no difference in the treatment regimen between the cohorts.

The sponsor may choose to cap enrollment of any one tumor type and/or FGFR alteration in order to allow representation of multiple tumor types and avoid analysis being influenced by any 1 tumor type or due to lack of response in 1 or more tumor subtypes.

A fresh biopsy at baseline (or archival tissue that was collected less than 12 months from date of screening) will be mandatory for participants whose tumors were not previously profiled at the reference lab. On-treatment and end of study biopsies are encouraged for participants with safely accessible lesions. Treatment will start on Day 1. Participants will undergo regular safety assessments during treatment as well as regular efficacy assessments. Participants will be allowed to continue administration in 21-day cycles until documented disease progression or unacceptable toxicity is reported.

4.2. Overall Study Duration

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

Once the study has reached the target enrollment, if there are approximately ≤ 3 participants on study for more than 6 months, 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 per Protocol. The investigator will be expected to monitor for and report any SAEs, AEs of special interest, and pregnancies, as detailed in Section 9. The remaining

participants are considered to be on study until a discontinuation criterion is met and written notification is provided to the sponsor.

4.3. Study Termination

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

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

5. STUDY POPULATION

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

5.1. Inclusion Criteria

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

1. Ability of the participant (or parent, guardian, or legally authorized representative) to comprehend and willingness to sign the ICF.
2. Age 18 years or older, inclusive at the time of signing the informed consent.
3. Histologically or cytologically confirmed solid tumor malignancy that is advanced or metastatic (Stage IIIB or IV per the American Joint Committee on Cancer, Cancer Staging Manual, 6th Edition) or is surgically unresectable.
4. Radiographically measurable disease (per RECIST v1.1 or RANO for primary brain tumors). Tumor lesions located in a previously irradiated area or in an area subjected to other loco-regional therapy are considered measureable if progression has been clearly demonstrated in the lesion.
5. Documentation of an FGFR1-3 gene mutation or translocation (see Section 8.4 and Appendix C).
6. Objective disease progression after at least 1 prior therapy, and there is no further approved therapy available that is likely to provide clinical benefit. Participants who are intolerant to or decline the approved therapy are eligible only if they have no therapy available that is likely to provide clinical benefit.
7. ECOG performance status 0 to 2.

8. Baseline archival tumor specimen (if less than 12 months from date of screening) available or willingness to undergo a pretreatment tumor biopsy to obtain the specimen. Must be a tumor block or approximately 15 unstained slides from biopsy or resection of primary tumor or metastasis.
9. Not eligible or able to participate in any other Incyte Sponsored Clinical Trial.
10. Willingness to avoid pregnancy or fathering children based on the criteria below.
    a. Men must agree to take appropriate precautions to avoid fathering children (with at least 99% certainty) from screening through 90 days after the last dose of study drug and must refrain from donating sperm during this period. Permitted methods that are at least 99% effective in preventing pregnancy (see Appendix A) should be communicated to the participants and their understanding confirmed.
    b. Women of childbearing potential must have a negative serum pregnancy test at screening and before the first dose on Day 1 and must agree to take appropriate precautions to avoid pregnancy (with at least 99% certainty) from screening through safety follow-up. Permitted methods that are at least 99% effective in preventing pregnancy (see Appendix A) should be communicated to the participants and their understanding confirmed.
    c. Women of nonchildbearing potential (ie, surgically sterile with a hysterectomy and/or bilateral oophorectomy OR ≥ 12 months of amenorrhea) are eligible.

5.2. Exclusion Criteria

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

1. Participants with advanced/metastatic bladder cancer or advanced/metastatic cholangiocarcinoma.
2. Participants with primary brain tumor may not be enrolled if they have received prior bevacizumab.
3. Prior receipt of a selective FGFR inhibitor.
4. Receipt of anticancer medications or investigational drugs for any indication or reason within 28 days before the first dose of pemigatinib. Participants must have recovered (≤ Grade 1 as per CTCAE v5.0) from AEs from previously administered therapies (excluding alopecia).
5. Concurrent anticancer therapy (eg, chemotherapy, radiation therapy, surgery, immunotherapy, biologic therapy, hormonal therapy, investigational therapy, or tumor embolization).
6. The participant cannot be a candidate for potentially curative surgery.
7. Current evidence of clinically significant corneal (including but not limited to bullous/band keratopathy, corneal abrasion, inflammation/ulceration, and keratoconjunctivitis) or retinal disorder (including but not limited to macular/retinal degeneration, diabetic retinopathy, retinal detachment) as confirmed by ophthalmologic examination.

8. Radiation therapy administered within 2 weeks of enrollment or first dose of study drug. Participants must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis. Evidence of fibrosis within a radiation field from prior radiotherapy is permitted with medical monitor approval. A 1-week washout is permitted for palliative radiation to non-CNS disease with medical monitor approval.
9. Untreated brain or CNS metastases or brain or CNS metastases that have progressed (eg, evidence of new or enlarging brain metastasis or new neurological symptoms attributable to brain or CNS metastases). Participants with previously treated and clinically stable brain or CNS metastases are eligible if there is no evidence of progression for at least 4 weeks after CNS-directed treatment as ascertained by clinical examination and brain imaging (MRI or CT scan) during the screening period and they are on a stable or decreasing dose of corticosteroids for at least 1 week.
10. Known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or in situ cervical cancer that has undergone potentially curative therapy.
11. Participants with laboratory values at screening defined in Table 8.

