MC1345
MCCC Addendum 2

Mayo Clinic Cancer Center

Pilot Study of Ponatinib in Biliary Cancer Patients with FGFR2 Fusions

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Drug Availability
Drug Company Supplied: Ponatinib *IND# 123324*

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

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Protocol Resources

Questions:	Contact Name:
Patient eligibility*, test schedule, treatment delays/interruptions/adjustments, dose modifications, adverse events, forms completion and submission	[redacted] Quality Assurance Specialist Phone: [redacted] E-mail: [redacted]
Protocol document, consent form, regulatory issues	[redacted], Research Protocol Specialist Phone: [redacted] Email: [redacted]
Adverse Events (AdEERS, MedWatch, Non-AER, AML/MDS)	[redacted] Phone: [redacted] E-mail: [redacted]

*No waivers of eligibility per NCI

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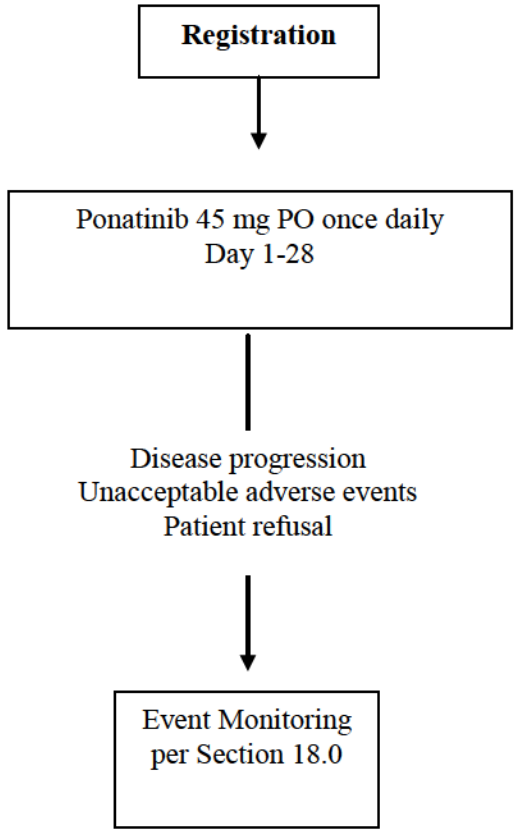
Schema



If a patient is deemed ineligible or a cancel, please refer to Section 13.0 for follow-up information.

* Cycle = 28days

Generic name: Ponatinib
Brand name(s): Iclusig™
Mayo Abbreviation: PONATINIB
Availability: provided by ARIAD Pharmaceuticals

1.0 Background

1.1 Biliary Cancers

Biliary cancers comprise malignant tumors of the intrahepatic and extrahepatic bile ducts, gallbladder and ampulla. Known risk factors for cholangiocarcinoma are the liver flukes *O. viverrini* and *C. sinensis* in high prevalence endemic regions in southeast Asia,[1-3] as well as primary sclerosing cholangitis,[4-7] Caroli's disease,[8] hepatitis B and hepatitis C,[9-14] obesity,[13] hepatolithiasis[15, 16] and thorotrast contrast exposure.[17, 18] Increased incidence of gallbladder cancer has been associated with gallstones, obesity, age, female gender, and *S. typhi, S. paratyphi, H. pylori and H. bilis* infections.[19] Regions of higher incidence include Chile[20] and Northern India/Pakistan.[19]

Surgical approaches such as resection and transplantation represent the only curative treatment approaches.[21] Unfortunately, most patients present with surgically unresectable or metastatic disease at diagnosis. Systemic therapy with gemcitabine and cisplatin has been established as the standard of care for patients with advanced disease.[22] However, most patients eventually experience progression of their disease and there is imminent need for novel therapeutic approaches.

1.2 FGFR Pathway in Cancer

Members of the FGFR family (FGFR1-4) have been associated with mutations, amplifications and translocation events with oncogenic potential.[23] FGFR fusions with oncogenic activity have been previously identified in bladder cancer (FGFR3),[24] lymphoma (FGFR1 and FGFR3),[25, 26] acute myeloid leukemia (FGFR1),[27] multiple myeloma,[28] myeloproliferative neoplasms[29] and most recently glioblastoma multiforme (FGFR1 and FGFR3).[30] Fusions involving FGFR family members may be both therapeutically relevant and actionable. The FGFR tyrosine kinase inhibitors (TKI) dovitinib[31] and NVP-BGJ398[32] are currently in clinical development and the FGFR TKI ponatinib[33] was recently approved by the FDA for use in T315I mutant chronic myelogenous leukemia. FGF7 (keratinocyte growth factor) has been previously linked to poor prognosis in patients with biliary tract cancer and a small molecule FGFR kinase inhibitor, Ki23057, has demonstrated efficacy in preclinical models.[34] FGFR2, FGFR3 and FGFR4 have been found to be overexpressed in biliary cancers, particularly those harboring IDH1 and 2 mutations.[35]

We have identified recurrent fusions of FGFR2 in patients with advanced intrahepatic cholangiocarcinoma in the setting of ongoing whole genome sequencing studies. Concomitant activation of the FGFR cascade (phosphor-FGFR2, increased expression of other FGFR members: FGFR3 and FGFR4) has been elucidated in these instances. We found fusions of FGFR2 with MGEA5, BICC1 or TACC3 in our study. The FGFR genes encode multiple structural variants through alternative splicing. Notably, the FGFR2-IIIb isoform was present in all of these fusions and has been shown to have selectivity for epithelial cells as opposed to the FGFR2-IIIc isoform, which is found selectively in mesenchymal cells.[36] Given that biliary cancers are of epithelial origin and that cancer associated fibroblasts have been implicated in the setting of a paracrine loop with cholangiocarcinoma tumor cells,[37, 38] further characterization of FGFR2-IIIb specific ligands, FGF7 and FGF10, which have no binding to FGFR2-IIIc, would be warranted. Paradoxically, FGFR2-IIIb has been described as a tumor suppressor in pre-clinical systems of bladder cancer and prostate cancer.[39, 40] As such, FGFR signaling is clearly context dependent and will exhibit variability in disparate tumor types.

Additional studies to characterize the prevalence of the recently identified FGFR2 aberrations in a larger cohort of biliary cancers are underway. *In vitro* functional studies characterizing the fusions are also underway.

We propose to study ponatinib prospectively in the context of a pilot study in patients with FGFR2 fusions that are identified through our real time whole genome analysis efforts.

1.2 Ponatinib

1.21 Chemical

AP24534 (United States Adopted Name [USAN]: ponatinib) is a novel, orally-available tyrosine kinase inhibitor (TKI). A primary target is BCR-ABL, an abnormal tyrosine kinase that is the hallmark of chronic myeloid leukemia (CML). BCR-ABL is expressed from a fusion gene formed by the rearrangement of the breakpoint cluster region (BCR) on chromosome 22 with the c-abl proto-oncogene (ABL) on chromosome 9 (BCR-ABL). Ponatinib is a new chemical entity prepared by chemical synthesis. The ponatinib active pharmaceutical ingredient (API) is the mono-hydrochloride salt (AP24534 hydrochloride, or AP24534 HCl). Ponatinib for investigational use is supplied as white opaque capsules containing nominally 2 mg, 5 mg or 15 mg of ponatinib or as 15 mg or 45 mg round, white, film-coated tablets.

1.22 Nonclinical

A preclinical development program has been completed to support clinical trials on ponatinib. In vitro assays demonstrated that ponatinib potently inhibits the kinase enzymatic activity of the T315I ABL kinase domain, as well as that of the native (unmutated) enzyme. In leukemia cell lines expressing these BCR-ABL variants, ponatinib potently inhibited BCR-ABL signaling, leading to inhibition of cellular proliferation and induction of apoptosis. Ponatinib also potently inhibits the proliferation of cell lines expressing other major clinically observed imatinib-resistant mutants of BCR-ABL. In vivo antitumor activity has been shown in tumor-bearing mouse models.

Ponatinib is also a potent inhibitor of certain other tyrosine kinases implicated in the initiation and progression of leukemias and other tumor types. In particular, it inhibits FLT3, which is frequently mutationally activated in acute myeloid leukemia (AML), and inhibits all members of the FGFR family, which are implicated in a variety of myeloproliferative disorders and solid tumor indications. Ponatinib also inhibits several other kinases, including KIT, RET, SRC, VEGFR, PDGFR, and TIE2. Taken together, the kinase inhibition profile of ponatinib suggests the potential for clinical activity in other hematologic and nonhematologic malignancies in addition to CML.

Preclinical safety assessment studies were performed on ponatinib including 6-month oral toxicology studies in rats and cynomolgus monkeys. The rat was shown to be the most sensitive species to the toxicologic effects of ponatinib. In the 6-month oral toxicology study in rats, the no observed adverse effect level (NOAEL) was 0.25 mg/kg/day. Higher dose levels of 0.75 and 2 mg/kg/day caused mortality of some animals. Histologic examination revealed decreased

numbers of chondrocytes along the physis in the femur at the 0.75 and 2 mg/kg/day dose levels,and lymphoid depletion was observed in the thymus at the 2 mg/kg/day dose level. The administration of ponatinib to cynomolgus monkeys for 6 months at oral dose levels of 0.25, 0.75 and 2 mg/kg/day was well tolerated with no ponatinib-related microscopic findings being observed at any dose level. Toxicity studies in pregnant rats demonstrated fetal malformations and embryo-fetal toxicity at dose levels of 1 and 3 mg/kg/day, respectively, and higher. In a phototoxicity study in pigmented rats, signs of minimal ocular phototoxicity were observed at 5 and 10 mg/kg.

