Academic and Community Cancer Research United (ACCRU)

A Phase I, Multi-Center, Open Label, Dose De-escalation and Expansion Study of Gemcitabine and Cisplatin with AG120 or Pemigatinib for Advanced Cholangiocarcinoma

For any communications regarding this protocol, please contact the person indicated on the Protocol Resource page. This is a stand-alone document found on the ACCRU web site [redacted]

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Statisticians: [redacted]

√ Study contributor(s) not responsible for patient care.

Drug Availability

Commercial Agents: Cisplatin
Gemcitabine

Investigational Agents: Ivosidenib
Pemigatinib

IND#: 141189

Research Coordinating Center

[redacted]

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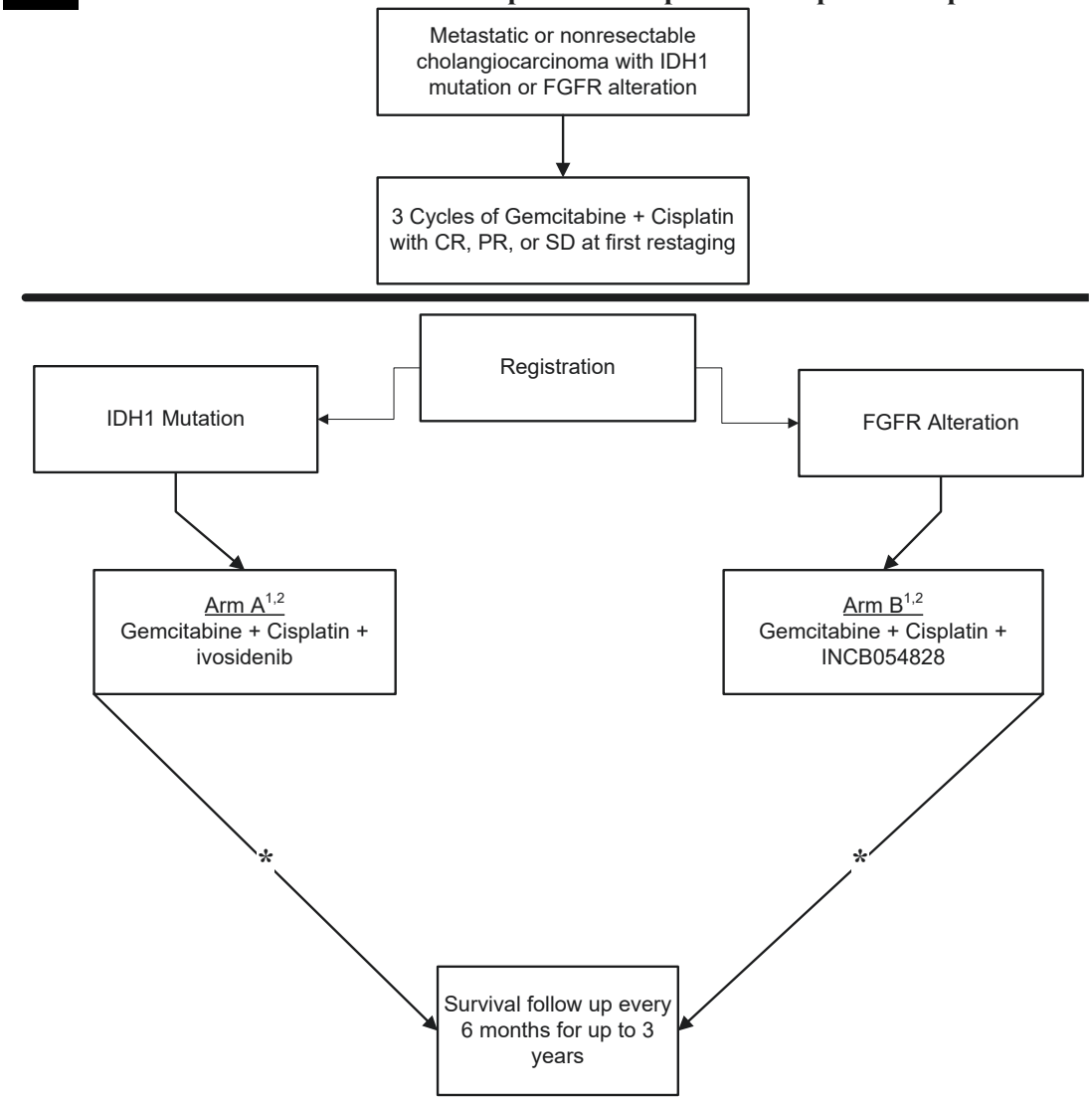
Schema

Prior to discussing protocol entry with the patient, call the ACCRU Registration Office [redacted] for dose level and to ensure that a place on the protocol is open to the patient.



Generic name: Ivosidenib (AG-120) Brand name (s): Tibsovo Availability: McKesson	Generic name: Pemigatinib (INCB054828) Brand name(s): Pemazyre Availability: Incyte
Generic name: Cisplatin Brand name(s): Platinol Availability: Commercial	Generic name: Gemcitabine Brand name(s): Gemzar Availability: Commercial

1.0 Background

1.1 Cholangiocarcinoma

Approximately 6000 patients are diagnosed with cholangiocarcinoma in the United States every year. Patients who present with unresectable or metastatic disease face a poor prognosis with a median survival of approximately 12 months and 5-year survival of < 10%. The ABC-02 trial established combination chemotherapy with gemcitabine and cisplatin as the standard frontline option in this setting. In this trial, patients were randomized to receive gemcitabine alone or combination chemotherapy with gemcitabine and cisplatin. Patients randomized to the combination arm realized improvement in progression free survival (PFS, 8 months vs 5 months) and overall survival (OS, 11.7 vs 8.1 mos.). This trial established combination chemotherapy with gemcitabine and cisplatin as the standard-of-care as initial treatment in fit patients with unresectable or metastatic cholangiocarcinoma.

The role of salvage therapy after progression on first-line therapy is poorly studied and in general is associated with poor outcomes. Outside of a clinical trial, most patients treated with second-line agents will be treated with a fluoropyrimidine, either alone (5FU or capecitabine) or in combination with oxaliplatin (FOLFOX) with a median PFS in the range of 2-3 months. The ongoing UK ABC-06 trial is evaluating the role of FOLFOX in this setting, randomizing patients to receive FOLFOX or "active symptoms control." With a lack of data demonstrating a convincing benefit of salvage therapy after patients are treated with frontline gemcitabine and cisplatin, there is no standard treatment in this setting. Unfortunately survival in this setting remains very poor.

1.2 Genomic Landscape in cholangiocarcinoma

With the advent of recent genomic profiling technologies including next generation sequencing (NGS) and concurrent robust drug development, molecular targeting is now a reality in cholangiocarcinoma more so than any other gastrointestinal malignancy. Approximately 1/3 of patients with intrahepatic cholangiocarcinoma will have a potentially actionable mutation with either an activating isocitrate dehydrogenase 1 (IDH1) mutation or FGFR alteration. Studies suggest the frequency of IDH1 mutations in intrahepatic cholangiocarcinoma is approximately 20%; similarly, the frequency of FGF/FGFR alterations in this same patient population is approximately 10 – 15%. Other potentially actionable mutations (e.g. BRCA, Her2, EGFR, PTEN, CDKN2A/B, etc.) are also identified in this population but occur at a much lower frequency than IDH1 mutations and FGF/FGFR alterations.

1.3 IDH1 mutations as therapeutic target in cholangiocarcinoma

The isocitrate dehydrogenase-1 (IDH1) protein is a metabolic enzyme that plays a critical role in the citric acid cycle, catalyzing the oxidative decarboxylation of isocitrate to produce carbon dioxide (CO2), alpha-ketoglutarate (alpha-KG), and adenine dinucleotide phosphate (NADPH). Mutations in IDH1 most commonly affect arginine-132 (R132H or R132C) resulting in a neomorphic gain-of-function activity. Namely, rather than synthesizing isocitrate, mutant IDH1 enzymes catalyze the reduction of alpha-KG to 2-hydroxyglutarate (2-HG). The abnormal accumulation of 2-HG has been shown to function as an oncometabolite, inhibiting alpha-KG dependent activities that impacts tumorigenesis through a variety of mechanisms. These changes result in epigenetic

changes, impacting chromatin structure and inducing histone and DNA hypermethylation.

Because of these findings suggesting IDH1 as a potential therapeutic target, efforts are underway involving IDH1 inhibition as an anti-cancer strategy. Ivosidenib is a novel, first-in-class, selective inhibitor of mutant IDH1that is currently FDA approved for patients with relapsed refractory AML harboring an IDH1 mutation. Ivosidenib is under clinical evaluation in patients with advanced IDH1 mutant solid tumors including cholangiocarcinoma. In an early phase I trial utilizing ivosidenib in patients with known IDH1 mutations, 73 patients with intrahepatic cholangiocarcinoma were treated including 24 in dose escalation with an additional 49 treated in an expansion cohort. Overall response rate (ORR) (CR or PR) was modest at 5.5%, with 4 subjects who achieved a PR, but 60% demonstrated disease control (SD 56%, PR 5%) with a 6 month PFS of 40.1% and 12 month PFS of 21.8%. Side effects of treatment include fatigue, nausea, vomiting, diarrhea, decreased appetite, dysgeusia and QT prolongation. This activity has led to the ongoing global randomized double-blinded placebo-controlled phase III ClarIDHy (trial NCT02989857) evaluating the role of ivosidenib vs. placebo in patients with cholangiocarcinoma harboring an IDH1 mutation who have failed at least 1 and no more than 2 prior systemic therapies.

1.4 FGFR alterations as therapeutic target in cholangiocarcinoma

The fibroblast growth factor receptor (FGFR) family is composed of 4 highly conserved receptors (FGFR1, FGFR2, FGFR3, FGFR4). Each is composed of an extracellular ligand binding domain, a single transmembrane domain, and an intracellular tyrosine kinase domain. When bound to its ligand, FGFRs will dimerize resulting in activation of the kinase domain with signal transduction including activation of mitogen-activated protein (MAP) kinase and phosphoinositide 3-kinase (PI3K) pathways as well as others. FGFR pathway activation promotes cell proliferation, survival and migration.

FGFR alterations including mutations, translocations, and amplifications have been implicated in tumorigenesis in many malignancies including intrahepatic cholangiocarcinoma. In general, these alterations result in constitutive receptor activation or aberrant ligand-dependent signaling with resultant dysregulation of FGFR activity which is seen as a critical component of tumorigenesis in cancers harboring these alterations.

As of 25 NOV 2019, 3 Incyte-sponsored clinical studies of pemigatinib in healthy participants (Studies INCB 54828-104, -105, and -106) were completed and 9 Incyte sponsored clinical studies of pemigatinib were ongoing and had treated at least 1 participant: 7 studies in participants with advanced malignancies (Studies INCB 54828 101, -102, -201, -202, -203, -207, and -302), 1 study in participants with hepatic impairment and healthy-matched participants (Study INCB 54828-107), and 1 study in participants with renal impairment and healthy-matched participants (Study INCB 548285-108). A total of 779 participants have been exposed to pemigatinib, and an additional 7 participants have been exposed to pemigatinib or gemcitabine and cisplatin in a randomized active controlled study (Study INCB 54828-302).

Pemigatinib Monotherapy in Participants with Previously Treated Cholangiocarcinoma (Study INCB 54828-202)
Efficacy of pemigatinib 13.5 mg QD on a 2-weeks-on/1-week-off schedule (i.e.,

intermittent schedule) in participants with advanced/metastatic or surgically unresectable cholangiocarcinoma who have disease progression after at least 1 previous systemic treatment was evaluated in Study INCB 54828-202. The ORR based on IRC-assessed, confirmed tumor responses among participants with tumors harboring FGFR2 rearrangements or fusions (Cohort A) was 35.5% (95% CI: 26.50, 45.35), including 3 complete responses (2.8%) and 35 partial responses (32.7%). The median DOR based on Kaplan-Meier analysis was 9.13 months (95% CI: 6.01, 14.49). All responders had at least 10 months of follow-up from initial response with the exception of 1 responder who had 6.9 months of follow-up from initial response. Observed DOR was at least 6 months in 24 responders (63.2%), at least 9 months in 16 responders (42.1%), and at least 12 months in 7 responders (18.4%).
There were no IRC-assessed, confirmed tumor responses in participants with cholangiocarcinoma with other FGF/FGFR alterations (Cohort B) or without FGF/FGFR alterations (Cohort C).

As of the data cutoff date, 147 participants with advanced/metastatic or surgically unresectable cholangiocarcinoma had received pemigatinib 13.5 mg QD on an intermittent schedule in Study INCB 54828-202. Nearly all participants (99.3%) had at least 1 TEAE, and the most frequently occurring TEAE was hyperphosphatemia (57.8%). Other TEAEs occurring in > 30% of participants included alopecia, diarrhea, fatigue, nausea, dysgeusia, stomatitis, constipation, decreased appetite, and dry mouth.
Sixty-seven participants (45.6%) had serious TEAEs, 7 (4.8%) of whom had serious events with a fatal outcome. Serious events occurring in > 2% of participants included abdominal pain and pyrexia in 7 participants (4.8%) each, cholangitis and pleural effusion in 6 participants (4.1%) each, and hyponatremia in 4 participants (2.7%). Events with fatal outcome included failure to thrive in 2 participants (1.4%) and bile duct obstruction, cholangitis, malignant neoplasm progression, pleural effusion, and sepsis in 1 participant (0.7%) each. None of these fatal events were assessed as related to pemigatinib.

Treatment-emergent AEs leading to pemigatinib treatment discontinuation occurred in 15 participants (10.2%). Acute kidney injury and intestinal obstruction in 2 participants (1.4%) each were the only events leading to discontinuation that occurred in more than 1 participant.

1.5 Study Rationale

Given the limited benefit of standard agents in the treatment of patients with metastatic cholangiocarcinoma and the relatively high likelihood of harboring a potentially targetable genomic alteration, our hypothesis is that we can improve clinical outcomes by introducing targeted therapies earlier in the treatment of this disease. With a lack of significant overlapping toxicity, we anticipate a favorable toxicity profile with anticipated improvement in disease control and survival. This trial is modelled as a proof of principle, designed primarily to evaluate the safety of this approach and hopefully realize a signal of efficacy in this population where improved outcomes are desperately needed.

1.6 Correlative Research

Plasma 2-hydroxyglutarate (2-HG) levels have been shown to be elevated in patients with cholangiocarcinoma harboring IDH1 mutations. In Arm A only, plasma 2-HG levels will be measured at baseline and on Cycle 4, D1 (+/- 2 days).

2.0 Goals

2.1 Primary

2.11 To evaluate the safety, tolerability, maximum tolerated dose (MTD) and/or recommended phase 2 dose, gemcitabine and cisplatin in combination with either ivosidenib or pemigatinib.

2.2 Secondary

2.21 To evaluate median and progression free survival (PFS) for 6 months per Investigator assessment.

2.22 To evaluate the rate of overall survival (OS) in patients treated with gemcitabine and cisplatin in combination with either ivosidenib or pemigatinib.

2.23 To describe the overall toxicity and adverse events profile associated with gemcitabine and cisplatin in combination with either ivosidenib or pemigatinib.

2.24 To determine the best response profile per RECIST 1.1 criteria in patients treated with gemcitabine and cisplatin in combination with either ivosidenib or pemigatinib.

2.3 Correlative Research

2.31 To measure plasma 2-hydroxglutarate (2-HG) levels ≤21 days prior to registration and at Cycle 4 Day 1 (+/- 2 days).

3.0 Patient Eligibility

Prior to discussing protocol entry with the patient, call the ACCRU Registration Office (507-284-2753) for dose level and to ensure that a place on the protocol is open to the patient.

3.1 Registration – Inclusion Criteria

3.11 Age ≥18 years

3.12 Histopathological diagnosis (fresh) or banked tumor biopsy sample collected within the last 3 years from the registration date consistent with nonresectable or metastatic cholangiocarcinoma and are not eligible for curative resection, transplantation, or ablative therapies.

3.13 Documented disease without any evidence of progression following at least 3 cycles of standard-of-care chemotherapy including gemcitabine and cisplatin as part of first-line systemic therapy.