Table 8: Exclusionary Laboratory Values

Laboratory Parameter		**Exclusion Criterion**
Hematology		
a	Platelets	$\leq 75 \times 10^9$/L (transfusion allowed with 2-week washout period)
b	Hemoglobin	≤ 9.0 g/L (transfusion allowed within 2-week washout period)
c	Absolute neutrophil count	$\leq 1.5 \times 10^9$/L
Hepatic		
d	ALT	≥ 3 × ULN
e	AST	≥ 3 × ULN (5 × ULN for liver mets)
f	Total bilirubin	≥ 1.5 × ULN (2.5 × ULN if Gilbert's syndrome or liver mets)
g	Alkaline phosphatase	≥ 3 × ULN
Renal		
h	Serum creatinine clearance	≤ 30 mL/minute based on Cockcroft-Gault formula
Chemistry		
i	Serum phosphate	> ULN
j	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

12. History of calcium and phosphate hemostasis disorder or systemic mineral imbalance with ectopic calcification of soft tissues (exception: 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. Gastrointestinal condition/disorder that may raise gastric and/or small intestinal pH that could interfere with absorption, metabolism, or excretion of pemigatinib.
14. Inability to swallow and retain oral medication.
15. Clinically significant or uncontrolled cardiac disease including unstable angina, acute myocardial infarction within 6 months from Day 1 of study drug administration, New York Heart Association Class III or IV congestive heart failure, and uncontrolled arrhythmia (participants with a pacemaker or with atrial fibrillation and well-controlled heart rate are allowed).
16. History or presence of an abnormal ECG that, in the investigator's opinion, is clinically meaningful. A screening QTcF interval > 480 milliseconds is excluded. For participants with an intraventricular conduction delay (QRS interval ≥ 120 milliseconds), the JTc interval may be used in place of the QTc with sponsor approval. The JTc must be ≤ 340 milliseconds if JTc is used in place of the QTc.
17. Active chronic or current infectious disease requiring systemic antibiotic, antifungal, or antiviral treatment within 2 weeks before enrollment (participants with asymptomatic chronic infections on prophylactic treatment are allowed).
18. Evidence of active HBV or HCV infection (defined as participants with elevated transaminases or cirrhosis. Participants with chronic HBV/HCV infection with no cirrhosis and no elevated transaminases are allowed).
19. Known HIV infection.
20. Current use of prohibited medication as described in Section 6.6.2.
21. Use of any potent CYP3A4 inhibitors or inducers or moderate CYP3A4 inducers within 14 days or 5 half-lives (whichever is longer) before the first dose of study drug.
22. Known hypersensitivity or severe reaction to pemigatinib or excipients of pemigatinib (refer to the IB).
23. Inability or unlikeliness of the participant to comply with the dose schedule and study evaluations, in the opinion of the investigator.
24. Inadequate recovery from toxicity and/or complications from a major surgery before starting therapy.
25. Women who are pregnant or breastfeeding.
26. Any condition that would, in the investigator's judgment, interfere with full participation in the study, including administration of study drug/treatment and attending required study visits; pose a significant risk to the participant; or interfere with interpretation of study data.
27. History of hypovitaminosis D requiring supraphysiologic doses (eg, 50,000 IU/week) to replenish the deficiency. Vitamin D supplements are allowed.

5.3. Lifestyle Considerations

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

Refrain from consumption of red wine, Seville oranges, 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, as this can influence the metabolism of the study drug.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened no more than 1 time.

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

5.5. Replacement of Participants

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

6. STUDY TREATMENT

6.1. Study Treatment Administered

Table 9 presents the study treatment information. Starting dose for all participants is 13.5 mg QD.

Table 9: Study Treatment Information

Study treatment name:	Pemigatinib
Dosage formulation:	Tablet
Unit dose strengths/dosage levels:	4.5 mg tablet/4.5 mg, 9 mg, 13.5 mg, and 18 mg
Route of administration:	Oral
Administration instructions:	1-4 tablet(s) taken every morning (unless otherwise directed)
Packaging and labeling:	Pemigatinib will be provided in bottles; each bottle will be labeled as required per country requirement.
Storage:	Room temperature (15-30°C)

6.2. Preparation, Handling, and Accountability

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

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

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

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

The investigational product must be used only in accordance with the Protocol. Tablets are not to be crushed, dissolved, or broken. The investigator will also maintain records adequately documenting that the participants were provided the specified study drug. These records should include dates, quantities, and any available batch or serial numbers or unique code numbers assigned to the investigational product and study participants.

Completed accountability records will be archived by the site. The investigator or designee will be expected to collect and retain all used, unused, and partially used containers of study drug until verified by the study monitor (unless otherwise agreed to by the sponsor). At the conclusion of the study, the investigator or designee will oversee shipment of any remaining study drug back to the sponsor or its designee for destruction according to institutional 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 SOP.

Instructions for participants regarding the handling of the study drug are in Appendix B.

6.3. Measures to Minimize Bias: Randomization and Blinding

Not applicable. This is an open-label, non-randomized study.

6.4. Study Treatment Compliance

Compliance with all study-related treatments and assessments 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 calculated by the sponsor based on the drug accountability documented by the site staff and monitored by the sponsor/designee (tablet counts). Participants will be instructed to bring all study drugs with them to the study visits in order for site personnel to conduct tablet counts to assess study drug accountability. The drug accountability documentation will be used by the sponsor to calculate treatment compliance.

6.5. Dose Modifications

Individual decision regarding dose modifications of pemigatinib should be made using clinical judgement 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.

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

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

Treatment with 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 has been delayed for more than 14 days before restarting treatment with pemigatinib. Refer to Table 10 for guidelines.

Table 10: Guidelines for Interruption and Restarting of Study Drug

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	
• 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 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.	Discontinue pemigatinib administration and follow-up per Protocol.

The sponsor recommends a maximum of 2 level dose reductions: participants treated at 13.5 mg can decrease to 9 mg, and if additional dose reduction is required, participants can decrease to 4.5 mg. Dose reductions below 4.5 mg are not allowed. The frequency of dosing (ie, QD) as well as the schedule (ie, continuous dosing) remain the same.

For participants who are up-titrated from 13.5 mg to 18 mg, a maximum of 2 dose level reductions is also recommended. The 18-mg dose can be decreased to 13.5 mg, and if additional dose reduction is required, participants can decrease to 9 mg. Dose reductions below 9 mg are not allowed.