1.23 Clinical

Iclusig received accelerated approval in the United States (US) (December 2012) and approval in the European Union (EU) (July 2013) for patients with refractory CML or Philadelphia chromosome-positive (Ph+) leukemias. As of 06 January 2014, 753 patients have received ponatinib therapy through clinical studies, and 1312 through global expanded access programs.

Following approval of ponatinib in the US and the EU, more than 900 patients have been treate with ponatinib commercially. Since the previous update to this Investigator Brochure (Version 5, 25 February 2013), regulatory actions were taken by ARIAD Pharmaceuticals (ARIAD) and/or the competent authorities following increased cumulative risk of vascular occlusive events observed in patients using ponatinib. From a development perspective, on 08 October 2013, the US Food and Drug Administration (FDA) placed a partial clinical hold on all new patient enrollments in clinical studies with ponatinib, and a phase 3 study (EPIC: AP24534-12-301) was terminated on 17 October 2013. From a postmarketing authorization perspective, prior approval supplement/type II variation were evaluated by the FDA and the European Medicines Agency (EMA), respectively, to revise ponatinib product information to include updated data and warning/precautions on arterial thromboembolic events, venous thromboembolic events, cardiac failure/left ventricular dysfunction (LVD), and cardiovascular deaths. The type II variation received a positive opinion from Europe's Committee for Human Medicinal Products (CHMP) on 21 November 2013. Subsequent to completion of the Type II variation procedure, a referral procedure under article 20 of regulation (EC) No. 726/2004 was triggered. In the US, while evaluation of new safety data was ongoing, the FDA requested ARIAD on 31 October 2013 to temporarily suspend commercial distribution and marketing of Iclusig in the US. On 20 December 2013, the FDA agreed with the revised US Prescribing Information, and commercialization of Iclusig was resumed in the US in January 2014. Additional information can be found within th Investigator's brochure.

1.3 Circulating tumor DNA based biomarkers

Cell-free tumor-specific DNA in circulating plasma (ctDNA) has been recently shown to be a potential biomarker for solid cancers. Specific mutations can be tracked in ctDNA and reflect disease burden in breast, ovarian, colorectal and other non-hematological cancers. Extensive analysis of selected plasma samples can provide insights into acquired resistance to molecularly targeted treatments and sub-clonal genomic evolution of cancers.

There is a dire need for accurate circulating biomarkers for cholangiocarcinomas. Analysis of ctDNA within this study provides an opportunity to develop a personalized biomarker for monitoring of tumor burden. Additional correlative analysis may allow identification of mechanisms that cause primary or acquired resistance to treatment ponatinib in cholangiocarcinoma. This may enable molecular stratification of cholangiocarcinoma for ponatinib or other molecularly targeted agents using circulating tumor DNA analysis.

2.0 Goals

2.1 Primary

2.11 To assess the clinical benefit rate (confirmed complete or partial response or stable disease for 4 or more cycles) of ponatinib in FGFR aberrant advanced biliary cancers

2.2 Secondary

2.21 To estimate progression free survival, overall survival, and CA19-9 response rate of these patients

2.22 To estimate the adverse event profile of ponatinib

2.3 Translational/Correlative Research

2.31 Establish preliminary correlations between FGFR2 fusions and evidence of any clinical benefit

2.32 Assess preliminary evaluation of FGFR2 pathway perturbation with ponatinib

2.33 To describe patient-reported health-related quality of life and symptoms

3.0 Patient Eligibility

3.1 Inclusion Criteria

3.11 Age ≥18 years

3.12 Histological/cytological confirmation of biliary cancer.

3.13 Confirmation of advanced biliary cancer that is refractory or intolerant to gemcitabine or fluoropyrimidine based therapy with FGFR2 fusion [using Next-Gen sequencing assays (such as Foundation One®) or fluorescent in situ hybridization (FISH) break-apart assays] or FGFR pathway mutation/amplification [using Next-Gen sequencing assays (such as Foundation One®)]. Assays must be performed in a CLIA certified laboratory and done as a CLIA validated test or RUO in a CLIA laboratory.

3.14 Measurable disease as defined in Section 11.0.

3.15 ECOG Performance Status (PS) 0, 1 or 2 (Appendix I).

3.16 The following laboratory values obtained ≤ 14 days prior to registration.
- Absolute neutrophil count (ANC) ≥ 1500/mm^3
- Platelet count ≥ 100,000/mm^3
- Hemoglobin ≥ 9.0 g/dL
- Total bilirubin ≤ 1.5 x upper limit of normal (ULN), unless due to Gilbert's syndrome
- Aspartate transaminase (AST) and Alanine Aminotransferase (ALT) < 3 x ULN
- Creatinine ≤ 1.5 x upper limit of normal (ULN)
- Serum lipase and amylase ≤ 2.5 x upper limit of normal (ULN). Note: If subject has tumor involvement in the liver ≤ 3 x ULN.

3.17 Negative pregnancy test done ≤ 7 days prior to registration, for women of childbearing potential only.

3.18 Recovered from prior radiotherapy and/or systemic therapy related toxicities to Grade ≤ 1

3.19a Provide informed written consent.

3.19b Life expectancy ≥ 3 months

3.19c Willing to return to enrolling institution for follow-up (during the Active Monitoring Phase of the study).

*Note: During the **Active Monitoring** Phase of a study (i.e., active treatment and observation), participants must be willing to return to the consenting institution for follow-up.*

3.19d Female and male patients who are fertile agree to use an effective form of contraception with their sexual partners from registration through 4 months after the end of treatment.

3.19e Ability to complete questionnaire(s) by themselves or with assistance.

3.2 Exclusion Criteria

3.21 Any of the following because this study involves an investigational agent 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

3.22 Co-morbid systemic illnesses or other severe concurrent disease which, in the judgment of the investigator, would make the patient inappropriate for entry into

this study or interfere significantly with the proper assessment of safety and toxicity of the prescribed regimens.

3.23 Immunocompromised patients and patients known to be HIV positive and currently receiving antiretroviral therapy. NOTE: Patients with a known history of HIV infection are not eligible for this trial.

3.24 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

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

3.26 Prior systemic chemotherapy, radiation therapy or major surgery ≤ 30 days prior to registration.

3.27 Concurrent use of any other approved or investigational anticancer agents, including hormonal agents

3.28 Prior nitrosourea or mitomycin C <= 6 weeks prior to registration.

3.29a Patients with gastrointestinal comoribidities that would affect intake or absorption of ponatinib

3.29b Untreated or progressive brain metastases

3.29c Prior treatment with or allergic reactions attributed to compounds of similar chemical or biologic composition to ponatinib

3.29d Clinically uncontrolled hypertension (diastolic blood pressure >90 mm Hg; systolic >140 mm Hg). NOTE: Patients with hypertension should be undergoing treatment at study entry for blood pressure control.

3.29e Previous or concurrent malignancy except adequately treated basal or squamous cell skin cancer, in situ carcinoma of the cervix, or other solid tumor treated curatively and without evidence of recurrence for at least 5 years

3.29f History of significant bleeding disorder unrelated to cancer

3.29g History of acute pancreatitis within 1 year prior to registration, chronic pancreatitis, alcohol abuse or uncontrolled hypertriglyceridemia (triglycerides >450 mg/dL)

3.29h Clinically significant, uncontrolled, or active cardiovascular disease, specifically including, but not restricted to:

- Any history of myocardial infarction, stroke, or revascularization
- Unstable angina or transient ischemic attack within 6 months prior to registration

- Congestive heart failure within 6 months prior to registration, or left ventricular ejection fraction (LVEF) less than lower limit of normal per local institutional standards within 6 months prior to registration
- History of clinically significant (as determined by the treating physician) atrial arrhythmia
- Any history of ventricular arrhythmia
- Active venous thromboembolism including deep venous thrombosis or pulmonary embolism that is not amenable to treatment with anticoagulants.
- Patients with congenital prolonged QT syndromes and abnormal baseline prolonged QTc (>450 ms in men and >470 ms in women).
- Patients with an ejection fraction ≤ 50% as assessed by a baseline echocardiogram.