NOTE: Refer to Section 11.0 for response criteria. Only patients receiving standard-of-care chemotherapy including gemcitabine and cisplatin as first-line therapy for unresectable or metastatic cholangiocarcinoma will be permitted to enroll in this trial. Prior systemic adjuvant chemotherapy is allowed as long as there was no evidence of recurrence within 6 months of completing the adjuvant therapy

3.14 Molecular testing result from CLIA-certified laboratory (using fresh tumor biopsy or most recent banked tumor tissue available) confirming that the tumor tissue has at least one of the following:

a. IDH1 gene mutation (R132C/L/G/H/S mutation)

b. FGFR2 gene alteration (See Appendix II for list of mutations permitting trial inclusion)

3.15 ECOG Performance Status (PS) of 0 or 1

NOTE: Form is available on the ACCRU website

3.16 Life expectancy ≥3 months.

3.17 At least one evaluable and measurable lesion by RECIST criteria as defined in Section 11.0 prior to beginning chemotherapy with gemcitabine and cisplatin.

NOTE: Subjects who have received prior local therapy (including but not limited to embolization, chemoembolization, radiofrequency ablation, hepatic arterial infusion, or radiation therapy) are eligible provided measurable disease falls outside of the treatment.

3.18 Recovered from toxicities associated with prior anticancer therapy to baseline unless stabilized under medical management.

3.19a The following laboratory values obtained ≤ 21 days prior to registration.

- Absolute neutrophil count ≥1,500/mm^3
- Platelet count ≥100,000/mm^3
- Hemoglobin ≥8 g/dL
- Serum total bilirubin ≤2.0 × upper limit of normal (ULN), unless considered due to Gilbert's disease. If Gilbert's disease or disease involving liver, serum total bilirubin ≤2.5 x ULN.
- Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 × ULN or ≤5.0 x ULN in the presence of liver metastases
- Have adequate renal function as evidenced by:

  a. Serum creatinine <1.5 × ULN
  OR
  b. Creatinine clearance ≥50 mL/min based on the Cockcroft-Gault glomerular filtration rate (GFR) estimation

Cockcroft-Gault Equation:

Creatinine clearance for males = $\frac{\textbf{(140 - age)(weight in kg)}}{\text{(72)(serum creatinine in mg/dL)}}$

Creatinine clearance for females = $\frac{\textbf{(140 - age)(weight in kg)(0.85)}}{\text{(72)(serum creatinine in mg/dL)}}$

- Serum phosphate ≤ institutional ULN and potassium within institutional normal range for Arm B only.

  NOTE: Supplemental potassium may be used to correct potassium prior to registration

3.19b Negative serum pregnancy test done ≤7 days prior to registration for women of childbearing potential only.

NOTE: Females of reproductive potential are defined as sexually mature women who have not undergone a hysterectomy, bilateral oophorectomy, or tubal occlusion or who have not been naturally postmenopausal (i.e., who have not menstruated) for ≥24 consecutive months (i.e., have not had menses at any time in the preceding 24 consecutive months).

3.19c Women of reproductive potential and fertile men must agree to use 2 effective forms of contraception (including at least 1 barrier form) from the time of giving informed consent throughout the study and for 90 days (both females and males) following the last dose of study drug.

NOTE: Effective forms of contraception are defined as hormonal oral contraceptives, injectables, patches, intrauterine devices, intrauterine hormone-releasing systems, bilateral tubal ligation, condoms with spermicide, or male partner sterilization.

3.19d Able to understand and willing to sign the informed consent form.

NOTE: A legally authorized representative may consent on behalf of a subject who is otherwise unable to provide informed consent if acceptable to and approved by the site's Institutional Review Board (IRB)/Independent Ethics Committee (IEC).

3.19e Able to comply with scheduled visits, treatment plans, procedures, and laboratory tests, including serial peripheral blood sampling during the study.

3.19f Willing to provide blood samples for correlative research purposes (see Sections 6.0and 14.0).

3.2 Registration - Exclusion Criteria

3.21 Prior therapy with either an IDH inhibitor or selective FGFR inhibitor.

IDH inhibitors: ivosidenib, FT-2012, etc.;
FGFR inhibitors: pemigatinib, BGJ-398, TAS-120, ARQ 087, or derazantinib, etc.

3.22 Progressive disease as best response on current standard-of-care chemotherapy including gemcitabine and cisplatin.

3.23 Known toxicity to standard-of-care chemotherapy including gemcitabine and cisplatin requiring cessation of this therapy.

3.24 Received radiotherapy to metastatic sites of disease ≤ 2 weeks prior to registration.

3.25 Underwent hepatic radiation, chemoembolization, or radiofrequency ablation ≤ 4 weeks prior to registration

3.26 Known symptomatic brain metastases requiring steroids.

NOTE: Subjects with previously diagnosed brain metastases are eligible if they have completed their treatment and have recovered from the acute effects of radiation therapy or surgery prior to study entry, have discontinued corticosteroid treatment for these metastases for at least 4 weeks and have radiographically stable disease for at least 3 months prior to registration.

NOTE: up to 10 mg per day of prednisone equivalent will be allowed.

3.27 Other active malignancy ≤ 5 years prior to registration.

EXCEPTIONS:

a. Non- melanoma skin cancer unless stage 1a or carcinoma-in-situ of the cervix.
b. Breast cancer with ongoing hormone therapy being administered as adjuvant therapy.

NOTE: If there is a history or prior malignancy, they must not be receiving other specific treatment

3.28 Major surgery ≤4 weeks prior to registration or have not recovered from post-surgery toxicities.

3.29a Any of the following because this study involves investigational agents whose genotoxic, mutagenic, and teratogenic effects on the developing fetus and newborn are unknown:

- Pregnant women
- Nursing women

- Men or women of childbearing potential who are unwilling to employ adequate contraception

3.29b **Arm A**: Use of strong CYP3A4 inducers or strong or moderate CYP3A4 inhibitors. In addition, sensitive CYP3A4 substrate medications with a narrow therapeutic window (Appendix III), unless they can be transferred to other medications ≤4 days or 5 half-lives (whichever is shorter) prior to registration

Arm B: Use of strong CYP3A4 inducers or inhibitors or moderate CYP3A4 inducers.

NOTE: Study PI approval is needed if continued use of CYP3A4 inducers or inhibitors. Approval can be obtained via email (documentation of approval/eligibility needed)

3.29c For Arm B only: Current evidence of clinically significant corneal (including but not limited to bullous/band keratopathy, corneal abrasion, inflammation/ulceration, and keratoconjuctivitis) or retinal disorder (including but not limited to central serous retinopathy, macular/retinal degeneration, diabetic retinopathy, retinal detachment) as confirmed by ophthalmologic examination.

3.29d Known history and/or current evidence of ectopic mineralization/ calcification, including but not limited to soft tissue, kidneys, intestine, myocardia, or lung, excepting calcified lymph nodes and asymptomatic arterial or cartilage/tendon calcification for Arm B only.

3.29e Known history of hypovitaminosis D requiring supraphysiologic doses to replenish the deficiency for Arm B only.

NOTE: Subjects receiving vitamin D food supplements are allowed.

3.29f7 Active infection requiring systemic anti-infective therapy or with an unexplained fever >38.5°C ≤7 days of registration.

NOTE: at the discretion of the Investigator, subjects with tumor fever may be enrolled.

3.29g Any known hypersensitivity to any of the components of ivosidenib or pemigatinib.

3.29h Significant, active cardiac disease ≤6 months prior to registration, including

- New York Heart Association (NYHA) Class III or IV congestive heart failure (Appendix IV)
- myocardial infarction
- unstable angina
- stroke

3.29i Have a heart-rate corrected QT interval (using Fridericia's formula) (QTcF) (Appendix V) ≥450 msec or other factors that increase the risk of QT prolongation or arrhythmic events (e.g., heart failure, hypokalemia, family history of long QT interval syndrome).

NOTE: Bundle branch block and prolonged QTcF interval are permitted with approval of the Medical Monitor.

3.29j Taking medications that are known to prolong the QT interval, unless they can be transferred to other medications ≥5 half-lives prior to registration or unless the medications can be properly monitored during the study.

NOTE: If equivalent medication is not available, QTcF should be closely monitored.

3.29k Known active hepatitis B (HBV) or hepatitis C (HCV) infections, known positive human immunodeficiency virus (HIV) antibody results, or acquired immunodeficiency syndrome (AIDS) related illness.

NOTE: Subjects with a sustained viral response to HCV or immunity to prior HBV infection will be permitted. Subjects with chronic HBV that is adequately suppressed per institutional practice will be permitted.

NOTE: HBV, HCV, and/or HIV testing is not required prior to trial registration

3.29l Any other acute or chronic medical or psychiatric condition, including recent (≤12 months of registration) or active suicidal ideation or behavior, or a laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the Investigator, would make the subject inappropriate for entry into this study.

3.29m Inability or unwillingness to swallow ivosidenib or pemigatinib or have significant GI disorder(s) that could interfere with absorption, metabolism, or excretion.

NOTE: Gastroesophageal reflux disease under medical treatment is allowed (assuming no drug interaction potential).

3.29n Have been committed to an institution by virtue of an order issued either by the judicial or administrative authorities.

3.29o Receiving any other investigational agent which would be considered as a treatment for the primary neoplasm.

4.0 Test Schedule

Tests and procedures	≤21 days prior to registration	Cycle 1 (+/- 2 days)			Day 1 of each new cycle (+/-3 days)	Cycle 4 Day 1 and every 9 weeks (+/- 2 days)	End of Treatment (At PD, withdrawal, or removal)	(30 Days after End of Treatment)[11]
		Day 1	Day 8	Day 15				
History and exam, vitals (blood pressure, pulse, temp), weight, ECOG PS[1]	X	X	X	X	X		X	X
Height	X							
Adverse event assessment[9]	X	X	X	X	X		X	X
Hematology[2]: CBC with differential, CEA, CA19-9	X	X	X	X	X		X	X
CMP[2]: with Mg and phos	X	X	X	X	X		X	X
Tumor measurement[3]	X					X	X	
EC G[5,R]	X	X	X	X	X			
Serum pregnancy test[6]	X	X			X			
Ophthalmologic testing[10]	X					X	X	
Mandatory blood sample (2-HG testing)[7,R]	X					X		
Patient Medication Diary[8]		X	X	X	X		X	

*Footnotes on the following page

1. History, physical examination, vital signs, weight, and ECOG PS to be performed at baseline and weekly throughout Cycle 1 (DLT period), then on Day 1 of each subsequent cycle. This is considered standard of care except for evaluations on C1D8 and C1D15 during the DLT period.
2. CBC with differential and chemistry panel to be performed at baseline and weekly throughout C1 (DLT period), then on D1 of each subsequent cycle. This is considered standard of care.
3. Chest, abdomen and pelvis cross-sectional imagining required at baseline and per table 4.0 above for response evaluation. Imaging modality according to investigator preference; options include CT C/A/P with IV contrast, MRI abdomen + pelvis + chest CT, MRI abdomen + pelvis + CXR. PET/CT and FDG-PET/CT are allowed as long as CT portion is of diagnostic quality and includes IV contrast. Same imaging modality to be used throughout the study.
4. Screening imaging required ≤21 days prior to registration; considered research-funded if previous imaging outside 21-day window.
5. ECG-Obtain ECG on ALL study subjects (ARM A & ARM B) at Screening. Then, for subjects assigned to ARM A (taking ivosidenib). ECG done on days 1, 8, & 15 in Cycle 1 and Day 1 of each new cycle (+/- 3 days), as well as when clinically indicated.
6. For women of childbearing potential only. Must be done ≤7 days prior to registration and on D1 of each cycle.
7. Arm A patients only (patients receiving ivosidenib): 2-hydroxyglutarate (2-HG) levels will be drawn ≤21 days prior to registration and at Cycle 4, day 1 (+/- 2 days) with first restaging scan.
8. The diary must begin the day the patient starts taking the medication and must be completed per protocol and returned to the treating institution OR compliance must be documented in the medical record by any member of the care team. Refer to Appendix I.
9. Any Adverse event assessment within 30 days of end of treatment will be recorded on the adverse event assessment form in the last cycle of treatment.
10. Ophthalmologic testing - Obtain eye exams on ALL study subjects (ARM A & ARM B) at Screening. Then, for subjects assigned to ARM B (taking Pemigatinib) - A comprehensive ophthalmological examination including OCT every 3 cycles (i.e., every 9 weeks) while a patient is receiving pemigatinib. After the first 6 months, ophthalmological exams for patients still on treatment with pemigatinib may be conducted every 3 months.
11. All solicited, and any other reportable AEs, that occurred within 30 days after EOT should be included on the Adverse Events: Solicited and Adverse Events: Other forms in the last Treatment folder.

R Research funded (see Section 19.0)

5.0 Grouping Factor

5.1 Mutation Status: IDH1 vs. FGFR/FGF

6.0 Registration Procedures

6.1 Safety Run-in

Prior to discussing protocol entry with the patient, call the ACCRU Registration Office (507-284-4130) for dose level and to ensure that a place on the protocol is open for the patient.

6.2 Registration Procedures (Safety Run-In and Expansion Cohort)
To register a patient, fax [redacted] a completed eligibility checklist to the Academic and Community Cancer Research United (ACCRU) Registration Office between 8 a.m. and 4:30 p.m. central time Monday through Friday.

6.21 Correlative Research

A mandatory correlative research component is part of this study. The patient will be automatically registered onto this component (see Sections 3.0 and 14.0).

6.22 Prior to accepting the registration, the registration/randomization application will verify the following:

- IRB approval at the registering institution
- Patient eligibility
- Existence of a signed consent form
- Existence of a signed authorization for use and disclosure of protected health information

6.23 Documentation of IRB approval must be on file in the Registration Office before an investigator may register any patients.

In addition to submitting initial IRB approval documents, ongoing IRB approval documentation must be on file (no less than annually) at the Registration Office [redacted] If the necessary documentation is not submitted in advance of attempting patient registration, the registration will not be accepted and the patient may not be enrolled in the protocol until the situation is resolved.

Submission of annual IRB approvals is required until the study has been closed through your IRB.

6.24 At the time of registration, the following will be recorded:

- Patient has/has not given permission to store and use his/her sample(s) for future research to learn about, prevent, or treat cancer

- Patient has/has not given permission to store and use his/her sample(s) for future research to learn, prevent, or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease)

- Patient has/has not given permission for ACCRU to give his/her sample(s) to outside researchers

6.25 Treatment on this protocol must commence at an ACCRU institution under the supervision of a medical oncologist

6.26 Treatment cannot begin prior to registration and must begin ≤14 days after registration.

6.27 Pretreatment tests/procedures (see Section 4.0) must be completed within the guidelines specified on the test schedule.

6.28a All required baseline symptoms (see Section 10.0) must be documented and graded.

6.28b Study drug is available on site.

6.28c Blood draw kit is available on site.

7.0 Protocol Treatment

7.1 Treatment Schedule - Use actual weight or estimated dry weight if fluid retention

7.11 Pretreatment medication

No premedication required for ivosidenib or pemigatinib required. Premedication for gemcitabine + cisplatin should be administered per institutional practice.

7.12 Treatment medication

Arm	Agent	Dose Level	Route	Day(s)	ReRx
A	Ivosidenib	Per current dose level (Max of 500mg)	Oral	1-21 (once daily)	Every 21 days
B	Pemigatinib	Per current dose level (Max of 13.5mg)	Oral	1-21 (once daily)	Every 21 days
A, B	Cisplatin	25 mg/m^2	IV	D1 & D8	Every 21 days
A, B	Gemcitabine	1000 mg/m^2	IV	D1 & D8	Every 21 days

7.2 Patients can be instructed in administration techniques and granted treatment independence with nursing staff approval. See section 15 for details of study drug administration.

7.3 For this protocol, the patient must return to the consenting ACCRU institution for evaluation at least every 21 days (+/- 3 days) during treatment.

7.4 Phase I – determination of Maximum Tolerated Dose (MTD)

7.41 Dose De-escalation

Dose level	ivosidenib	pemigatinib
-2	HOLD	4.5 mg
-1	250 mg	9 mg
0*	500 mg	13.5 mg

***starting dose level**

7.411 Treatment by a local medical doctor is not allowed.

7.412 Six patients will be treated at each dose level and observed for a minimum of 21 days to assess toxicities before new patients are treated. Doses will not be escalated in any individual patient.

7.413 Investigators are to contact the ACCRU Operations Office [redacted] as soon as any dose-limiting toxicity (DLT) occurs.