6.5.2. 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 11.

The use of diet modifications alone include food exchanges from high-phosphate foods to low-phosphate foods and can be implemented once serum phosphate levels are above the ULN but do not exceed 7.0 mg/dL. Diet modification should continue with the inclusion of phosphate binders once serum phosphate levels exceed 7.0 mg/dL. An example of a phosphate binder is sevelamer HCl (eg, Renegel®, Renvela®). Administration of phosphate binders should be 3 times per day (eg, with each meal) to reduce absorption of phosphate. Doses and frequency of doses should be based on the participant's tolerance for the binder and the control of serum

phosphate. 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 grading of hyperphosphatemia, please note that CTCAE v5.0 now has a category for hyperphosphatemia.

Table 11: 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. Monitor serum phosphate approximately twice a week and adjust the dose of binders as needed; continue to monitor serum phosphate at least twice a week until return to ≤ 7 mg/dL.	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	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 approximately twice a week until return to ≤ 7 mg/dL.	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.

6.5.3. Up-Titration

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

Participants who are titrated up to 18 mg QD will begin the next cycle at the new dose level and must agree to all Cycle 1 assessments. Up-titration may occur no earlier than Cycle 2 Day 1 so that subjects are observed for phosphate level and AEs for at least 1 cycle.

6.5.4. Criteria for Permanent Discontinuation of Study Drug

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

- Occurrence of an AE that is related to study drug that, in the judgment of the investigator or the sponsor's medical monitor, compromises the participant's ability to continue study-specific procedures or is considered to not be in the participant's best interest.
- An AE requiring more than 2 dose reductions.
- Persistent AE requiring a delay of therapy for more than 2 weeks (14 days) unless a greater delay has been approved by the sponsor.
- Increase in QT/QTc to > 500 milliseconds or to > 60 milliseconds over baseline. In case of a QTc > 500 milliseconds, the participant must be hospitalized and continuous ECG monitoring must be set up until the measure of the QTc interval decreases below 500 milliseconds and is acceptable in the opinion of the local cardiologist.

See Section 7 for discontinuation procedures.

6.6. Concomitant Medications and Procedures

All concomitant medications and treatments (including over-the-counter or prescription medicines, vitamins, vaccines, and/or herbal supplements) must be recorded in the eCRF. Any prior medication received up to 35 days before the first dose of study treatment and 30 to 35 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 after 30-35 days after the last dose of study treatment should be recorded for SAEs as defined in Section 9.2. Concomitant treatments/procedures that are required to manage a participant's medical condition during the study will also be recorded in the eCRF. The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.6.1. Restricted Medications and Procedures

Pemigatinib is predominantly metabolized by CYP3A4. There is an expected 50% increase in exposure in participants who concomitantly use CYP3A4 moderate inhibitors. However, as doses above the recommended Phase 2 dose of 13.5 mg QD have been tested (20 mg QD is tolerable), there is a sufficient safety margin. Therefore, the use of moderate CYP3A4 inhibitors is not prohibited but 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 organic cation transporter 2 substrates such as dofetilide and metformin.

Calcium-based phosphate binding medications should not be used due to a concern for soft tissue mineralization.

6.6.2. Prohibited Medications and Procedures

The following medications and measures are prohibited:

- 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.

7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Treatment

7.1.1. Reasons for Discontinuation

Participants **must** be discontinued from study treatment for the following reasons. 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 becomes pregnant.
- Consent is withdrawn.
  Note: Consent withdrawn means that the participant has explicitly indicated that they do not want to be followed any longer; in this case no further data, except data in public domain, may be solicited from or collected on the participant. Participants may choose to discontinue study treatment and remain in the study to be followed for progression and survival.
- Further participation would be injurious to the participant's health or well-being, in the investigator's medical judgment.
- Unacceptable toxicity as noted in Section 6.5.4.
- The study is terminated by the sponsor.
- The study is terminated by the local health authority, IRB, or IEC.
- Disease progression has been reported by radiology review.
- Other antineoplastic treatment is initiated, not including palliative radiation.

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 drug/treatment administration in the investigator's opinion, the sponsor should be consulted for instruction on handling the participant.

7.1.2. Discontinuation Procedures

In the event that the decision is made to permanently discontinue the study treatment, the EOT visit should be conducted. Reasonable efforts should be made to have the participant return for a follow-up visit. These visits are described in Table 3 and Table 4. The last date of the last dose of study drug and the reason for discontinuation of study treatment will be recorded in the eCRF.

If a participant is discontinued from study treatment:

- The study monitor or sponsor must be notified.
- The reason(s) for withdrawal must be documented in the participant's medical record and the primary reason for withdrawal must be included in the eCRF.
- The 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 drug–related toxicities resolve, return to baseline, or are deemed irreversible, whichever is longest.

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

7.2. Participant Withdrawal From the Study

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

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

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

See Table 3 and Table 4 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 country in which the study is being conducted as well as the IRB/IEC or study center.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection laws. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must provide consent to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.
- Participants who are rescreened are required to sign a new ICF.

8.1.2. Screening Procedures

Screening is the interval between signing the ICF and the day the participant is enrolled in the study (Cycle 1 Day 1). Screening may not exceed 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 35 days of Cycle 1 Day 1). For participants who are enrolled in the study, information associated with eligibility requirements must be entered into the appropriate eCRF pages.

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

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

8.1.3. Interactive Response Technology Procedure

Each participant will be identified in the study by a participant ID number, which is a combination of the site ID and participant number. Site staff should contact the IRT to obtain the participant ID number during screening. Upon determining that the participant is eligible for study entry, the IRT will be contacted to obtain the treatment assignment. Additionally, the IRT will be contacted as indicated in Table 3 to update the study drug supply. Additional details are provided in the IRT Manual.