3.29i Taking medications that are known to be associated with Torsades de Pointes (see Appendix XII)

3.29j Taking any medications or herbal supplements that are known to be strong inhibitors of CYP3A4 ≤14 days prior to registration. (see Section 9.9b)

4.0 Test Schedule

Cycle = 28 days

	Active Monitoring Phase						
Tests and procedures	≤14 days prior to registration	Cycle 1 Day 1 (± 2 days)prior to treatment	Cycle 1 Days 8, 15, 22 prior to treatment	Cycle 2 and beyond Day 1 (± 2 days) prior to treatment	Q 8 weeks from Cycle 1 Day 1 (± 5 days)	Every 3 Cycles starting at end of Cycle 3 (± 5 days)	End of treatment
History and exam, wt, ECOG	X			X			X
Height, Child Pugh score	X						
Vitals[3]	X	X	X	X			X
Hematology group WBC, ANC, Hgb, PLT	X	X	X	X			X
Chemistry group Sodium, potassium, chloride, bicarbonate, total protein, albumin, calcium, glucose, BUN, total bilirubin, creatinine, alkaline phosphatase, SGOT (AST), SGPT (ALT)	X	X		X			X
Amylase[R]	X	X	X	X			
Lipase[R]	X	X	X	X			
CA19-9		X		X[5]			
EKG[R]	X					X	
Echocardiogram	X			X[10]			
Tumor measurement and Imaging (CT or MRI as clinically	X[1]				X[2]		

indicated)							
Pregnancy test	X[4]						
Patient questionnaire booklet	X[9]			X[9]			
Adverse event assessment	X		X	X			
Research Archival Tissue (optional)	X[8]						
Research Tissue Biopsy (optional)				X[7,R]			X[6]
Research blood samples (Optional)	X			X			X

1. Imaging studies such as CT scans, and MRIs can be performed ≤28 days prior to registration. Use same imaging throughout the study. Assessment by physical exam should be done ≤14 days prior to registration.
2. Tumor assessment must be performed at least every 8 weeks. Tumor assessment should be performed at any time during the treatment cycle that disease progression is clinically suspected so that patient can go off treatment and receive other therapy.
3. Includes weight, blood pressure, pulse and temperature
4. Women of childbearing potential only. Must be done ≤7 days prior to registration.
5. Only to be collected if > ULN on Cycle 1 Day 1
6. If patient has experienced disease progression and at such time a standard of care biopsy is ordered by the treating physician, waste specimen will be collected, fresh frozen and stored for future correlative studies. Perform only if archival specimen was available.
7. Perform only if archival specimen was available.
8. Archival FFPE and/or fresh frozen tissue collected in setting of standard of care procedures.
9. Patient questionnaire booklet must be used; copies are not acceptable for this submission. Booklet should be completed by patient prior to review of treatment response and discussions of patient's general health since last treatment evaluation.

10 Echocardiograms to be completed at baseline and then every 2 cycles for the duration of study treatment.

R Research funded (see Section 19.0).

5.0 Stratification Factors: None.

6.0 Registration/Randomization Procedures

6.1 To register a patient, access the Mayo Clinic Cancer Center (MCCC) web page and enter the registration/randomization application. The registration/randomization application is available 24 hours a day, 7 days a week. Back up and/or system support contact information is available on the Web site. If unable to access the Web site, call the MCCC Registration Office at ([redacted] between the hours of 8 a.m. and 4:30 p.m. Central Time (Monday through Friday).

The instructions for the registration/randomization application are available on the MCCC web page [redacted] and detail the process for completing and confirming patient registration. Prior to initiation of protocol treatment, this process must be completed in its entirety and a MCCC subject ID number must be available as noted in the instructions. It is the responsibility of the individual registering the patient to confirm the process has been successfully completed prior to release of the study agent. Patient registration via the registration/randomization application can be confirmed in any of the following ways:

- Contact the MCCC Registration Office [redacted]. If the patient was fully registered, the MCCC Registration Office staff can access the information from the centralized database and confirm the registration.
- Refer to "Instructions for Remote Registration" in section "Finding/Displaying Information about A Registered Subject."

6.2 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 (fax: [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.

When the study has been permanently closed to patient enrollment, submission of annual IRB approvals to the Registration Office is no longer necessary.

6.3 Prior to accepting the registration, registration 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

6.4 An optional correlative research component is part of this study, there will be an option to select if the patient is to be registered onto this component (see Sections 14.0 and 17.0).

- Patient has/has not given permission to have a tissue biopsy at cycle 2, day 1.
- Patient has/has not given permission to allow any excess tissue collected while on this study to be used for research studies
- Patient has/has not given permission for blood collection at screening, Prior to each cycle, and at end of study to be used for research studies.

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

- Patient has/has not given permission for his/her tissue and blood sample(s) to be stored and used in future research of biliary cancer at Mayo Clinic
- Patient has/has not given permission for his/her tissue and blood sample(s) to be stored and used in future research at Mayo Clinic to learn about, prevent, or treat any other health problems
- Patient has/has not given permission for Mayo Clinic to give his/her tissue and blood sample(s) to researchers at other institutions

6.6 Treatment cannot begin prior to registration and must begin ≤ 7 days after registration.

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

6.8 All required baseline symptoms (see Section 10.6) must be documented and graded.

6.9a Treatment on this protocol must commence at a Mayo Clinic institution under the supervision of a medical oncologist.

6.9b Study drug is available on site.

6.9c Patient questionnaire booklet is available on site; copies are not acceptable for this submission.

7.0 Protocol Treatment

7.1 Treatment Schedule

Agent	Dose Level	Route	Day
Ponatinib	45mg once daily	PO	Days 1-28

7.2 For this protocol, the patient must return to the consenting institution for evaluation at least every 28 days (+/- 2 days) during treatment (Active Monitoring Phase).

7.3 Patients should receive low-dose aspirin (e.g. 81mg/day), as prophylaxis against arterial thrombotic events, if not contraindicated.

7.4 Patients should receive treatment with a statin, as prophylaxis against arterial thrombotic events, if not contraindicated. Atorvastation, 10-20 mg per day, is suggested.

8.0 Dosage Modification Based on Adverse Events

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 8.2)

Dose Level	Ponatinib
0*	45mg PO once daily
-1	30mg PO once daily
-2	15mg PO once daily

*Dose level 0 refers to the starting dose.

8.2

→ → *Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* unless otherwise specified* ← ←			
CTCAE System/Organ/Class (SOC)	**ADVERSE EVENT**	**AGENT**	**ACTION****
BASED ON INTERVAL ADVERSE EVENT			
Investigations	Neutrophil count decreased ≥ Grade 3	Ponatinib	Omit ponatinib Resume at 45 mg after recovery to ≤ grade 1 Recurrence at 45 mg: Omit ponatinib Resume at 30 mg after recovery to ≤ grade 1 Recurrence at 30 mg: Omit ponatinib Resume at 15 mg after recovery to ≤ grade 1 Recurrence at 15 mg: Discontinue ponatinib

→ → *Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* unless otherwise specified* ← ←			
CTCAE System/Organ/Class (SOC)	**ADVERSE EVENT**	**AGENT**	**ACTION****
	Platelet count decreased ≥ Grade 3		Omit ponatinib Resume at 45 mg after recovery to ≤ grade 1 Recurrence at 45 mg: Omit ponatinib Resume at 30 mg after recovery to ≤ grade 1 Recurrence at 30 mg: Omit ponatinib Resume at 15 mg after recovery to ≤ grade 1 Recurrence at 15 mg: Discontinue ponatinib
	Serum amylase increased ≥ Grade 3 with no radiographic findings	Ponatinib	Omit ponatinib Resume at 45 mg after recovery to ≤ grade 1 Recurrence at 45 mg: Omit ponatinib Resume at 30 mg after recovery to ≤ grade 1 Recurrence at 30 mg: Omit ponatinib Resume at 15 mg after recovery to ≤ grade 1 Recurrence at 15 mg: Discontinue ponatinib
	Serum amylase increased ≥ Grade 3 with radiographic findings or Grade 4	Ponatinib	Omit ponatinib Repeat imaging according to clinical care After resolution by imaging, resume at 30 mg after recovery to ≤grade 1 Recurrence at 30 mg: Repeat above Resume at 15 mg after recovery to ≤ grade 1 Recurrence at 15 mg: Discontinue ponatinib

→ → *Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* unless otherwise specified* ← ←			
CTCAE System/Organ/Class (SOC)	**ADVERSE EVENT**	**AGENT**	**ACTION****
	Alanine aminotransferase increased (ALT) and/or Aspartate aminotransferase increased (AST) ≥ Grade 3	Ponatinib	Omit ponatinib Resume at 30 mg after recovery to ≤ grade 1 Recurrence at 30 mg: Omit ponatinib Resume at 15 mg after recovery to ≤ grade 1 Recurrence at 15 mg: Discontinue ponatinib
	Alanine aminotransferase increased (ALT) **OR** Aspartate aminotransferase increased (AST) ≥ Grade 3 **AND** Blood bilirubin increased ≥ 2 x ULN **AND** Alkaline phosphatase > 2 x ULN	Ponatinib	Discontinue ponatinib
Gastrointestinal Disorders	Pancreatitis ≥ Grade 2	Ponatinib	Omit ponatinib Perform ultrasound or abdominal CT scan with contrast If imaging is positive, continue to omit ponatinib and repeat according to clinical care If imaging is negative, or after resolution by imaging, resume at 45 mg after recovery to ≤ grade 1 Recurrence at 45 mg: Repeat above, except resume at 30 mg after recovery to ≤ grade 1 Recurrence at 30 mg: Repeat above, except resume at 15 mg after recovery to ≤ grade 1 Recurrence at 15 mg: Discontinue ponatinib