7.414 Dosing will be de-escalated (as described in "study flow") if >/=2 DLTs at any given dose; if >/= 2 DLTs is seen at lowest dose level, consideration will be given to terminate the trial vs further dose reduction. A temporary enrollment hold will be enforced after each 6 patient cohort has been enrolled to evaluate for excessive toxicity. . If at any time the decision is made to pursue a further dose reduction other than as stated in the protocol, this will be addressed with a protocol amendment.

7.42 Definitions of DLT

An event is considered a dose limiting toxicity (DLT) if it meets the following criteria:
Occurs during the 3 weeks (during initial first cycle of combined therapy) after starting the study, and is assessed as having a possible causal relationship with AG120 or pemigatinib (possibly, probably or definitely related) AND Meets any of the following criteria:

- Grade 3 thrombocytopenia with bleeding.
- Grade 4 thrombocytopenia.
- Grade 3, 4 febrile neutropenia.
- Grade 4 neutropenia without fever lasting more than 7 days.
- Grade 4 anemia
- Any grade ≥ 3 non-hematologic toxicity with the following exceptions:

- Grade 3 hypomagnesemia or hyperphosphatemia which last ≤14 days with adequate supportive care for arm B only.
- Grade 3 nausea/vomiting or diarrhea lasting≤3 days with adequate antiemetic and other supportive care
- Any intolerable grade ≥ 2 toxicity warranting a dose reduction.

  Grade 3 or 4 QTcF prolongation
- Hy's Law (3 × ULN elevation of transaminases and concomitant 2 × ULN elevation of bilirubin without alternative etiology)
- Failure to receive at least 80% of the expected doses of AG120 or Pemigatinib. due to toxicity
- Uncontrolled hyperphosphatemia even with binders while taking Pemigatinib

8.0 Dosage Modification Based on Adverse Events

Strictly follow the modifications in this table for the first **two** cycles, until individual treatment tolerance can be ascertained. Thereafter, these modifications should be regarded as guidelines to produce mild-to-moderate, but not debilitating, side effects. If multiple adverse events are seen, administer dose based on greatest reduction required for any single adverse event observed. Reductions or increases apply to treatment given in the preceding cycle and are based on adverse events observed since the prior dose.

ALERT: *ADR reporting may be required for some adverse events (See Section 10)*

8.1 Dose Levels (Based on Adverse Events in Tables 8.3 and 8.4)

Dose levels for gemcitabine + cisplatin should be per institutional practice.

Dose Level	Ivosidenib	Pemigatinib
0*	500 mg	13.5 mg
-1	250 mg	9 mg
-2	HOLD	4.5 mg

* Dose level 0 refers to the starting dose.

8.2 Dose Modifications

Dose modifications for adverse events felt to be due to gemcitabine + cisplatin allowed per institutional practice.

Patients who stop chemo for reasons other than progression may continue on study drug until progression.

For any AE felt attributable to the study drug (ivosidenib or pemigatinib), including AEs not specifically mentioned below, the Investigator may decide to delay dosing or modify the dose of study drug based on clinical judgment. These decisions should be reviewed

with the study chair or co-chair prior to implementation.

Dose modifications of ivosidenib from 500 mg to 250 mg or pemigatinib from 13.5 mg to 9 mg to 4.5 mg will be permitted on study for management of AEs.

If more than one AE occurs that would require a dose modification, upon resolution of all AEs to baseline or Grade 1, study drug should be dose reduced to dose level -1 (Table 8.1). If the patient experiences a significant adverse event requiring a dose reduction at the start of the next cycle, then the dose will remain lowered for that entire subsequent cycle. If that cycle is completed with no further adverse events >Grade 2, then reescalation may be allowed, one level at a time, in the following cycles with approval from the study chair or co-chair. There will be no dose re-escalation if the patient has a DLT or a serious toxicity at the higher dose.

Dose delays for reasons other than management of AEs are discouraged. Dose delays up to 28 days will be permitted at the discretion of the Investigator for reasons including management of AEs and for mitigating circumstances (e.g., planned procedures.) Palliative biliary decompression procedures and/or palliative paracentesis will be permitted on study and will not require interruption of study drug.

Adverse events requiring a dose-reduction step for any or all drugs beyond the two dose-reduction steps (levels –1 and –2) will be at the discretion of the treating physician after discussion with the study chair or co-chair, if the decision is made for the patient to be kept on study. These dose reductions must be clearly recorded in reported clinical data.

If the subject cannot resume ivosidenib or pemigatinib within 28 days,, the subject should be discontinued from study medication. If study drug is discontinued, the subject will complete the EOT and continue to be followed as outlined in Protocol Sections 4.0 and 13.0.

Exemptions for patients holding study drug for >28 days may be considered for those subjects who are determined by the study chair or co-chair to have received clinical benefit from treatment.

If study drug is delayed for the management of an AE but chemotherapy is continued, the subject should resume study drug after resolution of AEs to baseline or Grade 1 at the next planned visit without changing current dosing cycle (e.g., if the subject did not start dosing at C3D1 due to management of an AE but may resume treatment with C3D8 or at any other time during the course of that given cycle. Resuming treatment will continue according to current cycle (i.e. if pemigatinib is resumed on C3D8, treatment break will continue as scheduled beginning on C3D15).

8.3 Table 1: Dose Modifications for Ivosidenib

Adverse Event	Action
Grade 2 nausea or vomiting (related or unrelated)	· Consider holding dose of ivosidenib until resolution of AE to Grade ≤1 within 28 days of supportive therapy. · Manage with supportive therapy according to the institutional standard of care. · May resume ivosidenib at same dose
Grade 3 adverse events (related, first event)	· Hold dose of ivosidenib until resolution to Grade ≤1 or baseline within 28 days of supportive therapy and then resume dose. · Manage with supportive therapy according to the institutional standard of care. · If the Grade 3 AE recurs (a second time), consider reducing ivosidenib to 250 mg in consultation with the study staff. Reescalation may be permitted after discussion with the study chair or co-chair · If the Grade 3 AE recurs (a third time) despite dose reduction of ivosidenib, then consider discontinuing ivosidenib in consultation with study chair or co-chair
Grade 4 adverse events (related, first event)	· Hold ivosidenib. · Manage with supportive therapy according to the institutional standard of care. · If the AE resolves to Grade ≤1 or baseline within 28 days, then restart ivosidenib dosing at 250 mg in consultation with the study chair or co-chair. · If the AE does not resolve to Grade ≤1 or baseline within 28 days, consider discontinuing study treatment in consultation with the study chair or co-chair. · If the Grade 4 AE recurs (a second time), despite dose reduction, ivosidenib should be discontinued in consultation with the study chair or co-chair.

NOTE: If PML is suspected, regardless of relationship to ivosidenib, dose should be held until final diagnosis is confirmed. If PML is confirmed as a diagnosis, then ivosidenib should be discontinued. If Guillain-Barre is confirmed as a diagnosis, ivosidenib should be discontinued.

8.31 QT prolongation in patients receiving ivosidenib

Prolongation of heart-rate corrected QT (QTc) interval has been observed in monkeys at relatively high doses of ivosidenib as well as in patients while receiving ivosidenib. Please refer to the current ivosidenib Investigator's Brochure for detailed information.

Subjects may be at increased risk for the development of QT prolongation when treated with ivosidenib combination with fluoroquinolones, azole antifungal agents, or serotonin (5-HT3) antagonists. Investigators need to

be vigilant regarding concomitant medications associated with QT prolongation, and if no other therapeutic options are available, monitor subjects receiving ivosidenib with the combination of these drugs, and evaluate ECG and electrolytes (including potassium, magnesium, and calcium) particularly in subjects presenting with nausea, vomiting, or diarrhea.

Subjects who experience prolongation of the heart-rate corrected QT interval, Fridericia's correction (QTcF) to > 480 msec (Grade ≥ 2) while treated with ivosidenib, should be promptly evaluated for causality of the QTc prolongation and managed according to the following guidelines and Table 2:

• Levels of electrolytes (potassium, calcium, and magnesium) should be checked and supplementation given to correct any values outside the normal range.
• Concomitant therapies should be reviewed and adjusted as appropriate for medications with known QT prolonging effects.
• If no other cause is identified and the Investigator believes it is appropriate, particularly if QTcF remains elevated (after above measures have been implemented, or as determined by the Investigator), study treatment may be interrupted, and an ECG should be rechecked in approximately 1 week after the QTcF prolongation was first observed or more frequently as clinically indicated. If QTcF has recovered or improved and the Investigator believes it is safe to do so, re-challenge with study treatment should be considered if held.
• ECGs should be conducted at least weekly (eg, at every scheduled visit) for 2 weeks following QTcF reduction </=480 msec.

Table 2: Management of QT Prolongation by CTCAE Grade

CTCAE Grade	Management
Grade 2	• The dose of study may be reduced to 250 mg QD without interruption of dosing. The dose of study treatment may be re-escalated to the prior dose in ≥ 14 days after QT prolongation has decreased to≤ Grade 1.
Grade 3	• Hospitalization for continuous cardiac monitoring and evaluation by a cardiologist should both be considered. • Dosing with study treatment will be interrupted. If QTcF returns within 30 msec of baseline or < 450 msec for males and < 470 msec for females within 14 days, treatment must be resumed at a reduced dose of 250 mg. • The dose of study treatment cannot be re-escalated following dose reduction for Grade 3 QTcF prolongation unless the prolongation was associated with an electrolyte abnormally of concomitant medication.
Grade 4	• Subjects should be admitted to a hospital for continuous cardiac monitoring and discharged only after review by a cardiologist. • Dosing with study treatment should be permanently discontinued.

8.4 Dose modifications for pemigatinib. Dose interruptions and modifications may occur for individual study subjects. The occurrence of toxicities (related or unrelated to study drug) will guide decisions for treatment interruptions and discontinuation for individual subjects.

Table 3: Guidelines for Interruption and Restarting of Pemigatinib

Adverse Event	Action
Transaminitis: AST or ALT >5.0 x ULN NOTE: In subjects with liver metastasis-related elevations at baseline, contact the sponsor to discuss clinical management and possible dose reductions.	**Step 1**: Interrupt study drug up to 4 weeks (28 days) until toxicity resolved to </= Grade 1 **Step 2**: Restart study drug at same dose. If assessed as related to study drug, restart study drug at next lower dose and monitor as clinically indicated.
Other toxicity (not transaminitis):	
Any other Grade 1 or Grade 2 toxicity	Continue study drug and treat toxicity, monitor as clinically indicated.
Any Grade 3 toxicity if clinically significant and not manageable by supportive care	**Step 1**: Interrupt study drug up to 4 weeks (28 days) until toxicity resolved to </= Grade 1 **Step 2**: If toxicity assessed as related to study drug, restart study drug at next lower dose and monitor as clinically indicated.
Any recurrent Grade 3 toxicity after 2 dose reductions	**Discontinue study drug and follow up per protocol. (Exceptions require approval of chair or co-chair)**
Any other grade 4 toxicity	**Discontinue study drug and follow up per protocol**

Due to the fact subjects may enter the study with extensive pretreatment toxicities, the dose reduction rules are provided as guidelines

For dose adjustments, it is recommended that a maximum of 2 dose level reductions: subjects administered 13.5 mg can decrease to 9 mg, and if additional dose reduction is required, subjects can decrease to 4.5 mg. Dose reductions below 4.5 mg are not allowed. The frequency of administration remains the same (once daily).

Adverse events that have a clear alternative explanation if transient (≤ 72 hours) abnormal laboratory values without associated clinically significant signs or symptoms may be exempt from dose – reduction rules.

8.5 Management of Hyperphosphatemia in patients receiving pemigatinib

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

Recommended approach for Hyperphosphatemia Management:

Serum Phosphate Level	Supportive Care	Guidance for Interruption/Discontinuation of INCB054828	Guidance for Restarting INCB054828
>5.5 mg/dL and ≤ 7 mg/dL	Initiate a low-phosphate diet	No action.	Not applicable.
>7 mg/dL and ≤ 10 mg/dL	Initiate/continue a low-phosphate diet and initiate phosphate-binding therapy once serum phosphate level is >7 mg/dL. Monitor serum phosphate at least twice a week and adjust the dose of binders as needed; continue to monitor serum phosphate at least twice a week until return to normal range.	If serum phosphate level continues to be >7 mg/dL and ≤ 10 gm/dL with concomitant phosphate-binding therapy for 2 weeks, or if there is recurrence of serum phosphate level in this range, interrupt INCB054828 for up to 2 weeks (not including the planned dose interruption per treatment cycle).	Restart at the same dose when serum phosphate level recurs at > 7 mg/dL, restart study drug with dose reduction.
> 10 mg/dL	Continue to maintain a low-phosphate diet, adjust phosphate-binding therapy, and start/continue phosphatidic agent. Continue to monitor serum phosphate at least twice a week until return to normal range.	If serum phosphate level is > 10 mg/dL for 1 week following phosphate-binding therapy and low phosphate diet *interrupt* study drug. If there is recurrence of serum phosphate level in this range following 2 dose reductions, *permanently discontinue* INCB054828.	Restart study drug at reduced dose with phosphate binders when serum phosphate is < 7mg/dL.

8.6 Criteria for Permanent Discontinuation of the Study Drug:

The occurrence of unacceptable toxicity not caused by the underlying malignancy will be presumed to be related to study drug treatment and will require that the study drug be permanently discontinued. Unacceptable toxicity is defined as follows:

- Occurrence of an AE that is related to treatment with the study drug that, in the judgement of the investigatory, compromises the subject's ability to continue study-specific procedures or is considered to not be in the subjects best interest,
- An AE requiring more than 2 dose reductions.

9.0 Ancillary Treatment/Supportive Care

9.1 Antiemetics may be used at the discretion of the attending physician.

9.2 Blood products and growth factors should be utilized as clinically warranted and following institutional policies and recommendations. The use of growth factors should follow published guidelines of the American Society of Clinical Oncology (ASCO). Recommendations for the Use of WBC Growth Factors: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol 2015;33:3199-3212.

9.3 Patients should receive full supportive care while on this study. This includes blood product support, antibiotic treatment, and treatment of other newly diagnosed or concurrent medical conditions. All blood products and concomitant medications such as antidiarrheals, analgesics, and/or antiemetics received from the first day of study treatment administration until 30 days after the final dose will be recorded in the medical records.

9.4 Diarrhea: This could be managed conservatively with loperamide. The recommended dose of loperamide is 4 mg at first onset, followed by 2 mg every 2-4 hours until diarrhea free (maximum 16 mg/day).

In the event of grade 3 or 4 diarrhea, the following supportive measures are allowed: hydration, octreotide, and other antidiarrheals.

If diarrhea is severe and associated with fever or severe neutropenia (grade 3 or 4), broad-spectrum antibiotics must be prescribed. Patients with severe diarrhea or any diarrhea associated with severe nausea or vomiting **should be carefully monitored** and given intravenous hydration and correction of electrolyte imbalances. Consider hospitalization

10.0 Adverse Event (AE) Reporting and Monitoring

The site principal investigator is responsible for reporting any/all adverse events to the sponsor as described within the protocol. Refer to the adverse event and serious adverse event sections of the protocol for detailed information.

The sponsor/sponsor-investigator is responsible for notifying FDA and all participating investigators in a written safety report of any of the following:

- Any suspected adverse reaction that is both serious and unexpected.
- Any findings from laboratory animal or in vitro testing that suggest a significant risk for human subjects, including reports of mutagenicity, teratogenicity, or carcinogenicity.
- Any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies, whether or not conducted under an IND and whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug.
- Any clinically important increase in the rate of a serious suspected adverse reaction over the rate stated in the protocol or Investigator's Brochure (IB).

Definitions

Adverse Event
Any untoward medical occurrence associated with the use of a drug in humans, **whether or not considered drug related**.

Suspected Adverse Reaction
Any adverse event for which there is a reasonable possibility that the drug caused the adverse event.

Expedited Reporting
Events reported to sponsor within 24 hours, 5 days or 10 days of study team becoming aware of the event.

Routine Reporting
Events reported to sponsor via case report forms

Events of Interest
Events that would not typically be considered to meet the criteria for expedited reporting, but that for a specific protocol are being reported via expedited means in order to facilitate the review of safety data (may be requested by the FDA or the sponsor).

10.1 Adverse Event Characteristics

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site:
[redacted]

a. Adverse event monitoring and reporting is a routine part of every clinical trial.

b. Identify the grade and severity of the event using the CTCAE version 5.0.

c. Determine whether the event is expected or unexpected (see Section 10.2).

d. Determine if the adverse event is related to the study intervention (agent, treatment or procedure) (see Section 10.3).

e. Determine whether the event must be reported as an expedited report. If yes, determine the timeframe/mechanism (see Section 10.4).

f. Determine if other reporting is required (see Section 10.5).