8.1.4. Demography and Medical History

8.1.4.1. Demographics and General Medical History

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

8.1.4.2. Disease Characteristics and Treatment History

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

8.2. Efficacy Assessments

8.2.1. Tumor Imaging

Objective assessment of tumor status is required using RECIST v1.1 (Eisenhauer et al 2009) and RANO (Wen et al 2010) for patients with primary brain tumors to determine responses and will be logged into the eCRF. The recommended method for measuring and following tumor burden will be CT scan to include the thorax, 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 or RANO.

The schedule for efficacy assessments will be at screening (this will be considered the baseline scan), every 9 weeks (every 3 cycles), and then at EOT (if applicable). Imaging should continue in 9-week intervals regardless of delays in cycle starts. For participants showing a response, a confirmatory scan may be performed a minimum of 4 weeks (per RECIST v1.1 and RANO) from the previous scan. For participants showing a progression based on radiologic review, treatment should be discontinued.

For participants who discontinue treatment for reasons other than disease progression, every effort should be made to continue monitoring their disease status by radiographic imaging until 1) start of new anticancer therapy, 2) documented disease progression, 3) death, or 4) end of study, whichever occurs first.

8.2.2. ECOG Performance Status

ECOG performance status (see Table 12) will be assessed at the visits specified in Table 3.

Table 12: 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.

8.2.3. Medical Resource Utilization and Health Economics

Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

[redacted]

8.3. Safety Assessments

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

8.3.1. Adverse Events

Adverse events will be monitored from the time the participant signs the ICF until at least 30-35 days after the last dose of study drug or until the start of new anticancer therapy, whichever occurs first. Adverse events that begin or worsen after informed consent should be recorded on the Adverse Events Form in the eCRF regardless of the assumption of a causal relationship with the study drug. 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 study drug. Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant, such as "How are you feeling?" is the preferred method to inquire about AE occurrences. Adverse events may also be detected when they are volunteered by the participant during the screening process or between visits, or through physical examinations, laboratory tests, or other assessments. The definition, reporting, and recording requirements for AEs are described in Section 9.

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

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

8.3.2. Physical Examinations

A medically qualified individual, such as a licensed physician, physician's assistant, or an advanced registered nurse practitioner, must perform physical examinations 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 drug. Investigators should pay special attention to clinical signs related to previous serious illnesses.

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

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

8.3.3. Vital Signs

Vital sign measurements (to be taken before blood collection for laboratory tests), include blood pressure, pulse, respiratory rate, and body temperature. Blood pressure and pulse will be taken with the participant in the recumbent, semirecumbent, or sitting position after approximately 5 minutes of rest. Weight will be assessed on Day 1 of each study cycle. 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 drug.

8.3.4. Electrocardiograms

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

The 12-lead ECGs will be interpreted by the investigator at the site to be used for immediate participant management. Additional 12-lead ECGs may be performed as clinically indicated to manage participant safety. The decision to include or exclude a participant or withdraw a participant from the study treatment based on an ECG flagged as "Abnormal, Clinically Significant" is the responsibility of the investigator, in consultation with the sponsor's medical monitor, as appropriate. Clinically notable abnormalities that are considered clinically significant in the judgment of the investigator are to be reported as AEs. In the event that a single QTc is > 480 milliseconds at screening, the participant may enroll if the average QTc for the 3 ECGs is ≤ 480 milliseconds or with approval from the medical monitor. For participants with an intraventricular conduction delay (QRS interval > 120 milliseconds) at screening, the JTc interval may be used in place of the QTc with medical monitor approval. The JTc must be ≤ 340 milliseconds if JTc is used in place of the QTc. In addition, the JTc interval should be used for all subsequent assessments.

8.3.5. Comprehensive Eye Examination

A comprehensive eye examination should be performed by a qualified ophthalmologist at screening, once every 3 cycles (± 7 days, starting at Cycle 3), at EOT, and as clinically indicated. The eye examination should include a visual acuity test, slit-lamp examination, and funduscopy

with digital imaging. Additional assessments (eg, optical coherence tomography) should be performed if clinically relevant retinal findings are observed on ophthalmologic exams and in participants with reported visual AEs or change in visual acuity, if the events or changes are suspected to be of retinal origin. Every effort should be made to ensure that all subsequent examinations are performed by the same ophthalmologist.

8.3.6. Laboratory Assessments

See Table 13 for the list of clinical laboratory tests to be performed and see Table 4 for the timing and frequency. The local laboratory will perform all clinical laboratory assessments for safety (ie, blood chemistries, hematology assessments, coagulation tests, endocrine function, and urinalysis), and a central laboratory will be used to study the translational samples at the end of the study.

Serum phosphate testing is required on a more frequent basis if a participant develops hyperphosphatemia during Cycle 1 and/or is up-titrated (see Table 4). Parathyroid hormone (endocrine) testing is required at baseline and Day 1 of every third cycle (starting with Cycle 3) as parathyroid hormone plays a role in calcium and phosphate hemostasis (Khundmiri et al 2016).

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 SoA (see Table 4). Information regarding collection, processing, and shipping of laboratory assessments is provided in the Laboratory Manual.

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 30-35 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 drug 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; see Section 9.2), then the result(s) of the **specific laboratory assessment(s)** must be recorded in the eCRF.