→ → *Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* unless otherwise specified* ← ←			
CTCAE System/Organ/Class (SOC)	**ADVERSE EVENT**	**AGENT**	**ACTION****
	Pancreatitis ≥ Grade 3	Ponatinib	Omit ponatinib Perform ultrasound or abdominal CT scan with contrast If imaging is positive, continue to omit ponatinib and repeat according to clinical care If imaging is negative, or after resolution by imaging, resume at 30 mg after recovery to ≤ grade 1 Recurrence at 30 mg: Repeat above, except resume at 15 mg after recovery to ≤ grade 1 Recurrence at 15 mg: Discontinue ponatinib
	Pancreatitis ≥ Grade 4	Ponatinib	Discontinue ponatinib
Nervous System Disorders	Stroke any Grade	Ponatinib	Discontinue ponatinib
	Peripheral sensory neuropathy ≥ Grade 2	Ponatinib	Please see section 8.43 below for guidance
Cardiac Disorders	Left ventricular systolic dysfunction ≥ Grade 3	Ponatinib	Omit ponatinib Resume at 45 mg after recovery to ≤ grade 1 Recurrence at 45 mg : Omit ponatinib Resume at 30 mg after recovery to ≤ grade 1 Recurrence at 30 mg: Omit ponatinib Resume at 15 mg after recovery to ≤ grade 1 Recurrence at 15 mg: Discontinue ponatinib
	Left ventricular systolic dysfunction ≥ Grade 4		Discontinue ponatinib
	Myocardial Infarction any Grade		Discontinue ponatinib

→ → *Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* unless otherwise specified* ← ←			
CTCAE System/Organ/Class (SOC)	**ADVERSE EVENT**	**AGENT**	**ACTION****
Skin and subcutaneous tissue disorders	Rash maculo-papular ≥ Grade 2 despite optimal symptomatic therapy	Ponatinib	Omit ponatinib Resume at 45 mg after recovery to ≤ grade 1 Recurrence at 45 mg: Omit ponatinib Resume at 30 mg after recovery to ≤ grade 1 Recurrence at 30 mg: Omit ponatinib Resume at 15 mg after recovery to ≤ grade 1 Recurrence at 15 mg: Discontinue ponatinib
	Rash maculo-papular ≥ Grade 3 despite optimal symptomatic therapy		Omit ponatinib Resume at 30 mg after recovery to ≤ grade 1 Recurrence at 30 mg: Omit ponatinib Resume at 15 mg after recovery to ≤ grade 1 Recurrence at 15 mg: Discontinue ponatinib
Vascular Disorders			
	Thromboembolic event ≥ Grade 1		Discontinue ponatinib

→ → *Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* unless otherwise specified* ← ←			
CTCAE System/Organ/Class (SOC)	**ADVERSE EVENT**	**AGENT**	**ACTION****
	Hypertension Grade 2 or 3		Antihypertensive medication should be initiated or optimized to achieve target blood pressure before interruption or dose reduction of the study treatment at the discretion of the investigator. If hypertension is persistent despite adequate anti-HTN therapy including titration of anti-HTN medication or introduction of additional anti-HTN medications, dose interruption and reduction is recommended according to the below guidelines: Hold ponatinib Resume at 30 mg after recovery to ≤ grade 1 Recurrence at 30 mg Omit ponatinib Resume at 15 mg after recovery to ≤ grade 1 Recurrence at 15 mg Discontinue ponatinib
	Hypertension ≥ Grade 4	Ponatinib	Omit ponatinib Resume at 30 mg after recovery to ≤ grade 1 Recurrence at 30 mg Omit ponatinib Resume at 15 mg after recovery to ≤ grade 1 Recurrence at 15 mg Discontinue ponatinib
Injury, poisoning and procedural complications	Wound complication ≥ Grade 2	Ponatinib	See section 8.47 for guidance
General disorders and administrative site conditions	Edema limbs ≥ Grade 2	Ponatinib	See section 8.45 for guidance
Eye Disorders	Eye Disorders – Other	Ponatinib	See section 8.44 for guidance

→ → *Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* unless otherwise specified* ← ←			
CTCAE System/Organ/Class (SOC)	**ADVERSE EVENT**	**AGENT**	**ACTION****
Other Non-Hematologic events	≥ Grade 3	Ponatinib	Omit drug and follow patient at least weekly until adverse event has resolved to grade ≤ 2, restart agent at next lower dose level. See sections 8.41 through 8.47 for guidance on other non-hematologic events

* Located at http:/ctep.cancer.gov/protocolDevelopment/electronic_applications.ctc.htm

** Use the following to describe actions in the Action column:

- Omit = Treatment is not given for the day/days that are omitted and will not be made up, but treatment may resume once the adverse event has resolved as mandated in Table 8.2. For example, if treatment is omitted on Day 8, but the adverse event has resolved by Day 15, treatment may resume on Day 15.
- Hold/Delay = Treatment can be made up as part of this cycle
- Discontinue = Treatment is totally stopped

NOTE: 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 the dose may be increased, at the investigator's discretion, one level at a time, in the following cycles.

NOTE: 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, if the decision is made for the patient to be kept on study. These dose reductions must be clearly recorded in reported clinical data.

8.3 A new course of treatment may begin on the scheduled Day 1 of a new cycle if:

- The ANC is ≥ 1500/μL;
- The platelet count is ≥ 75,000/μL;
- Any other Ponatinib related adverse event that may have occurred has resolved to ≤ Grade 1 or baseline severity.

If these conditions are not met on scheduled Day 1 of a new cycle, the subject will be evaluated at least weekly and the new cycle of treatment will not be initiated until the adverse event has resolved as described above.

When therapy is resumed it will be considered day one of this new cycle. If Ponatinib was halted during the previous cycle and was restarted with a one-level dose reduction without requiring an interruption for the remainder of the cycle, then that reduced dose level will be initiated on Day 1 of the new cycle. **If ponatinib was omitted for the remainder of the previous cycle or if the new cycle is delayed due to adverse event newly encountered on the scheduled Day 1**, then the scheduled cycle will be started with a one-level dose reduction. If the study drug cannot be restarted within 28 days of the

scheduled Day 1 of a given cycle, the patient will be removed from study treatment and will proceed to event monitoring.

8.4 Additional adverse event guidance:

8.41 Hepatotoxicity: Iclusig can cause hepatotoxicity, including liver failure and death. Fulminant hepatic failure leading to death occurred in an Iclusig-treated patient within one week of starting Iclusig. Two additional fatal cases of acute liver failure also occurred. The fatal cases occurred in patients with blast phase CML (BP-CML) or Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL). Severe hepatotoxicity occurred in all disease cohorts. Iclusig treatment may result in elevation in ALT, AST, or both. Monitor liver function tests at baseline, then at least monthly or as clinically indicated. Interrupt, reduce, or discontinue Iclusig as clinically indicated.

8.42 Pancreatitis: Clinical pancreatitis occurred in 6% (28/449) of patients (5%, grade 3) treated with Iclusig. Pancreatitis resulted in discontinuation or treatment interruption in 6% of patients (25/449). The incidence of treatment-emergent lipase elevation was 41%. Check serum lipase every 2 weeks for the first 2 months and then monthly thereafter or as clinically indicated. Consider additional serum lipase monitoring in patients with a history of pancreatitis or alcohol abuse. Dose interruption or reduction may be required. In cases where lipase elevations are accompanied by abdominal symptoms, interrupt treatment with Iclusig and evaluate patients for pancreatitis. Do not consider restarting Iclusig until patients have complete resolution of symptoms and lipase levels are less than 1.5 x ULN.

8.43 Neuropathy: Peripheral and cranial neuropathy have occurred in Iclusig-treated patients. Overall, 13% (59/449) of Iclusig-treated patients experienced a peripheral neuropathy event of any grade (2%, grade 3/4). In clinical trials, the most common peripheral neuropathies reported were peripheral neuropathy (4%, 18/449), paresthesia (4%, 17/449), hypoesthesia (2%, 11/449), and hyperesthesia (1%, 5/449). Cranial neuropathy developed in 1% (6/449) of Iclusig-treated patients (<1%, grade 3/4). Of the patients who developed neuropathy, 31% (20/65) developed neuropathy during the first month of treatment. Monitor patients for symptoms of neuropathy, such as hypoesthesia, hyperesthesia, paresthesia, discomfort, a burning sensation, neuropathic pain, or weakness. Consider interrupting Iclusig and evaluate if neuropathy is suspected.

8.44 Ocular Toxicity: Serious ocular toxicities leading to blindness or blurred vision have occurred in Iclusig-treated patients. Retinal toxicities including macular edema, retinal vein occlusion, and retinal hemorrhage occurred in 3% of Iclusig-treated patients. Conjunctival or

corneal irritation, dry eye, or eye pain occurred in 13% of patients. Visual blurring occurred in 6% of the patients. Other ocular toxicities include cataracts, glaucoma, iritis, iridocyclitis, and ulcerative keratitis. Conduct comprehensive eye exams at baseline and periodically during treatment.

8.45 Fluid Retention: Serious fluid retention events occurred in 3% (13/449) of patients treated with Iclusig. One instance of brain edema was fatal. In total, fluid retention occurred in 23% of the patients. The most common fluid retention events were peripheral edema (16%), pleural effusion (7%), and pericardial effusion (3%). Monitor patients for fluid retention and manage patients as clinically indicated. Interrupt, reduce, or discontinue Iclusig as clinically indicated.

8.46 Cardiac Arrhythmias: Symptomatic bradyarrhythmias that led to a requirement for pacemaker implantation occurred in 1% (3/449) of Iclusig-treated patients. Advise patients to report signs and symptoms suggestive of slow heart rate (fainting, dizziness, or chest pain). Supraventricular tachyarrhythmias occurred in 5% (25/449) of Iclusig-treated patients. Atrial fibrillation was the most common supraventricular tachyarrhythmia and occurred in 20 patients. For 13 patients, the event led to hospitalization. Advise patients to report signs and symptoms of rapid heart rate (palpitations, dizziness). Interrupt Iclusig and evaluate.