NOTE: All AEs reported via expedited mechanisms must also be reported via the routine data reporting mechanisms defined by the protocol (see Sections 10.6 and 18.0).

Each CTCAE term in the current version is a unique representation of a specific event used for medical documentation and scientific analysis and is a single MedDRA Lowest Level Term (LLT).

NOTE: A severe AE, as defined by the above grading scale, is NOT the same as serious AE which is defined in the table in Section 10.4.

10.2 Expected vs. Unexpected Events

Expected events - are those described within the Section 15.0 of the protocol, the study specific consent form, package insert (if applicable), and/or the investigator brochure, (if an investigator brochure is not required, otherwise described in the general investigational plan).

Unexpected adverse events or suspected adverse reactions are those not listed in Section 15.0 of the protocol, the study specific consent form, package insert (if applicable), or in the investigator brochure (or are not listed at the specificity or severity that has been observed); if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan.

Unexpected also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs but have not been observed with the drug under investigation.

10.3 Assessment of Attribution

When assessing whether an adverse event is related to a medical treatment or procedure, the following attribution categories are utilized:

Definite - The adverse event is clearly related to the agent(s).
Probable - The adverse event is likely related to the agent(s).
Possible - The adverse event may be related to the agent(s).
Unlikely - The adverse event is doubtfully related to the agent(s).
Unrelated - The adverse event is clearly NOT related to the agent(s).

Events determined to be possibly, probably or definitely attributed to a medical treatment suggest there is evidence to indicate a causal relationship between the drug/device and the adverse event.

10.31 **AEs Experienced Utilizing Investigational Agents and Commercial Agents on the <u>SAME</u> Arm (Combination)**

When commercial agents are used on the same treatment arm as an investigational agent, the **entire combination (arm) is then considered an investigational intervention for reporting**. These AEs should be assessed as specified in the appropriate **IND/IDE** reporting guidelines in Section 10.4

10.32 The following hospitalizations are not considered to be SAEs because there is no "adverse event" (i.e., there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care

- Planned hospitalizations required by the protocol or to administer protocol directed treatment (i.e. 131I therapy)
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed post study drug administration)
- Hospitalization for administration of study drug or insertion of access for administration of study drug
- Hospitalization for routine maintenance of a device (e.g., battery replacement) that was in place before study entry

10.33 Report any clinically important increase in the **rate** of a serious suspected adverse reaction (at your study) site over that which is listed in the protocol or investigator brochure as an expedited event.

10.34 Report an expected event that is greater in severity or specificity than expected as an expedited event

10.35 An investigational agent/intervention might exacerbate the expected AEs associated with a commercial agent. Therefore, if an expected AE (for the commercial agent) occurs with a higher degree of severity or specificity, expedited reporting is required. A list of known/expected AEs is reported in the investigator brochure, package insert or the literature, including AEs resulting from a drug overdose.

10.36 Death

10.361 Any death occurring within 30 days of the last dose, regardless of attribution to an agent/intervention under an IND/IDE requires expedited reporting within 24 hours.

10.362 Any death occurring greater than 30 days with an attribution of possible, probable, or definite to an agent/intervention under an IND/IDE requires expedited reporting within 24 hours.

10.363 Reportable categories of Death

- Death attributable to a CTCAE term.
- Death Neonatal: A disorder characterized by cessation of life during the first 28 days of life.
- Death NOS: A cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Sudden death NOS: A sudden (defined as instant or within one hour of the onset of symptoms) or an unobserved cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.

- Death due to progressive disease should be reported as Grade 5 "Disease Progression" under the (SOC) General Disorders and Administration Site Conditions. Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

10.37 Secondary Malignancy

A **secondary malignancy** is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

All secondary malignancies that occur following treatment with an agent under an IND/IDE to be reported. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (e.g., Acute Myeloctyic Leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

10.38 Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting.

10.39 Pregnancy

Prior to obtaining private information about a pregnant woman and her infant, the investigator must obtain consent from the pregnant woman and the newborn infant's parent or legal guardian before any data collection can occur. A consent form will need to be submitted to the IRB for these subjects if a pregnancy occurs. If informed consent is not obtained, no information may be collected.

In cases of fetal death, miscarriage or abortion the mother is the patient. In cases where the child/fetus experiences a serious adverse event other than fetal death, the child/fetus is the patient.

NOTE: When submitting ACCRU Adverse Event Report reports for "Pregnancy", "Pregnancy loss", or "Neonatal loss", the potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section. Include any available medical documentation.

10.4 Expedited Adverse Event Reporting Requirements

10.41 Expedited Reporting via the **ACCRU Adverse Event Expedited Report Form** for Adverse Events That Occur Within 30 Days[1] of the Last Dose of the Investigational Agent

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported to the sponsor within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs.	7 Calendar Days	24-Hour; 3 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs.	Not required	

Expedited AE reporting timelines are defined as:

- "24-Hour; 3 Calendar Days" - The AE must initially be reported within 24 hours of learning of the AE, followed by a complete expedited report within 3 calendar days of the initial 24-hour report.
- "7 Calendar Days" - A complete expedited report on the AE must be submitted within 7 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 3 calendar days for:

- All Grade 3, 4, and Grade 5 AEs

Expedited 7 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

Effective Date: May 5, 2011

10.411 Special Instructions

- In addition to the reporting requirements outlined in this protocol, sites are responsible for following site-specific reporting guidelines
- Submit the ACCRU Adverse Expedited Report Form to the ACCRU SAE Coordinator via email: [redacted] The ACCRU SAE Coordinator will forward to:

Agios:
The PI is responsible for sending expedited reports to Agios Medical Safety and Risk Management (MSRM) at [redacted] immediately but no later than 24 hours after regulatory submission.

The PI is responsible for emailing pregnancy and overdose reports to Agios Medical Safety and Risk Management (MSRM) at [redacted] within 10 calendar days of sponsor awareness.

Safety Reporting to Agios

A listing of all SAEs should be reported to Agios on a quarterly basis. Any adverse event requiring expedited reporting (serious, unexpected event suspected of being related to ivosidenib) should be cross-reported to Agios at the same time as submission to the authorities (within 24 hours of the site's awareness of the event).

Should the site become aware of a pregnancy or drug miss-dose/overdose, this should be reported to the Sponsor within 24 hours of becoming aware.

Reports should be submitted to: [redacted]

SAE Reporting to Incyte
Incyte: [redacted]

Incyte needs to be notified within 24 hours of learning of an event. Incyte also needs to be provided a completed SAE form via email. SAE reporting for each subject begins the day the informed consent is signed by the patient and within 30 days after subject has completed or discontinued from the study or has taken last dose of the study drug, or as described in the IST protocol.
SAEs, occurring using Incyte Study drug, are reported in accordance with the effective protocol. SAEs occurring with any another commercial drug are reported to manufacturer of that drug in accordance with regulations and protocol.
Initial Serious Adverse events (SAEs) and/or subsequent follow-up reports should be reported via email to: [redacted] SAE reports should be for a single subject. SAE forms will be e-mailed with a cover sheet and any additional attachments to the IST email address: [redacted]

Reporting of Pregnancy to Incyte

An "Initial Pregnancy Report" or equivalent must be completed in full and emailed to [redacted] within 24 hours of discovery of a pregnancy of a subject who has taken the Incyte product or the pregnancy of a partner for a subject who has taken the Incyte product. The "Follow-up Pregnancy Report Form" or equivalent must be completed and emailed to [redacted] within 30 days after delivery, so that Incyte is provided with information regarding the outcome of the pregnancy. If the pregnancy results in any events which meet the serious criteria (i.e., miscarriage or termination), the SAE reporting process needs to be followed and the timelines associated with an SAE should be followed.

- The ACCRU SAE Coordinator will forward to the ACCRU IND Coordinator [redacted] as appropriate. The ACCRU IND Coordinator will assist the sponsor-investigator in notifying the FDA if required.

  The Sponsor is responsible for sending expedited reports to Agios Medical Safety and Risk Management (MSRM) at [redacted] immediately but no later than 24 hours after regulatory submission.

  The Sponsor is responsible for emailing pregnancy <<and overdose reports>> to Agios Medical Safety and Risk Management (MSRM) at [redacted] within 10 calendar days of sponsor awareness.

10.5 Adverse Events of Special Interest (AESI)

AEs of Special Interest are defined by Agios and Incyte as a potential safety problem identified as a result of ongoing safety monitoring of their products. As such, surveillance for the AESIs noted in Section 10.51 MUST be undertaken at each treatment evaluation. Development of one of these AESIs (≥ Grade 1 unless otherwise noted) MUST be reported in terms of CTCAE v 5.0 grade and attribution in the manner and timeframe outlined in Section 10.6.

10.51 AEs of Special Interest

Ivosidenib:

System Organ Class (SOC)	Adverse event	Grade Severity to report
QT interval prolongation Investigations	Electrocardiogram QT corrected interval prolonged	Grade 2 or higher

Pemigatinib:

System Organ Class (SOC)	Adverse event	Grade Severity to report
Eye Disorders	Blurred vision, optic nerve disorder, retinal detachment	Grade 2 or higher
Eye Disorder-other	retinal pigment epithelium detachment, serous retinal detachment	Grade 2 or higher

QT prolongation
Prolongation of heart-rate corrected QT (QTc) interval has been observed in monkeys at relatively high doses of ivosidenib as well as in patients while receiving ivosidenib. Please refer to the ivosidenib Investigator's Brochure for detailed information.

Subjects may be at increased risk for the development of QT prolongation when treated with ivosidenib in combination with fluoroquinolones, azole antifungal agents, or serotonin (5-HT3) antagonists. Investigators need to be vigilant regarding concomitant medications associated with QT prolongation, and if no other therapeutic options are available, monitor subjects receiving ivosidenib with the combination of these drugs, and evaluate ECG and electrolytes (including potassium, magnesium, and calcium) particularly in subjects presenting with nausea, vomiting, or diarrhea.

Subjects who experience prolongation of the heart-rate corrected QT interval, Fridericia's correction (QTcF) to > 480 msec (Grade ≥ 2) while treated with ivosidenib, should be promptly evaluated for causality of the QTc prolongation and managed according to the following guidelines:

- Levels of electrolytes (potassium, calcium, and magnesium) should be checked and supplementation given to correct any values outside the normal range.
- Concomitant therapies should be reviewed and adjusted as appropriate for medication with known QT prolonging effects.
- If no other cause is identified and the investigator believes it is appropriate, particularly if QTc remains elevated (after above measures have been implemented, or as determined by the investigator), investigational product may be interrupted, and an ECG should be rechecked in approximately 1 week after the QTc prolongation was first observed, or more frequently as clinically indicated.
- If QTc has recovered or improved and the investigator believes it is safe to do so, re-challenge with ivosidenib should be considered if held. ECGs should be conducted at least weekly (e.g., at every scheduled visit) for 2 weeks following QTc reduction ≤ 480 msec.

- **If Grade 2** the dose of ivosidenib may be reduced without interruption of dosing. The ivosidenib dose may be re-escalated to the prior dose in ≥ 14 days after QT prolongation has decreased to ≤ Grade 1.
- **If Grade 3** when QTc prolongation is first observed hospitalization for continuous cardiac monitoring and evaluation by a cardiologist should both be considered. Dosing with ivosidenib will be interrupted. If QTc returns to within 30 msec of baseline or < 450 msec within 14 days, treatment may be resumed at a reduced dose. The ivosidenib dose cannot be re-escalated following dose reduction for Grade 3 QTcF prolongation unless the prolongation was associated with an electrolyte abnormality or concomitant medication.
- **If Grade 4** subjects should be admitted to hospital when QTc prolongation is first observed for continuous cardiac monitoring and be discharged only after review by a cardiologist. Dosing with ivosidenib should be permanently discontinued.

10.6 Other Required Reporting

10.61 Reporting Timelines and Mechanisms

Adverse Event	**Form(s) Needed**	**Site timeline to report to ACCRU**	**ACCRU timeline to report to Agios and Incyte**
Non-Serious Adverse Event	Adverse Events form (see CRF packet)	At each evaluation	Quarterly
Adverse Events of Special Interest (Section 10.51)*	Adverse Events of Special Interest Form**	At each occurrence	Within 1 business day of receipt
	Adverse Events form (if criteria in 10.5 is met)		Quarterly
Pregnancy (Section 10.39)	ACCRU Adverse Event Expedited Report Form**	At each occurrence	Within 1 business day of receipt
	Adverse Events form (if criteria in 10.5 is met)		Quarterly
Serious Adverse Events (Section 10.4)*	ACCRU Adverse Event Expedited Report Form**	At each occurrence	Within 1 business day of receipt
	Adverse Events form (see CRF packet)		Quarterly

* If an adverse event meets the criteria for both an AE of Special Interest and a Serious Adverse Event, please report only as a Serious Adverse Event.

** The Adverse Events of Special Interest Form and ACCRU Adverse Event Expedited Report Form are available on the ACCRU web site [redacted]

10.62 Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSOS) in general, include any incident, experience, or outcome that meets **all** of the following criteria:

1. Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied

2. Related or possibly related to participation in the research (in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and

3. Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Some unanticipated problems involve social or economic harm instead of the physical or psychological harm associated with adverse events. In other cases, unanticipated problems place subjects or others at increased *risk* of harm, but no harm occurs.

NOTE: If there is no language in the protocol indicating that pregnancy is not considered an adverse experience for this trial, and if the consent form does not indicate that subjects should not get pregnant/impregnate others, then any pregnancy in a subject/patient or a male patient's partner (spontaneously reported) which occurs during the study or within 120 days of completing the study should be reported as a UPIRTSO.

If the event meets the criteria for an UPIRTSO, submit to your IRB as required by your institutional policies.

10.63 Baseline and Adverse Event Evaluations

The following pre-treatment symptoms/conditions are to be graded at baseline and adverse events are to be graded at each evaluation using CTCAE v5.0 grading. If CTCAE v5.0 grading is not used, note the grading scale used in the table below

Both Arms

System Organ Class (SOC)	Adverse event/ Symptoms	Baseline	Each evaluation	Grading scale (if not CTCAE)
Blood and lymphatic system disorders	White blood cell decreased	X	X	
Blood and lymphatic system disorders	Platelet count decreased	X	X	
Blood and lymphatic system disorders	Anemia	X	X	
Blood and lymphatic system disorders	Neutropenia	X	X	
Investigations	AST Increased	X	X	
Investigations	ALT Increased	X	X	
Investigations	AlkPhos Increased	X	X	
Gastrointestinal disorders	Diarrhea		X	
	Number of stools per day	X		
Gastrointestinal disorders	Nausea	X	X	
Gastrointestinal disorders	Vomiting	X	X	
Metabolism and nutrition disorders	Anorexia	X	X	
General disorders and administration site conditions	Fatigue	X	X	

For Arm B only (INCB54828)

System Organ Class (SOC)	Adverse event/ Symptoms	Baseline	Each evaluation	Grading scale (if not CTCAE)
metabolism and nutrition disorders	Hyperphosphatemia[1]	X	X	
gastrointestinal disorders	mucositis oral[1]	X	X	
gastrointestinal disorders	Dry Mouth[1]	X	X	
Skin and subcutaneous tissue disorders	Alopecia[1]	X	X	
	Stomatitis[1]	X	X	
	Decreased appetite[1]	X	X	
Nervous system disorders	Dysgeusia[1]	X	X	
gastrointestinal disorders	Abdominal Pain[1]	X	X	
Investigations	Aspartate aminotransferase increased[1]	X	X	
Metabolism and nutrition disorders	Hypophosphatasemia[1]	X	X	
Metabolism and nutrition disorders	Dehydration[1]	X	X	
Eye disorders	Dry Eye[1]	X	X	
Musculoskeletal And connective tissue disorders	Pain in extremity[1]	X	X	
Investigations	Alanine aminotransferase increased[1]	X	X	
Respiratory, thoracic and mediastinal disorders	Cough[1]	X	X	
Eye disorders	Blurred vision[1]	X	X	
	Weight decreased[1]			

Investigations	alkaline phosphatase increased[1]	X	X	
Metabolism and nutrition disorders	Hyperglycemia[1]	X	X	
Musculoskeletal and connective tissue disorders	Back pain[1]	X	X	
	Onycholysis[1]	X	X	
Infections and Infestations	Paronychia[1]	X	X	
Musculoskeletal and connective tissue disorders	Arthralgia[1]	X	X	
Metabolism and nutrition disorders	Hyponatremia[1]	X	X	
Skin and subcutaneous tissue disorders	Nail discoloration[1]	X	X	

1. For patients in Arm A, check "Adverse event not evaluated".

10.64 Case Report Forms - Academic and Community Cancer Research United (ACCRU)
Submit the following AEs not specified in Section 10.4 (paper or electronic, as applicable)

10.641 Grade 1 and 2 AEs deemed *possibly, probably, or definitely* related to the study treatment or procedure.

10.642 Grade 3 and 4 AEs regardless of attribution to the study treatment or procedure

10.643 Grade 5 AEs (Deaths)

10.6431 Any death within 30 days of the patient's last study treatment or procedure regardless of attribution to the study treatment or procedure requires the submission of an Expedited Adverse Event report (see Section 10.4).