Table 13: Required Laboratory Analytes

Blood Chemistries	Hematology	Urinalysis With Microscopic Examination	Serology	Coagulation
Albumin Alkaline phosphatase ALT AST Amylase Bicarbonate or CO_2 Blood urea nitrogen or urea Calcium Chloride Creatinine Glucose Lactate dehydrogenase Lipase Magnesium Phosphate Potassium Sodium Total bilirubin Direct bilirubin (if total bilirubin is elevated above ULN) Total protein Uric acid Vitamin D (25-hydroxyvitamin D and 1,25-dihidrosyvitamin D)	Complete blood count, including: • Hemoglobin • Hematocrit • Platelet count • Red blood cell count • White blood cell count Differential count, including: • Basophils • Eosinophils • Lymphocytes • Monocytes • Neutrophils Absolute values must be provided for: • WBC differential laboratory results	Color and appearance pH and specific gravity Bilirubin Glucose Ketones Leukocytes Nitrite Occult blood Protein	Hepatitis B surface antigen Hepatitis B surface antibody Hepatitis B core antibody HCV antibody NOTE: If any of the above are positive, HBV-DNA, HCV-RNA to assess risk of reactivation	PT PTT or aPTT INR
			Endocrine Function	**Pregnancy Testing**
			PTH	Female participants of childbearing potential only require a serum test at screening and EOT and a urine pregnancy test before the first dose on Cycle 1 Day 1 and then on Day 1 of every cycle. Pregnancy tests (serum or urine) should be repeated if required by local regulations.

aPTT = activated partial thromboplastin time; INR = international normalized ratio; PT = prothrombin time; PTT = partial thromboplastin time
Note: Additional tests may be required, as agreed upon by the investigator and sponsor, based on emerging safety data.

8.3.6.1. Pregnancy Testing

A serum pregnancy test will be required for all women of childbearing potential during screening and at the EOT visit; participants going into hospice are not required to provide EOT pregnancy test. Urine pregnancy tests will be performed locally on Day 1 of each cycle, 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 drug and continue participation in the study.

If a pregnancy is confirmed by a serum pregnancy test, see Section 9.5 for reporting requirements.

8.3.6.2. Serology

Hepatitis screening assessments will be performed at the screening visit to assess infection and viral status; required analytes are shown in Table 13. Generally, hepatitis tests should be performed early in the screening process due to the length of time needed to obtain the results. Additional tests may be performed if clinically indicated.

8.4. Pharmacokinetic Assessments

Pharmacokinetic parameters are not evaluated in this study.

8.5. Pharmacodynamic and Translational Assessments

Pharmacodynamic parameters are not evaluated in this study.

8.5.1. Tumor for Genomics Testing for FGFR Genetic Alterations and Gene Expression

All potential participants must be evaluated for FGFR mutations and rearrangements before enrollment. Participants with local lab data documenting an FGFR1, FGFR2, or FGFR3 mutation or translocation (in-frame fusion regardless of fusion partner) are eligible. Confirmatory testing through the central genomics laboratory will be performed on all participants (not required when tissue already profiled at the reference lab); results from the central laboratory are not required prior to enrollment. Details for sample collection, processing, and shipping will be provided in the Laboratory Manual.

Appendix C contains a list of the most common recurrent activating FGFR mutations (excluding the kinase domain) that have been previously described, are present in somatic mutation databases, and/or are homologous to activating mutations present in another FGFR. Appendix C is not all-inclusive, as extremely rare or novel activating alterations may not be present in the list.

[redacted]

8.5.2. Blood for Mutational and Other Correlative Analysis

[redacted] Analysis of tumor mutational status will be conducted by the sponsor or its designee, and other assays relevant to the objectives of the study may be performed based upon emerging data. Details for sample collection, processing, and shipping will be provided in the Laboratory Manual. The correlative analyses may include assessment of markers of immune and inflammation status, including cytokines and soluble receptors, as well as examination of markers associated with tumor metabolism. Other assays relevant to the objectives of the study may be performed based upon emerging data. [redacted] Details for sample collection, processing, and shipping will be provided in the Laboratory Manual.

Blood or saliva will be collected at baseline for the purpose of tumor/normal matched sampling and assessment of germline versus somatic mutation status.

8.5.3. Tissue Biopsies

Tumor biopsies will be collected as specified below:

- **Screening:** Mandatory tumor tissue will be collected during screening. A fresh biopsy at screening is preferred; however, formalin-fixed paraffin embedded tissue is acceptable as long as the sample has been collected less than 12 months from date of screening (not required for participants who have already had tumor sequenced at the reference laboratory).

  Note: Fresh tumor biopsies should be taken from nontarget lesions when possible.
- **Optional on-treatment:** An on-treatment biopsy may be collected during Cycle 2, between Day 7 and Day 14, but is allowed to be performed at any cycle; the on-treatment biopsy should be performed on a study drug administration day, preferably between Day 7 and Day 14.

  Note: On-treatment biopsies should be taken from the same site as the screening biopsy whenever possible.
- **Optional end of treatment:** An EOT/at the time of progression biopsy is requested but not required from all participants. If EOT occurs less than 6 weeks after the on-treatment biopsy was performed, an EOT biopsy should not be performed.

8.6. 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.

8.7. End of Treatment

When the participant permanently discontinues study drug, whether the participant is terminating the study early or the participant has completed the study, the EOT visit should be conducted. If the EOT visit coincides with a regular study visit, the EOT evaluations will supersede those of

that scheduled visit, and the data should be entered in the EOT visit in the eCRF. The participant should be encouraged to return for the follow-up visit.

8.8. Follow-Up

8.8.1. Safety Follow-Up

The safety follow-up period is the interval between the EOT visit and the scheduled follow-up visit, which should occur 30 to 35 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 drug, 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- to 35-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.

8.8.2. Post-Treatment Disease Follow-Up

Participants who discontinue study treatment for a reason other than disease progression will move into the disease status follow-up period and should be assessed every 9 weeks ± 7 days by radiologic imaging to monitor disease status. Every effort should be made to collect information regarding disease status until:

- The start of new anticancer therapy: the start of the new treatment should be captured, but the participant should continue to have disease assessments until progressive disease.
- Disease progression (confirmed by a local radiologist).
- Death.
- The end of the study.

8.8.3. Survival Follow-Up

Once a participant has received the last dose of study treatment, 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, patient records, and public records/databases approximately 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 Meeting the Adverse Event Definition

- Any safety assessments (eg, ECG, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease).
- Abnormal laboratory test results constitute an AE if they are considered clinically meaningful, induce clinical signs or symptoms, require concomitant therapy, or require changes in study 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 drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

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.