8.47 Compromised Wound Healing and Gastrointestinal Perforation: Since Iclusig may compromise wound healing, interrupt Iclusig for at least 1 week prior to major surgery. Serious gastrointestinal perforation (fistula) occurred in one patient 38 days post-cholecystectomy.

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 (42) Update of Recommendations for the Use of Hematopoietic Colony-Stimulating Factors: Evidence-Based, Clinical Practice Guidelines. J Clin Oncol July 1, 2006, vol. 24 no. 19 3187-3205.

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 **Vascular Occlusion**

Arterial and venous thrombosis and occlusions, including fatal myocardial infarction, stroke, stenosis of large arterial vessels of the brain, severe peripheral vascular disease, and the need for urgent revascularization procedures have occurred in at least 27% of Iclusig-treated patients from the phase 1 and phase 2 trials. Iclusig can cause fatal and life-threatening vascular occlusion within 2 weeks of starting treatment. Iclusig can also cause recurrent or multi-site vascular occlusion.

The median time to onset of the first vascular occlusion event was 5 months. Iclusig can cause fatal and life threatening vascular occlusion in patients treated at dose levels as low as 15 mg per day.

Patients with and without cardiovascular risk factors, including patients age 50 years or younger, experienced these events. Vascular occlusion adverse events were more frequent with increasing age and in patients with prior history of ischemia, hypertension, diabetes, or hyperlipidemia (see Table 4).

Clinicians should consider whether the benefits of Iclusig treatment are expected to exceed the risks of therapy. In patients suspected of developing arterial thrombotic events, interrupt or stop Iclusig. A benefit-risk consideration should guide a decision to restart Iclusig therapy. Consider dose modification or discontinuation of Iclusig in patients who develop serious venous thromboembolism and **Monitor for evidence of thromboembolism and vascular occlusion. Interrupt or stop Iclusig immediately for vascular occlusion.**

9.5 **Hypertension**

Treatment-emergent hypertension occurred in 67% of patients (300/449). Eight (2%) treated with Iclusig in clinical trials experienced treatment-emergent symptomatic hypertension as a serious adverse reaction, including hypertensive crisis. Patients may require urgent clinical intervention for hypertension associated with confusion, headache, chest pain, or shortness of breath *[see Adverse Reactions (6)]*. In patients with baseline systolic BP<140 mm Hg and baseline diastolic BP<90mm Hg, 78% (220/282) experienced treatment-emergent hypertension; 49% (139/282) developed Stage 1 hypertension (defined as systolic BP≥140 mm Hg or diastolic BP≥90 mm Hg) while 29% developed Stage 2 hypertension (defined as systolic BP≥160 mm Hg or diastolic BP≥100 mm Hg). In 131 patients with Stage 1 hypertension at baseline, 61% (80/131) developed Stage 2 hypertension. Monitor and manage blood pressure elevations during Iclusig use and treat hypertension to normalize blood pressure. Interrupt, dose reduce, or stop Iclusig if hypertension is not medically controlled.

9.6 **Heart Failure**

Fatal and serious heart failure or left ventricular dysfunction occurred in 5% of Iclusig-treated patients (N =22). Eight percent of patients (N= 35) experienced any grade of heart failure or left ventricular dysfunction. Monitor patients for signs or symptoms consistent with heart failure and treat as clinically indicated, including interruption of Iclusig. Consider discontinuation of Iclusig in patients who develop serious heart failure

9.7 **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 antidiarrheals.

If diarrhea is severe (requiring intravenous rehydration) and/or 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 hospitalized** for intravenous hydration and correction of electrolyte imbalances.

9.8 **TLS:** Clinically significant Tumor Lysis Syndrome (TLS) has been reported at the initiation of treatment with TKIs in CML patients. The patients at risk of TLS are those with high tumor/leukemic burden prior to treatment. These patients should be monitored closely, especially at the initiation of treatment. Appropriate TLS precautions and prophylactic treatment (such as aggressive hydration with fluids and the initiation of allopurinol 600 mg/day or other appropriate treatments) should be initiated prior to the start of therapy for those at risk for TLS. Rasburicase and other appropriate treatments for hyperuricemia or TLS are permitted.

9.9a **Prolonged QTcF**: If a prolongation of QTcF is observed, it is important to perform serum electrolyte analysis (including potassium, calcium, and magnesium) and correct any significant abnormalities with supplements if below normal limits. It is also necessary to review all concomitant medications the patient is on and discontinue medications that are known or suspected to cause QT prolongation.
If no contributing reason is identified and the reason for QTcF prolongation is believed to be due to study medication, dose interruption and reduction guidelines for general non-hematologic toxicities in 8.2 for ponatinib should be followed. Additionally, weekly ECG monitoring is recommended for 4 weeks upon resumption of study drug, then monthly for 6 months, and then every 3 months for the remainder of the study, or more frequently as clinically indicated.

9.9b Based on *in vitro* studies, ponatinib is a substrate of CYP3A4/5 and to a lesser extent CYP2C8 and CYP2D6. Ponatinib also inhibits the P-glycoprotein (P-gp), ATP-binding cassette G2 (ABCG2) [also known as BCRP], and bile salt export pump (BSEP) transporter systems *in vitro*.

<u>Drugs That Are Strong Inhibitors of CYP3A Enzymes</u>
In a drug interaction study in healthy volunteers, co-administration of Iclusig with ketoconazole increased plasma ponatinib AUC0-inf and Cmax by 78% and 47%, respectively. When administering Iclusig with strong CYP3A inhibitors (e.g., boceprevir, clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole), the recommended starting dose should be reduced at the discretion of the treating physician. Patients taking concomitant strong inhibitors may be at increased risk for adverse reactions.

Drugs That Are Strong Inducers of CYP3A Enzymes
Coadministration of Iclusig with strong CYP3A inducers was not evaluated *in vitro* or in a clinical trial; however, a reduction in ponatinib exposure is likely. Coadministration of strong CYP3A inducers (e.g., carbamazepine, phenytoin, rifampin, and St. John's Wort) with Iclusig should be avoided unless the benefit outweighs the possible risk of ponatinib underexposure. Monitor patients for signs of reduced efficacy.

Drugs That Elevate Gastric pH
Coadministration of Iclusig with drugs that elevate the gastric pH was not evaluated in a clinical trial. Based on the chemical properties of ponatinib, elevated gastric pH may reduce bioavailability and exposure. Coadministration of Iclusig with drugs that elevate the gastric pH (e.g., proton pump inhibitors, H2 blockers, or antacids) should be avoided unless the benefit outweighs the possible risk of ponatinib underexposure. Monitor patients for signs of reduced efficacy.

Drugs That Are Substrates of the P-gp or ABCG2 Transporter Systems
In vitro studies demonstrate that Iclusig inhibits the P-gp and ABCG2 [also known as BCRP] transporter systems. The effect of coadministration of Iclusig with sensitive substrates of the P-gp (e.g., aliskiren, ambrisentan, colchicine, dabigatran etexilate, digoxin, everolimus, fexofenadine, imatinib, lapatinib, maraviroc, nilotinib, posaconazole, ranolazine, saxagliptin, sirolimus, sitagliptin, tolvaptan, topotecan) and ABCG2 [also known as BCRP] (e.g., methotrexate, mitoxantrone, imatinib, irinotecan, lapatinib, rosuvastatin, sulfasalazine, topotecan) transporter systems on exposure of these substrates has not been evaluated in clinical studies.

10.0 Adverse Event (AE) Reporting and Monitoring

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 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site: (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm)

10.11 Adverse event monitoring and reporting is a routine part of every clinical trial. First, identify and grade the severity of the event using the CTCAE version 4.0. Next, determine whether the event is expected or unexpected (see Section 10.2) and if the adverse event is related to the medical treatment or procedure (see Section 10.5). With this information, determine whether the event must be reported as an expedited report (see Section 10.). Expedited reports are to be completed within the timeframes and via the mechanisms specified in Sections 10.4. 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).

10.12 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). Grade is an essential element of the Guidelines and, in general, relates to **severity** for the purposes of regulatory reporting to NCI.

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.

10.13 Medical conditions/diseases present before starting study treatment are only considered adverse events if they worsen after starting study treatment (any procedures specified in the protocol). Adverse events occurring before starting study treatment but after signing the informed consent form are recorded. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms or require therapy, and are recorded.

10.14 Any serious adverse event occurring after the patient has provided informed consent, has started taking the study medication, and until 4 weeks after the patient has stopped study participation must be reported. This includes the period in which the study protocol interferes with the standard medical treatment given to a patient (e.g. treatment withdrawal during washout period, change in treatment to a fixed dose of concomitant medication). The period after discontinuing study drug may be extended if there is a strong suspicion that the drug has not yet been eliminated.

10.2 Expected vs. Unexpected Events

- The determination of whether an AE is expected is based on agent-specific information provided in Section 15.0 of the protocol and the study specific consent form.

- Unexpected AEs are those not listed in the agent-specific information provided in Section 15.0 of the protocol and the study specific consent form.

NOTE: "Unexpected adverse experiences" means any adverse experience that is neither identified in nature, severity, or frequency of risk in the information provided for IRB review nor mentioned in the consent form.