10.6432 Any death more than 30 days after the patient's last study treatment or procedure that is felt to be at least possibly treatment related must also be submitted with an Expedited Adverse Event report (see Section 10.4).

10.65 Late Occurring Adverse Events

Refer to the instructions in the Forms Packet (or electronic data entry screens, as applicable) regarding the submission of late occurring AEs following completion of the Active Monitoring Phase (i.e., compliance with Test Schedule in Section 4.0).

11.0 Treatment Evaluation Using RECIST Guideline

NOTE: This study uses protocol RECIST v1.1 template dated 2/16/2011. See the footnote for the table regarding measureable disease in Section 11.44, as it pertains to data collection and analysis.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (version 1.1) (Eisenhauer, 2009). Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the short axis measurements in the case of lymph nodes are used in the RECIST guideline.

11.1 Schedule of Evaluations: For the purposes of this study, patients should be reevaluated every 4 weeks

11.2 Definitions of Measurable and Non-Measurable Disease

11.21 Measurable Disease

11.211 A non-nodal lesion is considered measurable if its longest diameter can be accurately measured as ≥2.0 cm with chest x-ray, or as ≥1.0 cm with CT scan, CT component of a PET/CT, or MRI.

11.212 A superficial non-nodal lesion is measurable if its longest diameter is ≥1.0 cm in diameter as assessed using calipers (e.g. skin nodules) or imaging. In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

11.213 A malignant lymph node is considered measurable if its short axis is ≥1.5 cm when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm).

NOTE: Tumor lesions in a previously irradiated area are considered measurable disease under the following conditions:

- Evidence of progression exists following completion of radiation therapy

11.22 Non-Measurable Disease

11.221 All other lesions (or sites of disease) are considered non-measurable disease, including pathological nodes (those with a short axis ≥1.0 to <1.5 cm). Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable as well.

NOTE: ‘Cystic lesions’ thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target

lesions. In addition, lymph nodes that have a short axis <1.0 cm are considered non- pathological (i.e., normal) and should not be recorded or followed.

11.3 Guidelines for Evaluation of Measurable Disease

11.31 Measurement Methods:

- All measurements should be recorded in metric notation (i.e., decimal fractions of centimeters) using a ruler or calipers.

- The same method of assessment and the same technique must be used to characterize each identified and reported lesion at baseline and during follow-up. For patients having only lesions measuring ≥1 cm to <2 cm CT imaging must be used for both pre- and post-treatment tumor assessments.

- Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used at the same evaluation to assess the antitumor effect of a treatment.

11.32 Acceptable Modalities for Measurable Disease:

- Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.

- As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. The lesions should be measured on the same pulse sequence. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

- PET-CT: If the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time.

- FDG-PET: FDG-PET scanning is allowed to complement CT scanning in assessment of progressive disease [PD] and particularly possible 'new' disease. A ‘positive’ FDG-PET scanned lesion is defined as one which is FDG avid with an update greater than twice that of the surrounding tissue on the attenuation corrected image; otherwise, an FDG-PET scanned lesion is considered ‘negative.’ New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

b. No FDG-PET at baseline and a positive FDG-PET at follow-up:

i. If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.

ii. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT at the same evaluation, additional follow-up CT scans (i.e., additional follow-up scans at least 4 weeks later) are needed to determine if there is truly progression occurring at that site. In this situation, the date of PD will be the date of the initial abnormal PDG-PET scan.

iii. If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, it is not classified as PD.

11.33 Measurement at Follow-up Evaluation:

- In the case of stable disease (SD), follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 8 weeks (see Section 11.44).

- The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

- Cytologic and histologic techniques can be used to differentiate between PR and CR in rare cases (e.g., residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain.)

11.4 Measurement of Effect

11.41 Target Lesions & Target Lymph Nodes

- Measurable lesions (as defined in Section 11.21), up to a maximum of 5 lesions, representative of all involved organs, should be identified as "Target Lesions" and recorded and measured at baseline. <u>These lesions can be non-nodal or nodal (as defined in 11.21)</u>, where no more than 2 lesions are from the same organ and no more than 2 malignant nodal lesions are selected.

  NOTE: If fewer than 5 target lesions and target lymph nodes are identified, there is no reason to perform additional studies beyond those specified in the protocol to discover new lesions.

- Target lesions and target lymph nodes should be selected on the basis of their size, be representative of all involved sites of disease, and in addition should

be those that lend themselves to reproducible, repeated measurements. It may be the case that, on occasion, the largest lesion (or malignant lymph node) does not lend itself to reproducible measurements, in which circumstance the next largest lesion (or malignant lymph node) which can be measured reproducibly should be selected.

- Baseline Sum of Dimensions (BSD): A sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the baseline sum of dimensions (BSD). The BSD will be used as reference to further characterize any objective tumor response in the measurable dimension of the disease.

- Post-Baseline Sum of the Dimensions (PBSD): A sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the post-baseline sum of dimensions (PBSD). If the radiologist is able to provide an actual measure for the target lesion (or target lymph node), that should be recorded, even if it is below 0.5 cm. If the target lesion (or target lymph node) is believed to be present and is faintly seen but too small to measure, a default value of 0.5 cm should be assigned. If it is the opinion of the radiologist that the target lesion or target lymph node has likely disappeared, the measurement should be recorded as 0 cm.

- The minimum sum of the dimensions (MSD) is the minimum of the BSD and the PBSD.

11.42 Non-Target Lésions & Non-Target Lymph Nodes

Non-measurable sites of disease (Section 11.22) are classified as non- target lesions or non-target lymph nodes and should also be recorded at baseline. These lesions and lymph nodes should be followed in accord with 11.433.

11.43 Response Criteria

11.431 All target lesions and target lymph nodes followed by CT/MRI/PET-CT must be measured on re-evaluation at evaluation times specified in Section 11.1. Specifically, a change in objective status to either a PR or CR cannot be done without re-measuring target lesions and target lymph nodes.

NOTE: Non-target lesions and non-target lymph nodes should be evaluated at each assessment, especially in the case of first response or confirmation of response. In selected circumstances, certain non-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when complete response is identified in target disease or when progression in bone is suspected.

11.432 Evaluation of Target Lesions

- Complete Response (CR): All of the following must be true:

  a. Disappearance of all target lesions.
  b. Each target lymph node must have reduction in short axis to <1.0 cm.

- Partial Response (PR): At least a 30% decrease in PBSD (sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes at current evaluation) taking as reference the BSD (*see* Section 11.41).

- Progression (PD): At least one of the following must be true:

  a. At least one new malignant lesion, which also includes any lymph node that was normal at baseline (<1.0 cm short axis) and increased to ≥1.0 cm short axis during follow-up.

  b. At least a 20% increase in PBSD (sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes at current evaluation) taking as reference the MSD (Section 11.41). In addition, the PBSD must also demonstrate an absolute increase of at least 0.5 cm from the MSD.

  c. See Section 11.32 for details in regards to the requirements for PD via FDG-PET imaging.

- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR, nor sufficient increase to qualify for PD taking as reference the MSD.

11.433 Evaluation of Non-Target Lesions & Non-target Lymph Nodes

- Complete Response (CR): All of the following must be true:

  a. Disappearance of all non-target lesions.
  b. Each non-target lymph node must have a reduction in short axis to <1.0 cm.

- Non-CR/Non-PD: Persistence of one or more non-target lesions or non-target lymph nodes.

- Progression (PD): At least one of the following must be true:

  a. At least one new malignant lesion, which also includes any lymph node that was normal at baseline (<1.0 cm short axis) and increased to ≥1.0 cm short axis during follow-up.

b. Unequivocal progression of existing non-target lesions and non-target lymph nodes. (NOTE: Unequivocal progression should not normally trump target lesion and target lymph node status. It must be representative of overall disease status change.)

c. See Section 11.32 for details in regards to the requirements for PD via FDG-PET imaging.

11.44 Overall Objective Status

The overall objective status for an evaluation is determined by combining the patient's status on target lesions, target lymph nodes, non-target lesions, non-target lymph nodes, and new disease as defined in the following tables:

Target Lesions & Target Lymph Nodes	**Non-Target Lesions & Non-Target Lymph Nodes**	**New Sites of Disease**	**Overall Objective Status**
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
PR	CR Non-CR/Non-PD	No	PR
CR/PR	Not All Evaluated*	No	PR**
SD	CR Non-CR/Non-PD Not All Evaluated*	No	SD
Not all Evaluated	CR Non-CR/Non-PD Not All Evaluated*	No	Not Evaluated (NE)
PD	Unequivocal PD CR Non-CR/Non-PD Not All Evaluated*	Yes or No	PD
CR/PR/SD/PD/ Not all Evaluated	Unequivocal PD	Yes or No	PD
CR/PR/SD/PD/ Not all Evaluated	CR Non-CR/Non-PD Not All Evaluated*	Yes	PD

*See Section 11.431

** NOTE: This study uses the protocol RECIST v1.1 template dated 2/16/2011. For data collection and analysis purposes the objective status changed from SD to PR in the ACCRU protocol RECIST v1.1 template as of 2/16/2011 and to match RECIST v1.1 requirements.

11.45 Symptomatic Deterioration: Patients with global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time, and not either related to study treatment or other medical conditions, should be reported as PD due to "symptomatic deterioration." Every effort should be made to document the objective progression even after

discontinuation of treatment due to symptomatic deterioration. A patient is classified as having PD due to "symptomatic deterioration" if any of the following occur that are not either related to study treatment or other medical conditions:

- Worsening of tumor-related symptoms.
- Decline in performance status of >1 level on ECOG scale.

12.0 Descriptive Factors

12.1 Cohort: Safety Run-In vs. Expansion

13.0 Treatment/Follow–up Decision at Evaluation of Patient

13.1 Patients who are CR, PR, or SD will continue treatment per protocol until disease progression. Subsequent treatment is at the discretion of their attending physician.

13.2 Patients who develop PD at any time should go to event monitoring. These patients should be treated with alternative therapy if their clinical status is good enough to allow further therapy at treating physician's discretion.

13.3 Patients who stop gemcitabine and/or cisplatin for reasons other than progression may continue on study drug until progression.

13.4 Event Monitoring is not part of the Active Monitoring phase of a study and is defined as the time period when the participant is no longer following the protocol test schedule. During Event Monitoring, the data collection schedule is dictated by the protocol but the visit schedule is determined by clinical practice at each participating site. During the Event Monitoring Phase of the study, the participant is being monitored for key study events such as progression, new primaries, and death. Event monitoring should occur every 6 months (± 30 days) until death or a maximum of 36 months from Registration. Phone,, or virtual visits are permitted during Event Monitoring.

13.5 Follow-up Decisions during Active Treatment

Status During Treatment	Go To…
Complete response (CR), partial response (PR), stable disease (SD)	Continue protocol treatment
Off treatment for disease progression, alternative therapy, or withdrawal/refusal of treatment	Survival follow up/event monitoring Event Monitoring every 6 months (± 30 days) until death or up to 60 months from Registration per Section 18.0
Off treatment for any reason **other than** progression, alternative therapy, or withdrawal/ refusal of treatment	Survival follow up / Event monitoring 6 months (± 30 days) until death or up to 60 months from Registration per Section 18.0
Death or withdrawal/refusal of follow-up	No further follow-up

13.6 A patient is deemed *ineligible* if, after registration, it is determined that at the time of registration the patient did not satisfy each and every eligibility criteria for study entry. The patient may continue treatment off-protocol at the discretion of the physician as long as there are no safety concerns and the patient was properly registered. The patient will go directly to the event-monitoring phase of the study (or off study, if applicable).

- If the patient received treatment, all data up until the point of confirmation of ineligibility must be submitted. Event monitoring will be required per Section 18.0 of the protocol.

13.7 A patient is deemed a *major violation* if protocol requirements regarding treatment in Cycle 1 of the initial therapy are severely violated that evaluability for primary end point is questionable. All data up until the point of confirmation of a major violation must be submitted. The patient will go directly to the event-monitoring phase of the study. The patient may continue treatment off-protocol at the discretion of the physician as long as there are no safety concerns, and the patient was properly registered. Event monitoring will be required per Section 18.0 of the protocol.

13.8 A patient is deemed a *cancel* if he/she is removed from the study for any reason before any study treatment is given. On-study material and the Off Treatment Form must be submitted. No further data submission is necessary.

14.0 Body Fluid Biospecimens

14. 1 Blood/Blood Products Handling

14.11 **Kits will not be provided for this study.**

NOTE: Below are acceptable use cryovials for the repository. The site is responsible for ordering the cryovials.

Storage Conditions: -80°C & LN_2			
Manufacturer (Cat#):	**Capacity:**	**Expected Sample Type(s):**	**Manufacturer's specifications:**
Corning (430659)	2 mL	Calls, Plasma, Serum	2 mL Cryo (External Thread)
Corning (430488)	2 mL	Cells, Plasma, Serum, Tissue	2 mL Cryo (Internal Thread)
Sarstedt (72.694.107)	2 mL	DNA, Plasma, Serum, Whole Blood, WBC	2 mL Micro Tube
Thermo Scientific (5000-0020)	2 mL	Cells, Plasma, Serum, Whole blood	Cryogenic tubes
Fisher Scientific (02-707-361)	2 mL	CSF, Plasma, Serum, WBC, Whole blood	2 mL Micro Tube

14.12 All samples must be collected **Monday-Friday**.

14.13 Institution can use their own label. Specimen label must include the following unique identifiers:

- Study #
- Analyte Name (e.g., ivosidenib, 2-HG)
- Subject ID,
- Group, if applicable,
- Nominal timepoint (cycle, day),
- Nominal time, if serial collections occurred within one visit

Generic label

- If the generic label is acceptable and your institution requires no changes, please complete the "Investigator Sponsored Trial Label Approval Form" located on the ACCRU Website and return to Agios. Once accepted, immediate supply availability is subject to mutual agreement of timelines, quantities, and availability of study protocol.
- If the generic label is not acceptable, please complete the "Investigator Sponsored Trial Label Approval Form" located on the ACCRU website and return to Agios in addition to the Sponsor's specific label requirements. The Sponsor may provide their specific label requirements in three ways:
- Specify within the "Investigator Sponsored Trial Label Approval Form", Section B.
- Make adjustments within the attached word version with track changes enabled.
- Or if the sponsor has their own required label text document, Agios can review this on a case by case as well.

NOTE: It can take up to 8 weeks for a new label to be made if the generic label is not acceptable to your institution.

NOTE: A sample inventory form / requisition form must accompany the samples and shall also include the nominal and actual date and time of each blood sample drawn as well as contact information, should the lab have questions.

14.14 Collect and process all blood/blood products according to the table below.

14.141 Summary Table of Research Blood/Blood Products to Be Collected for This Protocol

Applicable Arms	Indicate if specimen is mandatory or optional	Collection tube description and/or additive (color of tube top)	Volume to collect per tube (number of tubes to be collected)	Blood product being processed and submitted by participating site	≤21 days prior to registration and Cycle 4 Day 1 and every 9 weeks (+/- 2 days)	Additional processing required at site after blood draw?	Storage /shipping conditions[1]
ivosidenib and 2-HG Analysis	Mandatory	K2 EDTA (purple top)	6 mL (1)	plasma	X	Yes	Freeze (-80 C)dry ice

1. After all samples have been processed, ship all specimens per processing and shipping instructions.

Processing Instructions:

1) Blood will be collected in each K2EDTA tube by direct venipuncture. Gently invert the tube approximately 8-10 times.
2) The date and time of each blood sample drawn will be recorded on the sample requisition.
3) The blood is required be processed in a timely manner. ***The time from collection to centrifuge should not exceed 60 minutes.***
4) **Blood samples will be cooled by an ice bath or equivalent until processed** and centrifuged at approximately 1500g at 2-8°C for approximately 15 minutes5) If plasma cannot be separated immediately into cryovials, they can be placed into an ice bath or equivalent.
5) Using a pipette, the plasma will be evenly divided into two 2 mL labeled cryovials for each analyte (one primary and one backup each for PD sample(s)) and maintained in the ice bath. Preferred volume is approximately 0.5 mL of plasma in each aliquot tube. If there is a short blood draw, please fill primary cryovials first.
6) **Plasma samples will then be stored and frozen at -80 °C ± 10 °C until shipment to BAP labs.**
7) The time between sample collection and placement in freezer ***should not exceed 120 minutes***.