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

Adverse Event and Serious Adverse Event Recording

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

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

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

Follow-Up of Adverse Events and Serious Adverse Events

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the originally completed eCRF.
- Any updated SAE data will be submitted to the sponsor (or designee) within 24 hours of receipt of the information.
- Once an AE is detected, it should be followed until it has resolved or until it is judged to be permanent; assessment should be made at each visit (or more frequently if necessary) of any changes in severity, the suspected relationship to the study 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 drug or study procedure[s]), all SAEs occurring after the participant has signed the ICF through 30-35 days after the last dose of study treatment ***or*** until the participant starts a new anticancer therapy, whichever occurs earlier) must be reported to the sponsor (or designee) within **24 hours** of learning of its occurrence, unless otherwise specified by the Protocol. The investigator will submit any updated SAE data to the sponsor (or designee) within 24 hours of it being available.

Investigators are not obligated to actively seek 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 Directive 2001/20/EC, or as per national regulatory requirements in participating countries.

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

Investigator safety reports must be prepared for suspected unexpected 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 PhV/designee (eg, C3i/Telerx). 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.

9.5. Emergency Unblinding of Treatment Assignment

Not applicable.

9.6. Pregnancy

Pregnancy, in and of itself, is not regarded as an AE unless there is suspicion that study 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 interrupted immediately (female participants only; see Section 6.5.1 for the maximum permitted duration of study drug interruption).
- If the female participant is no longer pregnant and meets the treatment continuation criteria within 28 days of the scheduled start of a cycle (or your maximum allowable time off study drug), study treatment may be resumed after approval has been received from the sponsor medical monitor.
- The investigator must complete and submit the Incyte Clinical Trial Pregnancy Form to the sponsor or its designee within **24 hours** of learning of the pregnancy.

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

to the sponsor's study drug to any pregnancy outcome, as well as follow-up to the first well-baby visit or the duration specified in local regulations, whichever is later. Refer to the Incyte Reference Guide for Completing the Clinical Trial Pregnancy Form.

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

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

9.7. Warnings and Precautions

Special warnings or precautions for the study drug, 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.

9.8. Product Complaints

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

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

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

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

10. STATISTICS

10.1. Sample Size Determination

Overall, the study plans to enroll approximately 50 participants. Assuming ORR is 30%, 50 participants will provide at least 80% power to test the null hypothesis of ORR ≤ 15% using a normal-approximate z test at 1-sided significance level of 0.05.

When a tumor subtype j within each cohort reaches 10 participants (or more), a statistical evaluation for ORR (p_j) within the subtype will be conducted. The tumor subtype j may be discontinued from further enrollment if the posterior probability $P(p_j < 0.15|n_j, N_j,\alpha, \beta) > 0.3$ where n_j is the number of responders in jth subtype, N_j is the number of participants with jth tumor subtype, α and β are parameters of the prior distribution and are set to be $\alpha = 1.7625$ and $\beta = 9.9875$ (Beta distribution with mean = 0.15, variance = 0.01). Tumor subtypes with at least 10 patients and $P(p_j < 0.15|n_j, N_j,\alpha, \beta) \leq 0.3$ may continue to enroll participants. Any tumor subtype j with at least 10 participants and $P(p_j > 0.30|n_j, N_j,\alpha, \beta) > 0.5$ may enroll up to 30 additional participants as an expansion cohort of the tumor subtype. These participants will not be counted towards the 50 participants planned for the study. At the end of the study, $P(p_j < 0.15|n_j, N_j,\alpha, \beta)$ and $P(p_j > 0.30|n_j, N_j,\alpha, \beta)$ will be evaluated for all tumor subtypes within each cohort (see Table 14 and Table 15). A cohort of at least 25 participants will provide > 0.8 probability of observing 6 responders if underlying response rate is 0.3. The initial calculation of these posterior probabilities of each tumor subtype will begin when 10 participants have completed the assessment for primary response.

These rules based on posterior probabilities are provided as guidance for recruiting participants and discontinuing recruitment due to lack of response. The decision to continue recruiting to a tumor subtype or discontinue recruitment will be made based on the degree of responses observed (eg, number of CRs), other relevant clinical parameters, and medical assessments.

In addition to the aforementioned process, other methods including but not limited to hierarchical Bayesian models may be used to decide if a tumor subtype in each cohort will discontinue enrollment or continue to enroll subjects.

Table 14: P(p<0.15|n/N,alpha=1.7625,beta=9.9875)

Number of Responders	Number of Participants						
	N = 4	N = 5	N = 6	N = 7	N = 8	N = 9	N = 10
0	0.7384	0.7693	0.7969	0.8215	0.8433	0.8626	0.8797
1	0.4501	0.4933	0.5347	0.5740	0.6112	0.6460	0.6785
2	0.2108	0.2467	0.2837	0.3213	0.3592	0.3970	0.4344
3	0.0763	0.0965	0.1190	0.1437	0.1703	0.1987	0.2284
4	0.0215	0.0297	0.0397	0.0516	0.0654	0.0812	0.0988
5		0.0073	0.0106	0.0150	0.0205	0.0272	0.0353
6			0.0023	0.0035	0.0053	0.0075	0.0105
7				0.0007	0.0011	0.0017	0.0026
8					0.0002	0.0003	0.0005
9						0.0001	0.0001
10							0.0000

Table 15: P(p>0.3|n/N,alpha=1.7625,beta=9.9875)

Number of Responders	Number of Participants						
	N = 4	N = 5	N = 6	N = 7	N = 8	N = 9	N = 10
0	0.0258	0.0188	0.0137	0.0100	0.0073	0.0053	0.0038
1	0.1044	0.0808	0.0622	0.0477	0.0364	0.0276	0.0209
2	0.2627	0.2152	0.1749	0.1411	0.1131	0.0901	0.0713
3	0.4790	0.4141	0.3544	0.3006	0.2527	0.2108	0.1746
4	0.6928	0.6286	0.5643	0.5013	0.4411	0.3846	0.3325
5		0.8040	0.7514	0.6952	0.6371	0.5783	0.5202
6			0.8816	0.8426	0.7984	0.7500	0.6985
7				0.9319	0.9051	0.8731	0.8362
8					0.9625	0.9453	0.9236
9						0.9801	0.9696
10							0.9898

10.2. Populations for Analysis

Populations for analysis are shown in Table 16.