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 and the adverse event.

10.31 **AEs Experienced Utilizing Investigational Agents and Commercial Agent(s) on the SAME Arm**

NOTE: When a commercial agent(s) is (are) used on the same treatment arm as the investigational agent/intervention (also, investigational drug, biologic, cellular product, or other investigational therapy under an IND), the entire combination (arm) is then considered an investigational intervention for reporting.

Routine Reporting

- Routine AE reporting for Phase 1 and Phase 2 clinical studies using an investigational agent /intervention in combination with a commercial agent is stated in the protocol. See Section 10.6.

- Routine AE reporting for Phase 3 clinical studies using an investigational agent/intervention and a commercial agent in combination must be reported as defined by the general guidelines provided by sponsors, Groups, Cancer Centers, or Principal Investigators. See Section 10.6.

Expedited Reporting

- An AE that occurs on a combination study must be assessed in accordance with the guidelines for investigational agents/interventions in Section 10.4, and where indicated, an expedited report must be submitted.

- An AE that occurs prior to administration of the investigational agent/intervention must be assessed as specified in the protocol. In general, only Grade 4 and 5 AEs that are unexpected with at least possible attribution to the commercial agent require an expedited report. Refer to Section 10.4 for specific AE reporting requirements or exceptions.

- Commercial agent expedited reports must be submitted to the FDA via MedWatch.

- 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, expedited reporting is required. The clinical investigator must determine severity.

10.4 Expedited Reporting Requirements for IND/IDE Agents

Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention [1, 2]

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 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	7 Calendar Days (see below timelines)	24-Hour 3 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in Section 10.41 of the protocol.
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. Please report to ARIAD within 2 business days.

[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

Additional instructions:
Use paper Adverse Event Expedited Report – Single Agent report available in forms packet (AdEERs). Fax a copy of the AdEERs report to ARIAD or ARIAD's designee within 2 business days of awareness of the serious adverse event to [redacted] **(back-up email:** [redacted] **Provide reports to ARIAD of all** adverse events related to the Study which have been submitted by Mayo Clinic to the

appropriate regulatory authorities in accordance with Applicable Law, within 24 hours after reporting including the submission documents.

Provide copies, along with the UPIRTSO cover sheet, by fax [redacted] to the MCCC Regulatory Affairs Unit (RAU) Risk Information Specialist who will determine and complete IRB reporting. The RAU will submit to the MCCC SAE Coordinator and the MCCC IND Coordinator to determine if FDA submission is needed.

EVENT TYPE	REPORTING PROCEDURE
Other Grade 4 or 5 Events and/or Any Hospitalizations During Treatment Not Otherwise Warranting an Expedited Report	Complete a Notification Form: Grade 4 or 5 Non-AER Reportable Events/Hospitalization Form electronically via the MCCC Remote Data Entry System or paper form within 5 working days of the date the clinical research associate (CRA) is aware of the event(s) necessitating the form. If an expedited written report has been submitted, this form does not need to be submitted.

10.41 Adverse Events of Special Interest (AESIs)

Vascular occlusive events have been identified as AESIs for ponatinib. These include arterial and venous thrombotic and occlusive adverse events that meet the criteria for SAEs (see section 10.1) and those adverse events that do not meet the SAE criteria. AESIs require ongoing monitoring by investigators and rapid identification and communication by the investigator to the study sponsor. All AESIs, whether SAEs or not, must be reported within 2 business days of the study sponsor awareness to ARIAD.

ARIAD has determined that the events listed below (whether considered serious or non-serious by investigators) should be considered AESIs:

A. Myocardial infarction: The Third Universal Definition of Myocardial Infarction (Thygesen et al, 2012) is used to define MI
B. Angina (newly diagnosed or worsening of existing angina or unstable angina)
C. Coronary artery disease (CAD) (newly diagnosed or worsening of existing CAD) or symptoms that may reflect cardiovascular disease (Thygesen et al, 2012)
D. Cerebrovascular ischemic disease including ischemic or hemorrhagic stroke, vascular stenosis, transient ischemic accident (TIA), cerebrovascular occlusive disease documented on diagnostic neuroimaging, or symptoms that may reflect cerebrovascular disease (Easton et al, 2009)
E. New onset or worsening of peripheral artery occlusive disease (eg, renal artery, mesenteric artery, femoral artery) or symptoms that may reflect peripheral vascular disease
F. Retinal vascular thrombosis, both venous and arterial
G. Venous thromboembolism where significant compromise of organ function or other significant consequences could result (eg, pulmonary embolism, portal vein thrombosis, renal vein thrombosis) or symptoms that may reflect venous thrombosis

ARIAD may request additional information to the study sponsor on observed AESIs and this information should be provided in a timely fashion (ie, within 2 business days of the study sponsor awareness).

All serious adverse events, whether "reportable" as defined in this protocol or not, must be reported to ARIAD. All expedited reports will be sent to ARIAD simultaneously or within 24 hours of study sponsor's submission to the competent authorities. Non-expedited SAE reports (except for AESIs) can be batched by the study sponsor and sent to ARIAD on a monthly basis. Also, any event of a vascular occlusive nature, either serious or non-serious, must be reported to ARIAD **within 2 business days** of the study sponsor's awareness.

The study PI or designee is responsible for faxing SAE reports to ARIAD Pharmaceuticals, Inc., at [redacted]. Reports may be emailed if fax is not available to [redacted]

10.42 Special Situations for Expedited Reporting

Exceptions to Expedited Reporting: EXPECTED Serious Adverse Events

An expedited report may not be required for specific Grade 1, 2 and 3 Serious Adverse Events where the AE is **EXPECTED**. Any protocol specific reporting procedures MUST BE SPECIFIED BELOW and will supersede the standard Expedited Adverse Event Reporting Requirements:

System Organ Class (SOC)	Adverse event/ Symptoms	CTCAE Grade at which the event will not be expeditedly reported
General disorders and administrations site conditions	Fatigue	Grade 3
Gastrointestinal Disorders	Nausea	Grade 3
	Vomiting	
	Diarrhea	
Investigations	Neutrophil count decreased	Grade 3 and Grade 4
	White blood cell count decreased	
	Platelet count decreased	
Blood and lymphatic system disorders	Anemia	Grade 3 and Grade 4

Specific protocol exceptions to expedited reporting should be reported expeditiously by investigators **ONLY** if they exceed the expected grade of the event and/or require hospitalization

10.5 Other Required Reporting

10.51 Persistent or Significant Disabilities/Incapacities

Any AE that results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions (formerly referred to as disabilities), congenital abnormities or birth defects, must be reported immediately if they occur at any time following treatment with an agent under an IND/IDE since they are considered to be a serious AE and must be reported to the sponsor as specified in 21 CFR 312.64(b).

10.52 Death

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.

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.

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 "Neoplasms benign, malignant and unspecified (incl cysts and polyps) – Other (Progressive Disease)"** under the system organ class (SOC) of the same name. 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.

10.53 Secondary Malignancy

4 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.

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

- Leukemia secondary to oncology chemotherapy (e.g., Acute Myelocytic 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.

10.54 Second Malignancy

6 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.

10.55 Pregnancy

To ensure patient safety, each pregnancy occurring while the patient is on study treatment must be reported to ARIAD within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.
Pregnancy should be recorded on a Clinical Study Pregnancy Form and reported by the investigator to the oncology ARIAD Drug Safety and Epidemiology (DS&E) department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the ARIAD study treatment of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

10.6 **Required Routine Reporting**
Adverse events to be graded at each evaluation and pretreatment symptoms/conditions to be evaluated at baseline per the CTCAE v4.0 grading unless otherwise stated in the table below:

System Organ Class (SOC)	Adverse event/Symptoms	Baseline	Each evaluation
General disorders and administrations site conditions	Fatigue	X	X
	Fever (Pyrexia)	X	X
	Edema limbs	X	X
Gastrointestinal Disorders	Nausea	X	X
	Vomiting	X	X
	# of stools	X	
	Diarrhea		X
	Constipation		X
	Abdominal pain	X	X
	Rash maculo-papular	X	X
Investigations	Neutrophil count decreased	X	X
	Platelet count decreased	X	X
	Cough	X	X
	Pneumonitis	X	X

10.61 Submit via appropriate MCCC Case Report Forms (i.e., paper or electronic, as applicable) the following AEs experienced by a patient and not specified in Section 10.6:

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

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

10.613 Grade 5 AEs (Deaths)

10.6131 Any death within 30 days of the patient's last study

treatment or procedure regardless of attribution to the study treatment or procedure.

10.6132 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 as a Grade 5 AE, with a CTCAE type and attribution assigned.

10.62 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). 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 8 weeks. In addition to a baseline scan, confirmatory scans should also be obtained 8 weeks following initial documentation of objective response.

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 not considered measurable disease.

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 at least 1 cm to less than 2 cm must use CT imaging 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.

- Chest X-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT scans are preferable.

- Physical Examination: For superficial non-nodal lesions, physical examination is acceptable, but imaging is preferable, if both can be done. In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

- 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.

  c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use

of FDG-PET in this circumstance has been described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

11.33 Measurement at Follow-up Evaluation:

- A subsequent scan must be obtained 8 weeks following initial documentation of an objective status of either complete response (CR) or partial response (PR).