14.2 Shipping

14.21 Verify ALL sections of the Blood Specimen Submission Form (see Forms Packet), Requisition Form (provided in kit), and specimen collection labels are completed and filled in correctly.

All sample shipments should be preceded by an email, phone call or fax prior to their receipt. All HIV positive or other known infectious sample shipments must be preceded by a phone call or facsimile prior to their receipt.

NOTE: Detailed sample inventory information must accompany the samples.

Lack of paperwork or illegible information will delay sample login and project initiation. Samples that are unclearly or incompletely labeled may not be able to be analyzed. Submission of sample inventory information in electronic form is encouraged.

14.22 Specimens must be shipped the Monday through Wednesday ONLY.

14.23 Ship Plasma aliquots tubes via Priority Overnight service frozen on dry ice.

14.24 Ship specimens via Priority Overnight service, **Monday-Wednesday** to **PPD** Receiving according to kit instructions. **Do not send samples on weekends or just prior to federal holidays.**

Ship samples to: PPD

14.3 Study Methodology and Storage Information

14.31 Blood/blood product samples will be collected for the following research

14.311 2-HG will be measured from plasma samples obtained in K2EDTA tubes. Analysis of 2-HG will be performed using a qualified LC-MS/MS (liquid chromatography tandem mass spectrometry) method. ivosidenib will be measured from plasma samples obtained in K2EDTA tubes. Analysis of ivosidenib will be performed using a validated LC-MS/MS method.

14.4 Return of Genetic Testing Research Results

No genetic specimens will be collected from non-slid tissue (body fluid) biospecimens for this study. If future genetic testing is being requested for stored specimens, patient reconsent is required.

15.0 Drug Information

IND number 144189
Investigator brochures: Investigator brochures for both agents are available on the ACCRU web site under study ACCRU-ICRN-1701.

15.1 **Ivosidenib (AG-120):**

15.11 **Background:** Ivosidenib (AG-120; also formerly known as AGI-16678) is a potent, selective, orally active small molecule inhibitor of mutated isocitrate dehydrogenase 1 (IDH1). Isocitrate dehydrogenase is a critical enzyme in the citric acid cycle catalyzing the oxidative decarboxylation of isocitrate to produce carbon dioxide (CO2) and alpha-ketoglutarate (α-KG).

15.12 **Formulation**: Ivosidenib is supplied as 50 mg, 200 mg, and 250 mg strength uncoated tablets, and as 250 mg strength film-coated (blue) tablets for oral administration. Ivosidenib 50 mg, 200 mg, and 250 mg tablets contain the inactive ingredients hypromellose acetate succinate, microcrystalline cellulose, croscarmellose sodium, sodium lauryl sulfate, colloidal silicon dioxide, and magnesium stearate. Ivosidenib 250 mg film-coated tablets also include the inactive ingredient Opadry® II Blue.

15.13 **Preparation and storage**: The recommended storage conditions and expiry (where required) are stated on the product label.

15.14 **Administration:** Subjects may take ivosidenib tablets with or without food. To minimize the effects of a high-fat meal on ivosidenib exposure, subjects should avoid consuming a high-fat meal when ivosidenib is administered with food. All subjects will also be advised to avoid grapefruit and grapefruit products.

15.15 **Pharmacokinetic information**:
Absorption: Ivosidenib was rapidly absorbed following both single and multiple dosing (median T_{max} from 1.92 to 4.0 hours on C2D1 of dose escalation) across the dose range studied. After reaching a peak, mean concentrations of ivosidenib declined in a bi-exponential manner, with a mean t½ of 71.8 to 138 hours after single dosing in Study AG120-C-001.
Metabolism: Predominantly metabolized by CYP3A4. Following administration with itraconazole, ivosidenib exposure was increased ~2.6-fold.
Excretion: Fecal excretion appeared to be the predominant route of elimination of the administered radioactive dose with an observed mean recovery of total radioactivity in urine and feces of 16.9% and 77.4%, respectively, over 15 days post dose in Study AG120-C-003.

15.16 **Potential Drug Interactions**:
In vitro studies showed that ivosidenib is predominantly metabolized by CYP3A4 and therefore, coadministration with inhibitors or inducers of CYP3A4 has the potential to affect ivosidenib exposure. Co-administration of 250 mg ivosidenib with a strong CYP3A4 inhibitor (itraconazole) increased single-dose AUC of ivosidenib by 169% with no change in C_{max}. Based on physiologically-based pharmacokinetic (PBPK) simulations, coadministration with ivosidenib and a strong CYP3A4 inhibitor (itraconazole) or moderate CYP3A4 inhibitor (fluconazole) is predicted to increase ivosidenib steady-state C_{max} by up to 52% and AUC by up to 90%. Increased ivosidenib plasma concentrations may increase the risk of QTc interval prolongation. Consider alternative therapies that are not strong or moderate CYP3A4 inhibitors during treatment with ivosidenib. If concomitant use of strong or moderate CYP3A4 inhibitors (e.g., strong inhibitors such as: posaconazole, voriconazole, itraconazole, erythromycin, clarithromycin, and moderate inhibitors such as: fluconazole, erythromycin, isavuconazole, diltiazem, and grapefruit juice) is unavoidable, monitor subjects for increased risk of QTc interval prolongation. Based on a PBPK simulation, coadministration of ivosidenib with a strong CYP3A4 inducer (rifampin) is predicted to decrease ivosidenib steady-state AUC by 33% and C_{max} by 19%. Avoid coadministration of strong CYP3A4 inducers with ivosidenib.

Ivosidenib is an inducer of CYP3A4 and may also induce CYP2B6, CYP2C8, and CYP2C9. Coadministration of ivosidenib with narrow therapeutic index drugs that are extensively metabolized by CYP3A4 (e.g., cyclosporine, fentanyl, everolimus, tacrolimus, sirolimus) or
CYP2C9 (e.g., phenytoin, warfarin) may result in decreased concentrations of these drugs. Investigators should consider alternative therapies that are not sensitive substrates of CYP3A4 or CYP2C9 during treatment with ivosidenib. Subjects should be monitored for loss of therapeutic effect of these medications if coadministration with ivosidenib cannot be avoided. International normalized ratio (INR) levels should be monitored more frequently in subjects receiving warfarin (a CYP2C9 substrate) during initiation or discontinuation of ivosidenib. Coadministration of ivosidenib may decrease the concentrations of hormonal contraceptives.

15.17 **Known potential toxicities**:

Adverse Events Occurring in >10% of Subjects Overall in Study AG120-C-001:

Diarrhea, fatigue, nausea, leukocytosis, febrile neutropenia, dyspnea, anemia, oedema peripheral, QT prolongation, pyrexia, cough, decreased appetite, arthralgia, constipation, hypokalemia, vomiting, dizziness, back pain, epistaxis, thrombocytopenia, pneumonia, headache, hypomagnesemia, rash, asthenia, abdominal pain, hypotension, IDH differentiation syndrome, hyperuricemia, pain in extremity, insomnia, stomatitis, chest pain, pleural effusion and pruritis.

Adverse Events Occurring in >10% of Subjects Overall in Study AG120-C-002:

Fatigue, nausea, diarrhea, vomiting, headache, decreased appetite, abdominal pain, oedema peripheral, anemia, constipation and back pain.

Adverse Events Occurring in >10% of Subjects Overall in Study AG120-881-C-001:

Diarrhea, hypocalcemia, anemia, hyperglycemia, pruritus, constipation, dysarthria, dysphagia, headache, hypokalemia, nausea, rash, seizure, tremor and WBC count decreased.

Adverse Events Occurring in >10% of Subjects in Study AG120-C-005 After Crossover to ivosidenib:

Diarrhea, nausea, anemia, ascites, fatigue, constipation, cough, decreased appetite and oedema peripheral.

15.18 **Drug procurement:**

Agios will supply ivosidenib to McKesson Specialty Pharmacy's Clinical Research Services. Each participating ACCRU treating location will order the drug from McKesson Specialty Pharmacy's Clinical Research Services. Fax or email the Drug Order Request Form (found on the ACCRU web site) to:

[redacted]

Each participating ACCRU treating location will be responsible for monitoring the supply of ivosidenib and will use the Drug Order Request Form to order additional supplies as needed.

Outdated or remaining drug is to be destroyed on-site as per procedures in place at each institution.

15.19 **Nursing Guidelines**

15.191 Ivosidenib has many drug to drug interactions. Assess patient's concurrent medications, including OTC medications and supplements

15.192 Gastrointestinal toxicity is the most commonly seen class of side effects with ivosidenib. Treat symptomatically and assess for effectiveness.

15.193 Patients with hematologic malignancies were more likely to experience grade 3 or higher toxicity versus those with solid tumors.

15.194 Hematologic toxicities were common. Monitor CBC w/diff. Instruct patient to report any unusual bruising or bleeding and/or signs/symptoms of infection to the study team.

15.195 Patients may experience QT prolongation. Monitor ECG per protocol recommendations. Use caution with other agents that may prolong the QTc interval.

15.196 Rarely patients may experience Guillain-Barre Syndrome or leukoencephalopathy. Instruct patients to report any new neurologic symptoms to the study team immediately.

15.197 Patients can experience dehydration with electrolyte abnormalities. Monitor chemistry panel as ordered per protocol.

15.2 **Pemigatinib (INCB054828):**

15.21 **Background:** Pemigatinib is an inhibitor of the FGFR family of receptor tyrosine kinases that is proposed for the treatment of malignant diseases or other diseases related to FGFR dysregulation. Aberrant signaling through FGFR resulting from gene amplification or mutation, chromosomal translocation, and ligand-dependent activation of the receptors has been demonstrated in multiple types of human cancers.

15.22 **Formulation**: Pemigatinib drug substance is a white to off-white to light brown to yellow solid. The pemigatinib drug product is formulated as immediate release tablets in strengths of 0.5, 2, 4.5, 9 and 13.5 mg. The tablets of all strengths contain the active drug substance along with the excipients microcrystalline cellulose, sodium starch glycolate, and magnesium stearate.

15.23 **Preparation and storage**: Pemigatinib should be stored as detailed on the investigational product labeling.

15.24 **Administration:** The effect of food on pemigatinib exposure is modest and is not expected to be clinically significant; as a result, pemigatinib may be administered orally either with or without food.

15.25 **Pharmacokinetic information**:
Time to peak, serum: 0.5 - 6 hours
Clearance: 11.2 L/hour
Distribution: Volume of distribution – 151 L
Metabolism: In vitro studies suggested that pemigatinib is predominantly metabolized by CYP3A4.
Pemigatinib is not a potent inhibitor or inducer of the major CYPs evaluated.
Half-life elimination (mean): 20.2 hours

15.26 **Potential Drug Interactions**:
The data from Study INCB 54828-104 demonstrated a clinically significant effect on pemigatinib exposure when a potent CYP3A4 inhibitor (itraconazole) or inducer (rifampin) is coadministered, and physiologically based pharmacokinetic modeling showed that coadministration of a moderate CYP3A4 inducer decreased the pemigatinib AUC by at least 50%.%. Thus, concomitant use of moderate CYP3A4 inducers and potent CYP3A4 inducers or inhibitors are prohibited. The use of moderate CYP3A4 inhibitors are not prohibited but should involve careful monitoring. In addition, the data from Study INCB 54828-106 demonstrated a modest effect on the overall exposure of pemigatinib following coadministration of the gastric pH–modifying agents esomeprazole and ranitidine. Therefore, pemigatinib can be dosed without respect to concomitant use of PPIs or H2 antagonists.
In vitro transport studies indicated that pemigatinib is a substrate of both P-gp and BCRP, but it is unlikely that efflux by these 2 transporters plays an important role in the oral absorption of pemigatinib. Pemigatinib is an inhibitor of P-gp, OCT2, and MATE1. However, at the proposed therapeutic dose, physiologically based pharmacokinetic modeling showed that a clinical drug-drug interaction is unlikely to occur as a result of pemigatinib-mediated inhibition of these transporters.

Refer to the study Protocols for details regarding restricted and prohibited concomitant medications.

15.27 **Known potential toxicities**:
Summary of Treatment-Emergent Adverse Events Reported in ≥ 10% of Participants in Studies INCB 54828-101, INCB 54828-201 and INCB 54828-202: Hyperphosphatemia, fatigue, dry mouth, alopecia, constipation, stomatitis, diarrhea, nausea, decreased appetite, dysgeusia, anemia, abdominal pain, vomiting, dry eye, weight decreased, arthralgia.
Common (1 to < 10%): nail toxicity

15.28 **Drug procurement:**
Incyte will supply the drug order form for pemigatinib (INCB054828) to participating sites. Sites are to complete the Investigational Supplies Shipment and Receipt Verification Form and email to:
[redacted]

Each participating ACCRU treating location will be responsible for monitoring the supply of pemigatinib (INCB054828) and will use the Drug Order Request Form to order additional supplies as needed.
Outdated or remaining drug is to be destroyed on-site as per procedures in place at each institution.

15.29b **Nursing Guidelines**

15.291 Due to the early investigational nature of this agent, not all side effects can be known at this time. Monitor patients closely and report any side effects to the treating provider/study team.
15.292 Gastrointestinal side effects can be seen including nausea, vomiting, constipation, and diarrhea. Treat symptomatically and monitor for effectiveness.
15.293 Monitor LFT's. Report elevated LFT's to the treating provider.
15.294 Patients may have visual changes, including blurred vision and dry eyes. Instruct patients to report any dry eyes, pain and/or visual changes to the study team immediately.
15.295 Patients may report fatigue, monitor hemoglobin as anemia can be seen. Instruct patients on energy conserving lifestyle.
15.296 Pemigatinib may be administered with or without food.

15.3 Cisplatin (Platinol®)

Please refer to the FDA-approved package insert for cisplatin for product information, extensive preparation instructions, and a comprehensive list of adverse events.

15.31 Background

Cisplatin inhibits DNA synthesis by the formation of DNA cross-links; denatures the double helix; covalently binds to DNA bases and disrupts DNA function; may also bind to proteins. Cisplatin can also bind two adjacent guanines on the same strand of DNA producing intrastrand cross-linking and breakage.

15.32 Formulation

Commercially available for injection as: Solution [preservative free]: 1 mg/mL (50 mL, 100 mL, 200 mL)

15.33 Preparation, Storage, and Stability

Refer to package insert for complete preparation and dispensing instructions. Store intact vials at room temperature and protect from light. Do not refrigerate solution, a precipitate may form. Further dilution stability is dependent on the chloride ion concentration and should be mixed in solutions of sodium chloride concentrations at least 0.3% NaCl. Further dilutions in 0.9% NaCl, D_5/0.45% NaCl, or D_5/0.9% NaCl to a concentration of 0.05-2 mg/mL are stable for 72 hours at 4ºC to 25ºC. The infusion solution should have a final sodium chloride concentration equal to or greater than 0.2% NaCl.

15.34 **Administration**

Refer to the treatment section for specific administration instructions. When administered as sequential infusions, observational studies indicate a potential for increased toxicity when platinum derivatives (carboplatin, cisplatin) are administered before taxane derivatives (docetaxel, paclitaxel). Pretreatment hydration with 1-2 L of fluid is recommended prior to cisplatin administration; adequate hydration and urinary output (> 100 mL/hour) should be maintained for 24 hours after administration. Hydration may be accomplished by adding the appropriate dose of cisplatin to 750 mL 0.5 D5/0.45% NaCl with 25 grams of Mannitol (approximating 1000 mL final volume) and infused over 2 hours. The IV rate of administration has varied from a 15- to 120-minute infusion, 1 mg/minute infusion, 6- to 8-hour infusion, 24-hour infusion, or per protocol; maximum rate of infusion of 1 mg/minute in patients with CHF.