Table 16: Populations for Analysis

Population	Description
Efficacy evaluable	The efficacy evaluable population includes all enrolled participants who received at least 1 dose of study drug. The efficacy evaluable population will be used for the summary of demographics, baseline characteristics, participant disposition, and analyses of all efficacy data.
Safety	The safety population includes all enrolled participants who received at least 1 dose of study drug. All safety analyses will be conducted using the safety population.
Per protocol	The per protocol population includes all efficacy evaluable population participants who are sufficiently compliant with the protocol.

10.3. Level of Significance

The overall level of significance is 1-sided 0.05.

10.4. Statistical Analyses

10.4.1. Primary Analysis

The primary endpoint of the study is ORR. Objective response rate is defined as the proportion of participants who achieved a CR or a PR based on RECIST v1.1 or RANO, as assessed by local radiological review. This analysis will be based on the efficacy evaluation population. Participants who do not have sufficient baseline or on-study response assessment information to be adequately assessed for response status will be included in the denominators in the calculation of ORR. The 90% CI for the ORR will be estimated using the Clopper-Pearson method. The p-value from the exact binomial test will be provided.

The ORR will also be analyzed based on the per protocol population as a sensitivity analysis.

10.4.2. Secondary Efficacy Analysis

Secondary efficacy analysis will be conducted for the efficacy evaluable population.

Progression-free survival is defined as the time from date of first dose of study drug to the date of progressive disease or death, whichever is first. Progressive disease is evaluated based RECIST v1.1, or RANO, by the local radiographic review. Participants who are alive without progression before analysis cutoff date will be censored. Censoring for PFS will follow FDA guidance. Progression-free survival data will be analyzed by the Kaplan-Meier method.

For objective responders, DOR is defined as the time from the date a participant first achieves CR or PR based on RECIST v1.1 or RANO until the date of first documented disease progression based on RECIST v1.1 or RANO or death. Participants who are alive without progression before analysis cutoff date will be censored. Censoring of DOR will follow the same algorithm as the censoring of PFS. Duration of response data will be analyzed by the Kaplan-Meier method.

Disease control rate, defined as the proportion of participants who achieved best overall response of CR, PR, or SD per RECIST v1.1 or RANO, and its exact 90% CI will be calculated in each cohort.

Overall survival is defined as the time from date of first dose of study drug to death due to any cause. Participants without death observed at the time of the analysis will be censored at last date known to be alive. Overall survival will be analyzed by the Kaplan-Meier method.

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 drug/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 (eg, laboratory, vital signs) will be summarized with descriptive statistics. Clinically notable abnormal values will be flagged and tabulated based on predefined criteria.

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

Descriptive statistics and mean change from baseline will be determined for each ECG parameter at each assessment time. Electrocardiogram results will be reviewed for clinically notable abnormalities according to predefined criteria (see Section 8.3.4). Participants exhibiting clinically notable ECG abnormalities will be listed.

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

[redacted]

10.5. Interim Analysis

No formal interim analysis is planned. However, each tumor subtype within each cohort will be assessed when 10 or more participants are enrolled.

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.

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 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 privacy 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 local data protection laws.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 5 years after study completion unless local regulations or institutional policies require a longer retention period. 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.

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

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

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

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APPENDIX A. INFORMATION REGARDING EFFECTIVENESS OF CONTRACEPTIVE METHODS

For male participants in the study:

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

For female participants in the study:

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

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[a]
  - oral
  - intravaginal
  - transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation[a]
  - oral
  - injectable
  - implantable[b]
- Intrauterine device[b]
- Intrauterine hormone-releasing system[b]
- Bilateral tubal occlusion[b]
- Vasectomized partner[b][c]
- Sexual abstinence[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. INSTRUCTION TO PARTICIPANTS FOR HANDLING STUDY DRUG (PEMIGATINIB)

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

- Store the study drug at room temperature.
- Only remove the number of tablets needed at the time of administration.
- Not to remove doses in advance of the next scheduled administration.
- Make every effort to take doses on schedule.
- Report any missed doses/lost tablets.
- Not to crush, dissolve, or break tablets
- To take study drug with a full glass of water.
- If the participant vomits after taking study drug, the participant should not take another dose.
- To keep study drug in a safe place and out of reach of children.
- To bring all used and unused study drug bottles/kits 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 C. FGFR MUTATIONS AND TRANSLOCATIONS

Please follow instructions outlined in the Investigator Site Files for screening/enrolling participants. For FGFR alterations not present on this list, the study sponsor must be consulted for enrollment.

All in-frame fusions of FGFR1-3 or FGFR2 intron 17 rearrangements are allowed in Cohort A regardless of fusion partner.

Table C1 lists the nonkinase domain mutations in FGFR1-3 allowed in Cohort B without prior consultation with the sponsor. This list contains alterations considered oncogenic or likely oncogenic (excluding the kinase domain) based on known or previously described activating mutations, and/or are present in somatic mutation databases. This list is not all-inclusive, as some rare mutations may not have met our inclusion cutoff criteria.