- 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 (as there often will be), 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, but 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 Lesions & 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/Chest X-ray/physical examination 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:

For Patients with Measurable Disease

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 MCCC 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 to >3 level on ECOG scale.

12.0 Descriptive Factors

12.1 Anatomic Subtype: Intrahepatic cholangiocarcinoma vs Perihilar cholangiocarcinoma vs Distal cholangiocarcinoma vs Gallbladder vs Other (specify)

12.2 Family history of cancer: Yes vs No vs Unknown

12.3 Number of first degree relatives who have had cancer: 0 vs 1 vs 2 vs 3 vs 4 vs >/=5 vs Unknown

12.4 Primary risk factors:
- 12.4.1 Primary sclerosing cholangitis: Yes vs No vs Unknown
- 12.4.2 Cirrhosis: Yes vs No vs Unknown
- 12.4.3 Hepatitis C: Yes vs No vs Unknown
- 12.4.4 Hepatitis B: Yes vs No vs Unknown
- 12.4.5 Diabetes mellitus: Yes vs No vs Unknown
- 12.4.6 Choledochal cyst: Yes vs No vs Unknown
- 12.4.7 Non-Alcoholic Fatty Liver Disease: Yes vs No vs Unknown
- 12.4.8 Smoking: Yes vs No vs Unknown
- 12.4.9 Crohn's disease: Yes vs No vs Unknown
- 12.4.10 Ulcerative colitis: Yes vs No vs Unknown
- 12.4.11 Liver fluke infestation: Yes vs No vs Unknown
- 12.4.12 Caroli's disease: Yes vs No vs Unknown
- 12.4.13 Thorotrast exposure: Yes vs No vs Unknown

12.5 Definitive surgical procedure performed: Simple segmental resection vs Multiple segmental resections vs Lobectomy vs Extended lobectomy vs Whipple operation vs Bile duct resection and anastomosis or hepaticojejunostomy vs Other (specify)

12.6 Child-Pugh Classification (see Appendix X): Grade A (5-6 points) vs Grade B (7-9 points) vs Grade C (10-15 points)

12.7 ISHAK Fibrosis Score: 0 no fibrosis vs 1,2 portal fibrosis vs 3,4 fibrous septa vs 5 nodular formation and incomplete cirrhosis vs 6 established cirrhosis

12.8 Evidence of PSC in adjacent tissue: Ductopenia vs Ductal or ductular proliferation vs Concentric fibrosis of intrahepatic duct vs None

13.0 Treatment/Follow–up Decision at Evaluation of Patient

13.1 Patients who are CR, PR, or SD will continue treatment per protocol.

13.2 Patients who develop PD while receiving therapy will go to the event monitoring phase.

13.3 Patients who go off protocol treatment for reasons other than PD will go to the event monitoring phase per Section 18.0.

13.4 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.

- If the patient never received treatment, on-study material and the End of Active Treatment/Cancel Notification Form must be submitted. No further data submission is necessary.

13.5 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.

13.7 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 End of Active Treatment/Cancel Notification Form must be submitted. No further data submission is necessary.

14.0 Body Fluid Biospecimens

14.1 Body Fluid Biospecimens

14.11 Circulating tumor DNA analysis

Plasma samples will be collected pre-treatment, at the beginning of each cycle of treatment and at the end of active monitoring. These samples will be used to quantify tumor-specific somatic mutations, pre-identified in tumor biopsy analysis to assess whether ctDNA can track disease burden as seen on imaging in cholangiocarcinoma. A subset of these samples will be analysed using more extensive genomic methods such as whole exome sequencing to assess the potential of using ctDNA for molecular stratification and monitoring of acquired resistance.

14.12 Body fluid biospecimen submission

Study	**Optional or Mandatory**	**Body fluid**	**Tube**	**Volume**	**<14 days prior to registration**	**Cycle 2 and beyond Day 1**	**End of treatment**	**Process at site**	**Temperature conditions for storage**
ctDNA analysis plasma samples[1]	Optional	Blood	EDTA	10mL (2)	X	X	X	Y	Fractionated to plasma, 1mL aliquots stored at -80

1. If tumor biopsies or additional treatments are being administered the same day, blood samples for circulating DNA analysis should be collected before any tumor manipulation or treatment
2. Peripheral Blood Mononuclear Cells (PBMCs) should be isolated from the same blood sample as plasma at pre-registration screening visit and cycle 2 day 1 by isolating the buffy coat.

14.13 Collection and processing

Blood samples can be collected in EDTA tubes and processed as described in the lab processing instructions document. It's critical that blood samples are centrifuged twice as described as soon as possible and within approximately two hours of collection to minimize the possibility of WBC lysis that can affect our ability to measure ctDNA.

14.14 Shipping and Handling
All samples will be kept at Mayo Clinic Scottsdale campus in -80 freezer space until lab is ready for processing.

14.141 Kits will not be used for this study.

14.142 Shipping Specimens
Verify ALL sections of the Specimen Submission Forms are completed and filled in correctly.

Ship specimens via Priority Overnight service, **Monday – Thursday ONLY,** to:

Mayo Clinic
[redacted]

Do not send samples the day before, the day of, or the observed day of a national holiday.

All specimens must be shipped Monday – Thursday ONLY.

15.0 Drug Information

15.1 Ponatinib (AP24534, Iclusig™)

15.11 **Background**: Ponatinib (AP24534) is a novel, orally-available tyrosine kinase inhibitor (TKI). A primary target is BCR-ABL, an abnormal tyrosine kinase that is the hallmark of chronic myeloid leukemia (CML). BCR-ABL is expressed from a fusion gene formed by the rearrangement of the breakpoint cluster region (BCR) on chromosome 22 with the c-abl proto-oncogene (ABL) on chromosome 9 (BCR-ABL). Other targets of clinical interest include the kinases c-KIT (KIT), ret proto-oncogene (RET), and Fms-like tyrosine kinase-3 (FLT3).

15.12 **Formulation**: Ponatinib is a new chemical entity prepared by chemical synthesis. The ponatinib active pharmaceutical ingredient (API) is the mono-hydrochloride salt (AP24534 hydrochloride, or AP24534 HCl).

Ponatinib for investigational use is supplied as 15 mg and 45 mg round, white, film-coated tablets. The tablet formulation includes inactive ingredients lactose monohydrate, microcrystalline cellulose, sodium starch glycolate, colloidal silicon dioxide, magnesium stearate, polyethylene glycol, talc, polyvinyl alcohol, and titanium dioxide.

15.13 **Preparation and storage**: Ponatinib drug product is recommended for storage at controlled room temperature (20°C to 25°C [68°F to 77°F]).

15.14 **Administration:** Ponatinib tablets should be taken once daily, at approximately the same time each day.

In a study to assess the effect of both a high-fat and a low-fat meal on the bioavailability and pharmacokinetics of ponatinib, neither type of diet impacted the PK ponatinib. Ponatinib may be administered without regard to food intake.

15.15 **Pharmacokinetic information**:
a) Absorption – Maximum ponatinib blood levels generally occurred 4 to 6 hours following administration of ponatinib and the median t_{max} in the 15 through 60 mg cohorts was 4 hours. The mean steady-state Cmax and AUC appeared to increase in a manner approximately proportional with increasing dose, particularly in the 15- to 60-mg dose range. In the 15 mg cohort, the geometric mean Cmax on Day 29 was 48.5 nM (coefficient of variation [% CV] 49.3). Notably, daily doses of 15 mg achieved steady state C_{max} plasma concentrations that surpassed 40 nM, a concentration that is sufficient to inhibit viability of cells expressing all BCR-ABL mutants tested (by >50%), including T315I, and to suppress the emergence of any mutant clones in a preclinical mutagenesis assay.
b) Distribution – In vitro, ponatinib was found to be 99.9% bound to plasma proteins.
c) Metabolism – CYP3A4 and to a lesser extent CYP2C8, CYP2D6 and CYP3A5 are involved in the phase I metabolism of ponatinib in vitro. Ponatinib is also metabolized by esterases and/or amidases.
d) Excretion – Hepatic elimination is the major excretory route for ponatinib in humans. Following a single oral dose of 14C-labeled ponatinib, approximately 87% of the radioactive dose is recovered in the feces and approximately 5% in the urine. The steady-state terminal elimination half-life after oral administration of ponatinib in patients was between 20 and 29 hours for doses ≥15 mg.

15.16 **Potential Drug Interactions**: Based on in vitro studies, DDIs due to either CYP inhibition or induction by ponatinib are highly unlikely in

clinical trials using the recommended daily dose of 45 mg, and in investigational trials including doses as high as 60 mg. In vitro studies also demonstrate that human CYP3A4 is involved in the metabolism of ponatinib. In view of this, a drug interaction study was performed with a strong CYP3A4 inhibitor in healthy subjects. Ketoconazole co-administration increased ponatinib C_{max} and AUC by 47% and 78%, respectively. Also considering the role of CYP3A4 in the metabolism of ponatinib, a drug interaction study is underway with the strong CYP3A4 inducer rifampin. Results are not yet available. Since CYP3A4 contributes to the metabolism of ponatinib, strong inducers or inhibitors of CYP3A4 should be used with caution or avoided altogether.