15.35 **Pharmacokinetic Information**

Distribution: Rapidly into tissue; high concentrations in kidneys, liver, ovaries, uterus, and lungs

Protein binding: >90%

Metabolism: Nonenzymatic; inactivated (in both cell and bloodstream) by sulfhydryl groups; covalently binds to glutathione and thiosulfate

Half-life elimination: Initial: 20-30 minutes; Beta: 60 minutes; Terminal: ~ 24 hours; Secondary half-life: 44-73 hours

Excretion: Urine (>90%); feces (10%)

15.36 **Potential Drug Interactions**

Increased Effect/Toxicity: Delayed bleomycin elimination with decreased Glomerular filtration rate. When administered as sequential infusions, observational studies indicate a potential for increased toxicity when platinum derivatives (carboplatin, cisplatin) are administered before taxane derivatives (docetaxel, paclitaxel).

Decreased Effect: Sodium thiosulfate and amifostine theoretically inactivate drug systemically; have been used clinically to reduce systemic toxicity with administration of cisplatin.

Herb/Nutraceutical Interactions: Avoid black cohosh, dong quai in estrogen-dependent tumors.

15.37 **Known Potential Adverse Events**

Consult the package insert for the most current and complete information.

Common known potential toxicities, > 10%:
Central nervous system: Neurotoxicity: Peripheral neuropathy is dose and

duration dependent
Dermatologic: Mild alopecia
Gastrointestinal: Nausea and vomiting
Hematologic: Anemia, leukopenia (nadir day 18-23, recovery by day 39, dose related), thrombocytopenia (nadir day 18-23, recovery by day 39, dose related)
Hepatic: Liver enzymes increased
Renal: Nephrotoxicity (acute renal failure and chronic renal insufficiency)
Otic: Ototoxicity, manifested as high frequency hearing loss; ototoxicity is especially pronounced in children

Less common known potential toxicities, 1% - 10%:
Local: Tissue irritation

Rare known potential toxicities, <1% (Limited to important or life-threatening):
Alopecia, ageusia, anaphylaxis, aortic thrombosis, autonomic neuropathy, bradycardia, cardiac arrhythmia, cardiac failure, cerebrovascular accident, extravasation, hemolytic anemia (acute), hemolytic-uremic syndrome, hiccups, hypercholesterolemia, hyperuricemia, hypocalcemia, hypokalemia, hypomagnesemia, hyponatremia, hypophosphatemia, increased serum amylase, leukoencephalopathy, myocardial infarction, neutropenic enterocolitis, optic neuritis, pancreatitis, papilledema, peripheral ischemia (acute), phlebitis, SIADH, tachycardia, thrombotic thrombocytopenic purpura

15.38 Drug Procurement

Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

15.39 Nursing Guidelines

15.391 May react with aluminum IV set, forming a black precipitate and losing its potency.

15.392 Assess laboratory values prior to drug administration, especially CBC, platelets, creatinine.

15.393 Patient should be hydrated before administration. Stress post infusion hydration maintenance to reduce risk of nephrotoxicity.

15.394 Administer aggressive antiemetic therapy pre- and post-treatment.

15.395 Monitor for signs of neurotoxicity and ototoxicity. Instruct patient to report any numbness, burning, or tingling in hands and feet to health care team. Also instruct patient to report any changes in hearing or ringing in the ears to health care team.

15.396 Monitor magnesium and potassium levels, and for signs and symptoms of hypomagnesemia and hypokalemia, supplements may be needed.

15.397 Instruct patient about alopecia.

15.398 Use cautiously with loop diuretics as these may increase the risk of ototoxicity.

15.39a Monitor for signs and symptoms of allergic reactions. Treat according to institutional practice.

15.39b Monitor renal function tests.

15.4 Gemcitabine (Gemzar®)

Please refer to the FDA-approved package insert for gemcitabine for product information, extensive preparation instructions, and a comprehensive list of adverse events.

15.41 Background

Gemcitabine is a pyrimidine antimetabolite that inhibits DNA synthesis by inhibition of DNA polymerase and ribonucleotide reductase, specific for the S-phase of the cell cycle. Gemcitabine is phosphorylated intracellularly by deoxcytidine kinase to gemcitabine monophosphate, which is further phosphorylated to active metabolites gemcitabine diphosphate and gemcitabine triphosphate. Gemcitabine diphosphate inhibits DNA synthesis by inhibiting ribonucleotide reductase; gemcitabine triphosphate incorporates into DNA and inhibits DNA polymerase.

15.42 Formulation

Commercially available for injection:
Powder for reconstitution: 200 mg and 1 gram vials.
Solution for injection: 38 mg/mL 200 mg, 1 gm, and 2 gm vials. MUST BE DILUTED BEFORE USE.

15.43 Preparation, Storage, and Stability

Powder for reconstitution
Store intact vials at room temperature. Reconstitute the 200 mg vial with preservative free 0.9% NaCl 5 mL or the 1000 mg vial with preservative free 0.9% NaCl 25 mL. Resulting solution is 38 mg/mL. Dilute with 50-500 mL 0.9% NaCl or D_5W to concentrations as low as 0.1 mg/mL. Reconstituted vials are stable for up to 35 days and infusion solutions diluted in 0.9% NaCl are stable up to 7 days at 23ºC when protected from light; however, the manufacturer recommends use with 24 hours for both reconstituted vials and infusion solutions. Do not refrigerate.

Solution for injection
Store intact vials at refrigeration temperature between 2º to 8ºC (36º to 46ºF). Do not freeze. Each vial contains a gemcitabine concentration of 38 mg/mL. The appropriate amount of drug should be further diluted with 50-500 mL 0.9% NaCL or D_5W to concentrations as low as 0.1 mg/mL. When prepared as directed, diluted gemcitabine solutions are stable for 24 hours at controlled room temperature.

15.44 **Administration**

Refer to the drug treatment section of the protocol for specific administration directions and infusion rates. Gemcitabine is normally infused IV over 30 minutes. NOTE: Prolongation of the infusion time > 60 minutes has been shown to increase toxicity. Gemcitabine is being investigated in clinical trials for fixed dose rate infusion administration at doses from 1000 mg/m^2 to 2200 mg/m^2 at a rate of 10 mg/m^2/minute. Prolonged infusion times increase the accumulation of the active metabolite, gemcitabine triphosphate. Patients who receive gemcitabine fixed dose rate infusions experience more grade three and four hematologic toxicities.

15.45 **Pharmacokinetic Information**

Distribution: Infusions <70 minutes: 50 L/m^2; Long infusion times: 370 L/m^2

Protein binding: Negligible

Metabolism: Metabolized intracellularly by nucleoside kinases to the active diphosphate (dFdCDP) and triphosphate (dFdCTP) nucleoside metabolites

Half-life elimination:
Gemcitabine: Infusion time ≤ 70 minutes: 42-94 minutes; infusion time 3-4 hours: 4-10.5 hours
Metabolite (gemcitabine triphosphate), terminal phase: 1.7-19.4 hours

Time to peak, plasma: 30 minutes after completion of infusion
Excretion: Urine (92% to 98%; primarily as inactive uridine metabolite); feces (<1%)

15.46 **Potential Drug Interactions**

Increased Effect/Toxicity: Gemcitabine may increase the levels/effects of fluorouracil. Gemcitabine may enhance the adverse pulmonary effects of bleomycin.

Ethanol/Nutrition/Herb Interactions Ethanol: Avoid ethanol (due to GI irritation).

15.47 **Known Potential Adverse Events**

Consult the package insert for the most current and complete information.

Common known potential toxicities, > 10%:
Cardiovascular: Peripheral edema, edema
Central nervous system: Drowsiness
Dermatologic: Skin rash, alopecia
Gastrointestinal: Nausea/vomiting, diarrhea, stomatitis
Hematologic: Anemia, thrombocytopenia, neutropenia, hemorrhage Hepatic: Transaminases increased, alkaline phosphatase increased, bilirubin increased
Infection: Infection

Renal: BUN increased
Respiratory: Dyspnea, flu-like symptoms
Miscellaneous: Fever
Less common known potential toxicities, 1% - 10%:
Central nervous system: Paresthesia
Local: Injection site reactions
Renal: Creatinine increased
Respiratory: Bronchospasm

Rare known potential toxicities, <1% (Limited to important or life-threatening):
Adult respiratory distress syndrome, anaphylactoid reaction, anorexia, arthralgia, bullous skin disease, capillary leak syndrome, cardiac arrhythmia, cardiac failure, cellulitis, cerebrovascular accident, constipation, desquamation, digital vasculitis, gangrene of skin or other tissue, hemolytic-uremic syndrome, hepatic failure, hepatic veno-occlusive disease, hepatotoxicity (rare), hyperglycemia, hypertension, hypocalcemia, hypotension, increased gamma-glutamyl transferase, interstitial pneumonitis, myocardial infarction, neuropathy, petechiae, pulmonary edema, pulmonary fibrosis, radiation recall phenomenon, renal failure, respiratory failure, reversible posterior leukoencephalopathy syndrome, sepsis, supraventricular cardiac arrhythmia, thrombotic thrombocytopenic purpura

15.48 **Drug Procurement**

Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

15.49 **Nursing Guidelines**

15.491 Monitor CBC, differential, PLTs prior to each dose. Myelosuppression is the principal dose-limiting factor. Modification may be considered by physician when bone marrow suppression is suspected.

15.492 Evaluate hepatic and renal function prior to initiation of therapy and periodically thereafter. Closely observe those patients with a history of preexisting mild renal impairment or hepatic insufficiency. Encourage hydration.

15.493 GEMZAR clearance is affected by age and gender. Grade 3/4 thrombocytopenia has been more common in elderly women.

15.494 Antiemetics may be required for probable mild to moderate nausea and vomiting. Assess for their effectiveness.

15.495 Instruct patient in management of possible mild diarrhea and stomatitis.

15.496 GEMZAR may cause fever in the absence of clinical infection. Fever can be accompanied by other flu-like symptoms. Instruct patient to report fever or flu-like symptoms to healthcare team. Treat symptoms as they occur.

15.497 Macular or finely granular maculopapular eruptions were experienced by 30% of patients tested. Instruct patients to report any skin changes.

15.498 Instruct patient to report any respiratory changes.

15.499 Burning may occur at the injection site. May apply heat during infusion to minimize pain.

16.0 Statistical Considerations and Methodology

16.1 Study Design:

This phase Ib dose de-escalation study is designed to assess safety and tolerability of ivosidenib or pemigatinib in combination with cisplatin and gemcitabine in patients with advanced or metastatic cholangiocarcinoma.

There will be a separate Phase Ib arm and safety run-in cohort for each group: patients with a known IDH1 R132 mutation (ivosidenib, gemcitabine, cisplatin - Treatment Arm A) and patients with FGFR genetic alteration (pemigatinib, gemcitabine, cisplatin - Treatment Arm B). The design of each of these Phase Ib arms is identical.

16.11 *Primary Endpoint*:

The primary endpoint of this trial is the safety and tolerability of the regimen as measured by the incidence of significant toxicity A significant toxicity (dose limiting toxicity, DLT) is defined in Section 7.53 that is possibly, probably, or definitely related to treatment (ivosidenib or pemigatinib in combination with cisplatin and gemcitabine).

16.12 *Safety Run-In Cohorts*:

To ensure safety of treating patients with ivosidenib or pemigatinib in combination with cisplatin and gemcitabine, an initial 6 patients will be enrolled for each arm and treated for adverse events assessment. These patients will be enrolled in a cohort of 6+6 design.

<u>IDH1 R132 Mutation Arm (</u>Ivosidenib<u>):</u>

The first cohort of 6 patients for the IDH1 R132 mutation arm will receive 500 mg ivosidenib (dose level 0). If less than 2 patients in this first cohort experience a DLT (See Section 7.53), then 500 mg of ivosidenib (dose level 0) will be the recommended phase II dose and the study will continue to enroll to the accrual goal.

If DLTs are observed in two or more patients in the initial cohort of 6 (at dose level 0) then an additional 6 patients will be enrolled to dose level -1 and will receive 250 mg of ivosidenib. If less than 2 patients enrolled at 250 mg of ivosidenib(dose level -1) experience DLTs then the recommended Phase II dose will be 250 mg of ivosidenib (dose level -1) and the study will continue to enroll to the accrual goal. If 2 or more patients enrolled at 250 mg ivosidenib (dose

level -1) experience DLTs then the study team will temporarily suspend accrual and review the toxicity data.

FGFR genetic Alterations Arm (Pemigatinib): The first cohort of 6 patients for the FGFR genetic alterations arm will receive 13.5 mg Pemigatinib (dose level 0). If less than 2 patients in this first cohort experience a DLT (See Section 0), then 13.5 mg of Pemigatinib will be the recommended phase II dose and the study will continue to enroll to the accrual goal.

If DLTs are observed in two or more patients in the initial cohort of 6 (at dose level 0), then an additional 6 patients will be enrolled to dose level -1 and will receive 9 mg of Pemigatinib. If less than 2 patients enrolled at 9 mg of Pemigatinib (dose level -1) experience DLTs then the recommended Phase II dose will be 9 mg of Pemigatinib (dose level -1) and the study will continue to enroll to the accrual goal.

If 2 or more patients enrolled at 9 mg of Pemigatinib (dose level -1) experience DLTs, then an additional 6 patients will be enrolled to dose level -2 and will receive 4.5 mg of Pemigatinib. If less than 2 patients enrolled at 4.5 mg of Pemigatinib (dose level -2) experience DLTs then the recommended Phase II dose will be 4.5 mg of Pemigatinib (dose level -2) and the study will continue to enroll to the accrual goal. If 2 or more patients enrolled at 4.5 mg of Pemigatinib experience DLTs, then the study team will temporarily suspend accrual and review the toxicity data.

16.13 *Sample Size*:

A total of 18 evaluable patients (6-12 accrued from run-in phase and continue to accrue until 18 patients) per arm will provide preliminary data to determine safety and tolerability. We anticipate enrolling an additional 2 patients per arm to account for ineligibilities, cancelations, major violations, and other reasons. Thus, the maximum accrual is 40 ((18+2) + (18+2)) patients in total.

16.14 *Accrual and Study Duration*:

The anticipated accrual rate is approximately 2 patients per month for each arm. Therefore, the accrual period for this study is expected to be approximately 3-6 months for the safety run-in cohorts and an additional 3-6 months for the expansion cohort. The final analysis can begin approximately 17 months after the trial begins, i.e. as soon as the last patient accrued has been observed for 27 weeks.

16.2 Data & Safety Monitoring:

16.21 The study chair(s) and the study statistician will review the study at regular intervals to identify accrual, adverse event, and any endpoint problems that might be developing. The Mayo Clinic Data Safety Monitoring Board (DSMB) is responsible for reviewing accrual and safety data for this trial at least twice a year, based on reports provided by the Statistical Office.

16.22 Adverse Event Stopping Rules: The stopping rules specified below are based on the knowledge available at study development. We note that the Adverse Event Stopping Rule may be adjusted in the event of either (1) the study re-opening to accrual or (2) at any time during the conduct of the trial and in consideration of newly acquired information regarding the adverse event profile of the treatment(s) under investigation.

The study team may choose to suspend accrual because of unexpected adverse event profiles that have not crossed the specified rule below.

In addition to the stopping rules associated with the safety run-in cohort (see Section 7.53), accrual to the expansion cohort of either arm of this study will be temporarily suspended if at any time we observe events considered at least possibly related to study treatment (i.e. an adverse event with attribute specified as "possible", "probable", or "definite") that satisfy either of the following:

- Once accrual to the expansion cohort has begun (Phase II recommended dose determined), if 33% or more of AE evaluable patients from either the expansion cohort or patients still being treated at the recommended phase II dose from the safety run-in cohort experience a DLT (See Section 7.53) then the trial will be temporarily suspended and the study team will review the toxicity data. A decision will be made to either amend the protocol or permanently close the study. Where AE evaluable is defined as any submission of Adverse Event Assessment data via CRFs and/or expedited reporting.

We note that we will review grade 4 and 5 adverse events deemed "unrelated" or "unlikely to be related", to verify their attribution and to monitor the emergence of a previously unrecognized treatment-related adverse event.

16.3 Analysis Plans:

The analysis plan outlined below will be applied independently to each arm.