Table C1: Known/Presumed Activating Point Mutations of FGFR1-3 Allowed in Cohort B

Gene	Alteration	Position	Gene	Alteration	Position	Gene	Alteration	Position
FGFR1	S24F	24	FGFR2	S24F	24	FGFR3	A99T	99
FGFR1	G70R	70	FGFR2	A97T	97	FGFR3	S131L	131
FGFR1	S125L	125	FGFR2	R178C	178	FGFR3	R175C	175
FGFR1	T141R	141	FGFR2	R203C	203	FGFR3	R196C	196
FGFR1	P150S	150	FGFR2	R203H	203	FGFR3	R200C	200
FGFR1	R189C	189	FGFR2	R210Q	210	FGFR3	R248C	248
FGFR1	S251F	251	FGFR2	S252F	252	FGFR3	S249C	249
FGFR1	P252R	252	FGFR2	S252L	252	FGFR3	S249F	249
FGFR1	P252T	252	FGFR2	S252P	252	FGFR3	S249Y	249
FGFR1	G315E	315	FGFR2	S252W	252	FGFR3	D333N	333
FGFR1	G315R	315	FGFR2	P253F	253	FGFR3	G342C	342
FGFR1	Y372C	372	FGFR2	P253L	253	FGFR3	S351C	351
FGFR1	Y374C	374	FGFR2	P253R	253	FGFR3	G370C	370
FGFR1	C379R	379	FGFR2	S267P	267	FGFR3	S371C	371
FGFR1	C381R	381	FGFR2	W290C	290	FGFR3	Y373C	373
FGFR1	R445L	445	FGFR2	G305R	305	FGFR3	G375C	375
FGFR1	R445Q	445	FGFR2	G305W	305	FGFR3	G380R	380
FGFR1	R445W	445	FGFR2	A315S	315	FGFR3	A391E	391
FGFR1	G818R	818	FGFR2	A315T	315	FGFR3	A391V	391
			FGFR2	D336G	336	FGFR3	R399C	399
			FGFR2	D336N	336			
			FGFR2	C342F	342			
			FGFR2	C342G	342			
			FGFR2	C342R	342			
			FGFR2	C342S	342			
			FGFR2	C342W	342			
			FGFR2	C342Y	342			
			FGFR2	S347C	347			
			FGFR2	S351C	351			
			FGFR2	S354C	354			
			FGFR2	S372C	372			
			FGFR2	Y375C	375			
			FGFR2	C382F	382			
			FGFR2	C382G	382			
			FGFR2	C382R	382			
			FGFR2	C382Y	382			
			FGFR2	M391R	391			
			FGFR2	V395D	395			
			FGFR2	E777K	777			

APPENDIX D. CYP3A4 INHIBITORS AND INDUCERS

CYP3A4 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

CYP3A4 Inhibitors

Inhibitors	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

Inhibitors	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. RANO RESPONSE CRITERIA

Criterion	CR	PR	SD	PD
T1 Gadolinium enhancing disease	None	≥ 50% ↓	< 50% ↓ but < 25% ↑	≥ 25% ↑[a]
T2/FLAIR	Stable or ↓	Stable or ↓	Stable or ↓	↑[a]
New Lesion	None	None	None	Present[a]
Corticosteroids	None	Stable or ↓	Stable or ↓	NA[b]
Clinical Status	Stable or ↑	Stable or ↑	Stable or ↑	↓[a]
Requirement for response	All	All	All	Any[a]

CR = complete response; FLAIR = fluid-attenuated inversion recovery; NA = not applicable; PD = progressive disease; PR = partial response; RANO = Response Assessment in Neuro-Oncology; SD = stable disease.

Note: Adapted from Wen et al 2010.

[a] Progression occurs when this criterion is present.

[b] Increase in corticosteroids alone will not be taken into account in determining progression in the absence of persistent clinical deterioration.

APPENDIX F. PROTOCOL AMENDMENT SUMMARY OF CHANGES

Document	Date
Amendment (Version) 1:	14 JUN 2019

Amendment 1 (14 JUN 2019)

Overall Rationale for the Amendment:

The overall rationale for the amendment was to clarify sample collection and dose strength. Specifically, the collection of blood or saliva at baseline was added, and tumor tissue previously tested at the reference laboratory will not need to be resubmitted or retested for validation. The dose strength to be used in this study will be 4.5 mg, though doses of 4.5, 9, 13.5, and 18 mg may be tested. Additional items were added to this amendment and are listed below.

1. **Section 1, Protocol Summary (Table 3: Schedule of Activities)**

   Description of change: A note was added to indicate that study drug will be collected only at Cycles 2+ and EOT.

   Rationale for change: Study drug will not be collected on Day 8 or Day 15.

2. **Section 1, Protocol Summary; Section 4.1, Overall Design; Section 8.5.1, Tumor for Genomics Testing for FGFR Genetic Alterations and Gene Expression; Section 8.5.3, Tissue Biopsies**

   Description of change: Language was added to indicate that a biopsy at baseline is not mandatory for participants who had tumor tissue previously tested.

   Rationale for change: Tumor tissue previously tested at the reference lab will not need to be resubmitted or retested for validation.

3. **Section 1, Protocol Summary (Table 4: Schedule of Laboratory Assessments); Section 8.5.2, Blood for Mutational and Other Correlative Analysis**

   Description of change: Additional genomic testing (blood or saliva) was added.

   Rationale for change: The laboratory will be performing this test at baseline for the purpose of tumor/normal matched sampling and assessment of mutation status.

4. **Section 6.1, Study Treatment Administered (Table 9: Study Treatment Information)**

   Description of change: The dose strength/dosage levels and administration instructions were updated.

   Rationale for change: Tablets will be 4.5 mg only.

5. **Section 6.2, Preparation, Handling, and Accountability; Section 9.4, Reporting of Serious Adverse Events**

   Description of change: References to the Study Reference Manual were removed.

   Rationale for change: A Study Reference Manual will not be provided.

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

Signature Manifest

Document Number: IC-DEV-PROT-AMEND-0484 **Revision:** 0

Title: 54828-MA-TA-208 Protocol Amendment 1

All dates and times are in Eastern Standard Time.

APPROVAL: 54828-MA-TA-208 PR AM1

Approval and Release

Name/Signature	Title	Date	Meaning/Reason
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Quick Approval

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Name/Signature	Title	Date	Meaning/Reason
[redacted]		21 Jun 2019, 11:08:43 AM	Approved