16.31 Primary Endpoint

The primary endpoint for each arm of this phase Ib study is the incidence of significant toxicity at 3 weeks. A significant toxicity is defined as a Dose Limiting Toxicity (as defined in Section 7.53) that is possibly, probably, or definitely related to treatment. DLTs will be evaluated starting in the first cycle of combination treatment and up to 3 weeks of combination treatment. Toxicities will be assessed using the CTEP Active Version of the CTCAE. This data will be assessed in evaluating the tolerability of the regimen for future studies. All patients meeting the eligibility criteria who have signed a consent form and have begun combination treatment will be considered evaluable for significant toxicity. Patients, who do not experience a DLT but withdraw from protocol therapy prior to 3 weeks, will not be evaluable for the primary endpoint. Incidence of significant toxicity at3 weeks will be estimated separately by arm and will be defined as the number of patients with significant toxicity within 3 weeks of combination treatment divided by the total number of evaluable patients.

16.32 Definitions and Analyses of Secondary Endpoints

The secondary objectives of this phase Ib study are exploratory and hypothesis-generating in nature. These analyses will be purely descriptive. No formal analyses will be made comparing the two arms

16.321 Overall Survival

Survival time is defined to be the length of time from start of study therapy to death due to any cause. All patients meeting the eligibility criteria that have signed a consent form and begun treatment will be

considered evaluable for estimation of the survival distribution. The distribution of overall survival for both arms of the study will be estimated separately using the Kaplan-Meier (Reference) method.

16.322 Progression Free Survival

Progression Free Survival time is defined as the time from the start of study therapy to documentation of disease progression. Patients who die without documentation of progression will be considered to have had tumor progression at the time of death. Patients who are still alive and have not progressed will be censored for progression at the time of the last disease evaluation. The time-to-progression distribution will be estimated separately for both arms, using the Kaplan-Meier method. Early efficacy signals via PFS endpoint will be assessed in an exploratory fashion.

16.323 Adverse Events Profile

The number and severity of all adverse events (overall, by dose-level, and by tumor group) will be tabulated and summarized in this patient population. The Grade 3+ adverse events will also be described and summarized in a similar fashion. This will provide an indication of the level of tolerance for this treatment combination in this patient group.

16.324 Toxicity Profile

The term toxicity is defined as adverse events that are classified as either possibly, probably, or definitely related to study treatment. Non-hematologic toxicities will be evaluated via the ordinal CTC standard toxicity grading. Hematologic toxicity measures of thrombocytopenia, neutropenia, and leukopenia will be assessed using continuous variables as the outcome measures (primarily nadir) as well as categorization via CTC standard toxicity grading.

Overall toxicity incidence as well as toxicity profiles by dose level, patient and tumor site will be explored and summarized. Frequency distributions, graphical techniques and other descriptive measures will form the basis of these analyses.

16.325 Response Profile

Best Response is defined to be the best objective status recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria. RECIST 1.1 criteria will be used for tumor evaluation and patients will be re-evaluated every prior to treatment in cycle 3 and then in odd subsequent cycles.

Responses will be summarized by simple descriptive summary statistics delineating complete and partial responses as well as stable and progressive disease in this patient population (overall and by tumor group). The number of responses may indicate further evaluation for specific tumor types in a Phase II setting.

16.33 Laboratory Correlates

Exploratory analyses on plasma 2-hydoxglutarate (2-HG) levels will be conducted. The will be analyzed at baseline and after multiple doses of ivosidenib. As data permit, these data will be summarized by descriptive statistics, including mean, median and standard deviation. Correlations between these laboratory values and other outcome measures like response, and dose levels will be carried out in an exploratory manner.

16.4 Inclusion of Women and Minorities

This study will be available to all eligible patients regardless of race, gender, or ethnic group.

There is no information currently available regarding differential agent effects of either regimen in subsets defined by gender, race, or ethnicity, and there is no reason to expect such differences exist. Therefore, although the planned analyses will, as always, look for differences in treatment effect based on gender and racial groupings, the samples sizes are not increased in order to provide additional power for such subset analyses.

To predict the characteristics of patients likely to enroll in this trial we have reviewed the Mayo registration classified by race and gender. This revealed that roughly 3% of patients registered into cancer trials during the past five years could be classified as minorities and about 50% of patients were women. . Expected sizes of racial by gender subsets are shown in the following table:

Ethnic Category	**Sex/Gender**			
	Females	**Males**	**Unknown**	**Total**
Hispanic or Latino	2	2		4
Not Hispanic or Latino	18	18		36
Ethnic Category: Total of all subjects*	20	20		40
Racial Category				
American Indian or Alaskan Native	0	0		0
Asian	0	0		0
Black or African American	1	1		2
Native Hawaiian or other Pacific Islander	0	0		0
White	19	19		38
Racial Category: Total of all subjects*	20	20		40

**These totals must agree. Enter actual estimates (not percentages)*

Ethnic Categories:	**Hispanic or Latino** – a person of Cuban, Mexican, Puerto Rico, South or Central American, or other Spanish culture or origin, regardless of race. The term “Spanish origin” can also be used in addition to “Hispanic or Latino.” Not Hispanic or Latino

Racial Categories:	**American Indian or Alaskan Native** – a person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment. **Asian** – a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (NOTE: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.) **Black or African American** – a person having origins in any of the black racial groups of Africa. Terms such as "Haitian" or "Negro" can be used in addition to "Black or African American." **Native Hawaiian or other Pacific Islander** – a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands. **White** – a person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

17.0 Pathology Considerations/Tissue Biospecimens: None.

18.0 Records and Data Collection Procedures

All data must be entered by Remote Date Entry (RDE) and completed by qualified and authorized personnel. Access the RAVE system through the iMedidata portal at [redacted]
All data on the CRF must reflect the corresponding source document. Please refer to the ACCRU website for instructions
[redacted]

18.1 Submission Timetables

NOTE: All reports must be de-identified, and labeled with study number, ACCRU patient ID number, and initials.

Initial Material(s)

CRF	**Active-Monitoring Phase** (Compliance with Test Schedule Section 4.0)
Institutional Contacts	≤ 2 weeks after registration
On-Study Form	
Adverse Events: Baseline	
On-Study: Prior Surgery[1]	
On-Study: Prior Radiation[1]	
On Study: Prior Systematic Therapy	
RECIST Measurements: Baseline	
Supporting Documentation: Baseline[2]	
Laboratory Tests and Results: Baseline	
Patient Status: Baseline	
Off Treatment	Submit ≤2 weeks after registration if withdrawal/refusal occurs prior to beginning protocol therapy

1. Submit only if applicable.
2. Attach pathology report, imaging report, molecular testing result, and clinical note in RAVE on the Supporting Documentation: Baseline form.

Test Schedule Material(s)

CRF	Active-Monitoring Phase (Compliance with Test Schedule Section 4.0)	
	At each evaluation during treatment	At end of treatment
Treatment (Intervention) Form	X	X
Treatment (Intervention):Dose modifications, Omissions, and Delays[2]	X	X
Adverse Event: Solicited	X	X
Adverse Events: Other[2]	X	X
Dose Limiting Toxicities[2, 3]	X	
RECIST Measurements	X	X
Supporting Documentation[1]	X	X
Specimen Submission: Blood	X	X
Day 1 Laboratory Tests and Results	X	
Day 8 Laboratory Tests and Results (Cycle 1 Only)[3]	X	
Day 15 Laboratory Tests and Results (Cycle 1 Only)[3]	X	
Patient Status: Treatment (Intervention)	X	X
Off Treatment		X
Consent Withdrawal[2]	X	X
Consent Withdrawal: Specimen Only[2]	X	X
Consent Withdrawal: All Follow-Up[2]	X	X
ACCRU Deviation Form[2]	X	X
Notice of New Primary[2]	X	X

1. Attach a copy of imaging report for restaging or progression in RAVE on the Supporting Documentation form if disease is evaluated.
2. Submit only if applicable.
3. For Cycle 1 only.

Follow-up Material(s)

CRF	Event Monitoring Phase/Survival Follow-Up[1]				
	q. 6 months until PD[2]	At PD[2]	After PD q. 6 mos.	Death	At Each Event Occurrence
Patient Status: Survival and Disease Status Follow-up/Event Monitoring	X	X	X	X	
Supporting Documentation[2]		X			
Adverse Events: Late[3]	X		X	X	
Consent Withdrawal (choose appropriate form)[3] • Consent Withdrawal: Specimen Only • Consent Withdrawal: All Follow-up	X		X		
Lost to Follow-up[3]	X		X		
ACCRU Deviation[3]					X
Notice of New Primary[3]					X

1. Patients are followed in Event Monitoring for a maximum of 3 years from registration.
2. Attach a copy in RAVE for documentation of progression on the Supporting Documentation Form.
3. Submit only if applicable.

19.0 Budget

19.1 Each site should review the test schedule (Section 4.0), taking into account local and regional coverage policies, to determine which items are standard of care and which are research at their site. Refer to the payment synopsis for funding provided per accrual for covering study costs, as well as any additional invoiceables that may be allowed.

19.2 Tests to be research funded: Mandatory blood samples for correlative research.

19.3 Other budget concerns:

19.31 Ivosidenib will be supplied by Agios. Pemigatinib (INCB054828) will be supplied by Incyte. Cisplatin and Gemcitabine will not be supplied, but is commercially available.

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APPENDIX I – PATIENT MEDICATION DIARY

Instructions:

- Please indicate on the calendar below *every* day that you take your study medication by placing the dose taken on the line under the date.
- If you miss a dose, place a "**0**" under the date, but remember to take your prescribed dose at the next regularly scheduled time.
- Bring ***all*** bottles and any unused study medication along with this diary when you return for your next appointment.

Study Drug	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**
Date							
Ivosidenib							
pemigatinib							
Comments							

Study Drug	**Day 8**	**Day 9**	**Day 10**	**Day 11**	**Day 12**	**Day 13**	**Day 14**
Date							
Ivosidenib							
pemigatinib							
Comments							

Study Drug	**Day 15**	**Day 16**	**Day 17**	**Day 18**	**Day 19**	**Day 20**	**Day 21**
Date							
Ivosidenib							
pemigatinib							
Comments							

Study Drug	**Day 22**	**Day 23**	**Day 24**	**Day 25**	**Day 26**	**Day 27**	**Day 28**
Date							
Ivosidenib							
pemigatinib							
Comments							

Date:_____ Participant's Signature:_____

Area Below Only To Be Completed by Coordinator

Number of pills returned_____ **Study Coordinator Initials_____**

Date_____ **Discrepancy Yes_____No_____**

Appendix II - list of eligible gene alterations

ARM A: Any R132C/L/G/H/S mutation

ARM B: FGFR1/2/3 and FGF alterations as listed below:

1) FGFR1-3 fusions or FGFR2 rearrangements (only FGFR fusions or rearrangements with an intact kinase domain would be eligible)

2) Known or likely activating mutations (excluding kinase domain) in *FGFR1-3* (See Table 1)

3) *FGFR2* in frame insertions or deletions in the extracellular domain and FGFR2 truncating alterations in exon 18 based on emerging evidence (Table 2 for FGFR2 in frame insertions or deletions, and Table 3 for truncating alterations).

4) Specifically, **EXCLUDE** *FGFR* amplifications, *FGF* amplifications or *FGFR* mutations in the kinase domain

Appendix III - Prohibited medications

ARM A:

Prohibited medications and certain foods are not allowed in this study while subjects are receiving study drug.

Strong CYP3A Inducers	CYP3A Substrates with a Narrow Therapeutic Window
Avasimibe, carbamazepine, phenytoin, rifampin, rifabutin, St. John's wort	Alfentanil, astemizole[1], cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, everolimus, sirolimus, tacrolimus, terfenadine[1]
	Sensitive P-gp Substrates with a Narrow Therapeutic Window
	Aliskiren, ambrisentan, colchicine, dabigatran etexilate, digoxin, everolimus, fexofenadine, imatinib, maraviroc, ranolazine, sirolimus talinolol, tolvaptan, topotecan

Note that this is not an exhaustive list. For an updated list, see the following link: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm
CYP or P-gp substrates with a narrow therapeutic window refers to drugs whose exposure-response relationship indicates that small increases in their exposure levels by the concomitant use of CYP inhibitors may lead to serious safety concerns (eg, Torsades de Pointes).
[1] Withdrawn from the United States market because of safety reasons.

Inhibitor	Therapeutic Class	Inhibitor dosing (oral)
		Potent CYP3A Inhibitors (yielding substrate AUCr > 5)
indinavir /RIT	Protease Inhibitors	800/100 mg BID (1 day)
tipranavir/RIT	Protease Inhibitors	500/200 mg BID (2 days)
ritonavir	Protease Inhibitors	3 doses of 100 mg over 24 h
cobicistat (GS-9350)	None	200 mg QD (14 days)
indinavir	Protease Inhibitors	800 mg TID (7 days)
ketoconazole	Antifungals	400 mg QD (4 days)
troleandomycin	Antibiotics	500 mg single dose
telaprevir	Antivirals	750 mg TID (16 days)
danoprevir / RIT	Antivirals	200/100 mg QD (14 days)
elvitegravir / RIT	Treatments of AIDS	150/100 mg QD (10 days)
saquinavir / RIT	Protease Inhibitors	1000/100 mg BID (14 days)
lopinavir / RIT	Protease Inhibitors	400/100 mg BID (2 days)
itraconazole	Antifungals	200 mg QD (4 days)
voriconazole	Antifungals	200 mg BID (9 days)
mibefradil	Calcium Channel Blockers	100 mg single dose
LCL161	Cancer Treatments	600 mg single dose
clarithromycin	Antibiotics	500 mg BID (7 days)
posaconazole	Antifungals	400 mg BID (7 days)
telithromycin	Antibiotics	800 mg QD (6 days)
grapefruit juice DS[2]	Food Products	240 mL TID (2 days) and 90 min, 60 min, 30 min prior to midazolam
conivaptan	Diuretics	40 mg BID (5 days)
nefazodone	Antidepressants	100-200 mg BID (12 days)
nelfinavir	Protease Inhibitors	1250 mg BID (14 days)
saquinavir	Protease Inhibitors	1200 mg TID (5 days)
idelalisib	Kinase Inhibitors	150 mg BID (8 days)
boceprevir	Antivirals	800 mg TID (6 days)

Inducers	Therapeutic class	Object (oral, unless otherwise specified)	% ↓ AUC	% ↑ oral CL	Precipitant Dose (oral)
		Potent Inducers (AUC decreased by ≥ 80% or CL increased by more than 5 fold (400%))			
rifampin	Antibiotics	budesonide	99.7	36904.5	600 mg QD (7 days)
mitotane	Other Antineoplastics	midazolam	94.5	Not Provided	maximum of 3.5 g TID (chronic therapy)
avasimibe	Other Antilipemics	midazolam	93.5	Not Provided	750 mg/day (7 days)
phenytoin	Anticonvulsants	nisoldipine	89.5	Not Provided	200-450 mg/day (chronic treatment)
carbamazepine	Anticonvulsants	quetiapine	86.6	643.1	200 mg TID (26 days)
enzalutamide	Antiandrogens	midazolam	85.9	Not Provided	160 mg QD (85±3 days)
St John's Wort	Herbal Medications	midazolam	80.0	Not Provided	300 mg TID (14 days)
rifabutin	Antibiotics	delavirdine	Not Provided	458.0	300 mg QD (14 days)
phenobarbital	Anticonvulsants	verapamil	76.6	400.9	100 mg QD (21 days)

Appendix IV
New York Heart Association Classification

Class	Symptomatology
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
III	Marked limitation of physical activity. Comfortable at rest, less than ordinary activity results in fatigue, palpitation, dyspnea, anginal pain.
IV	Unable to carry on any physical activity without discomfort. Symptoms at rest. If any physical activity is undertaken, discomfort is increased.

Appendix V

Fridericia's Formula:

$$QTcF=QT/RR^{1/3}$$

Appendix VI

Medications Known to Prolong the QT Interval

Amiodarone	dofetilide	grepafloxacin	moxifloxacin	quinidine
Astemizole	dolasetron	halofantrine	norfloxacin	sevoflurane
azithromycin	domperidone	haloperidol	ofloxacin	sotalol
bepridil	droperidol	ibutilide	ondansetron	sparfloxacin
chloroquine	erythromycin	itraconazole	palonosetron	terfenadine
chlorpromazine	escitalopram	ketoconazole	pentamidine	thioridazine
ciprofloxacin	flecainide	levofloxacin	pimozide	voriconazole
citalopram	gatifloxacin	levomethadyl	posaconazole	
clarithromycin	gemifloxacin	mesoridazine	probucol	
disopyramide	granisetron	methadone	procainamide	

*For a complete and updated (ongoing) list of medications, please use the following link: [redacted]