Based on the chemical properties of ponatinib, elevated gastric pH may reduce bioavailability and exposure. Coadministration of ponatinib with lansoprazole, a drug that elevates the gastric pH, is currently under investigation in a clinical trial; however, results are not yet available. Coadministration of ponatinib with drugs that elevate the gastric pH (eg, proton pump inhibitors, H2 blockers, or antacids) should be avoided unless the benefit outweighs the possible risk of ponatinib underexposure.

In vitro studies demonstrate that ponatinib inhibits the P-gp and ABCG2 [also known as BCRP] transporter systems. The effect of coadministration of ponatinib with sensitive substrates of the P-gp and ABCG2 [also known as BCRP] transporter systems on exposure of these substrates has not been evaluated in clinical studies.

Drugs that are extensively bound to plasma proteins might displace ponatinib from binding sites in plasma and ponatinib might displace other drugs bound to plasma proteins. Caution should be observed when administering concomitant medications, such as warfarin, propranolol, phenytoin, and diazepam, which are extensively bound to plasma protein.

15.17 **Known potential toxicities:**

Side effects frequently reported (more than 10% of patients) include: An upper respiratory infection like the common cold, Low blood counts including white blood cells (which may increase the risk of infection), platelets (which may increase the risk of bleeding) or red blood cells (which can cause you to feel tired), Decreased appetite, Trouble getting adequate amount or quality of sleep, Headache, Dizziness, High blood pressure, Shortness of breath, Cough, Pain in the belly, Diarrhea, Vomiting, Constipation, Nausea, Increase lipase level (an enzyme measured in the blood that reflects function of the pancreas, Elevations in lipase may indicate inflammation of the pancreas), Increase liver enzymes (AST and ALT) which can indicate damage to cells in the liver, Skin Rash (reddened skin or red rash with or without raised bumps), Dry Skin, Pain that may occur in the joints, muscles, bone, back or limbs, Muscle cramps and pain, Fatigue, Weaknes, Abnormal buildup of fluid which may cause swelling in the hands, feet, ankles, feet, face or all over your body, Fever, Pain

Side effects less frequently reported (1 – 10% of patients)
Pneumonia (an inflammation of the lung, generally caused by infection, that may be accompanied by cough, phlegm, fever, sharp chest pain, shaking chills, sweating, difficulty breathing and requires immediate medical attention), Inflammation or infection of one or more hair follicles. A hair follicle is an opening in the skin that encloses a strand of hair from which the hair grows, Febrile neutropenia (a condition marked by fever and lower-than-normal number of neutrophils in the blood which could increase the risk of infection), Dehydration, Low levels of important electrolyte levels in your blood including abnormally low levels of sodium (which can cause fatigue, nausea, headache), low levels of potassium (which can cause irregular heartbeats), low levels of calcium (which can cause muscle spasms, twitches or cramps or numbness/tingling in your fingers, toes and around your mouth), and low levels of phosphorus (which can cause bone pain, confusion, muscle weakness), High blood sugar levels, High concentration of uric acid in the blood which could result in inflammation of a joint ("gout"), problems with urination or kidney stone, fever, chills, fatigue, Increased triglyceride levels (blood fat), Weight decreased, Confusional state (delirium), is a state that you might unclear in your mind about something, Cerebrovascular accident, commonly known as a stroke, is an episode in which some of the brain tissue is damaged by a disruption of blood flow to the brain and may cause sudden, weakness or numbness on one side of the body, difficulty speaking and requires immediate medical attention, Cerebral infarction, an area of brain tissue damaged by a disruption of blood to the brain, Lack of energy, or lack of interest in doing things, Migraine headache, Cranial or peripheral neuropathy, conditions in which nerves that come from the brain (cranial nerves) which supply the face and eyes and nerves that come from the spinal cord (peripheral nerves) have been damaged which may cause visual disturbances, numbness, tingling, prickling sensation, and either decreased or increased sensitivity of the skin to touch or pain or the ear to sound, Transient ischemic attacks, commonly known as a TIA or mini stroke, a TIA is an episode in which some of the brain tissue is damaged by a disruption of blood flow to the brain that may cause sudden weakness or numbness on one side of the body, difficulty speaking and requires immediate medical attention, Eye problems can occur including dry eye, blurred vision, eye irritation or pain, redness of the eye and less frequently, cataracts, glaucoma (a condition of increased pressure in the eye which can lead to loss of vision), and inflammation or an ulcer of the cornea which is the clear, dome- shaped tissue on the front of your eye that covers the pupil and the iris, Myocardial infarction, commonly known as heart attack, a myocardial infarction is an episode in which some of the heart's blood supply is severely cut off or restricted, causing the heart muscle to suffer and die from lack of oxygen, Pain, discomfort or pressure in the chest caused by insufficient blood supply to the heart muscle, Pericardial effusion (an abnormal buildup of fluid inside the sac that covers the heart which may cause chest pain, difficulty breathing and

fever), Irregular heart rhythms including atrial fibrillation (an abnormal rapid or irregular heart rhythm which may cause light-headedness, shortness of breath or weakness) and abnormally rapid or slow heart rates, Narrowing of blood vessels restricting blood flow to areas away from the center of the body such as legs, arms, toes, fingers, ear lobes, and penis, Condition of decreased oxygen supply to the areas away from the center of the body such as legs, arms, toes, fingers, ear lobes, and penis, Muscle pain caused by too little blood flow during walking or exercise, Blood clot in a major vein in the legs or pelvis, Flushing or hot flush (becoming very red in the face, and often other areas of the skin. Sometime may be a feeling of warmth that spreads over the body most strongly felt in the head and neck region), Obstruction of a blood vessel in the lungs resulting in fluid build-up in the lungs, Pleural effusion (an abnormal buildup of fluid in the lining of the lungs which may cause chest pain, cough, or shortness of breath), Bleeding such as nosebleeds or petechiae (in which tiny purple or red dots appear on the skin due to bleeding under the skin's surface), Voice impairment, such as hoarseness, Increased pressure of the blood vessels in your lung, which causes symptoms such as shortness of breath during routine activity (for example, climbing two flights of stairs), tiredness, chest pain, and a racing heartbeat, Inflammation of the pancreas (an organ in the abdomen which produces insulin and certain digestive enzymes, e.g., amylase, which will be released into the blood, when the pancreas is diseased or inflamed), which may affect the function of the pancreas and which may cause pain in the abdomen (belly), sometime can be severe and may increase blood sugar, Stomach acid, or occasionally bile flows back (refluxes) into your food pipe (esophagus), which can cause heartburn, Inflammation of the mucous lining of any of the structures in the mouth, including cheeks, gums, tongue, lips, throat and roof or floor of the mouth, Indigestion or upset stomach, Bloating, Abdominal discomfort, Dry mouth, An increase in the blood of a substance (bilirubin) produced by the liver that could indicate liver disease and in high amounts can cause yellowing of the skin and eyes, Increased enzymes in the blood, alkaline phosphatase (ALP) and gamma-glutamyltransferase (GGT), Skin problems which may include rash, may be itchy or painful, dry with flaking or peeling skin, sometime over large area of your body (dematitis exfoliative); bruise, redness, change or lose color of your skin, due to bleeding underneath the skin; darkening or thickening of the outer layer of your skin, Hair loss, Itching, Excessive sweating sometimes during sleep, Neck pain, Chest pain not due to heart disease, Impotence (inability to achieve or maintain an erection long enough to engage in sexual intercourse), Chills, Flu like symptoms, which include fever, chills, body aces, nausea, loss of appetite, Feeling sick or discomfort, Bacterial infection of the tissue just below the skin surface, Erythema multiforme (a rash with spots that may look like a target)

Side effects infrequently reported (Less than 1% of patients)
A severe infection in the body, sometime known as blood poisoning, which can cause difficulty breathing, coagulation of the blood, malfunction of your organs and is usually treated in an intensive care unit of a hospital, A condition that occurs after the start of anti-cancer

treatment in which the dying tumor cells release their contents into the blood and cause changes to important blood chemicals and may cause damage to organs including the kidneys, heart and liver, Blood vessels inside your skull become blocked by blood clot, which is one of the causes of stroke, Blood vessels inside your eyes become blocked by blood clot, which may cause severe damage to your eyes, you might not be able to see clearly and sometime even blindness could happen, Poor peripheral circulation is a condition in which the blood vessels can not supply enough blood to your feet or leg; you will experience numbness and cramping in the feet and lower legs. You may also have tingling sensation in the feet and toes, Splenic infarction is a condition in which oxygen supply to the spleen is interrupted, leading to partial or complete infarction (tissue death due to oxygen shortage) in the spleen, Bleeding that can be serious and can lead to death including bleeding in the brain or in the gastrointestinal tract (which extends from the mouth to the anus), Hepatotoxicity a condition in which your liver is damaged and can not function well, Sudden, severe increase in blood pressure occurring in individuals who have untreated high blood pressure or have stopped taking antihypertensive medication, Erythema nodosum (an inflammation of the fat cells under the skin that causes tender lesions on the skin), Formation of an abnormal connection between internal organs in the belly that are not normally connected, QT Prolongation is a change in electrocardiography (ECG). ECG is a study of the electrical system of the heart that may indicate an increased risk of serious abnormalities in the heart's rhythm, Hypersensitivity

15.18 **Drug procurement:** Drug will be provided free of charge to study participants by Ariad Pharmaceuticals.

15.19 **Nursing Guidelines:**

15.191 Respiratory symptoms are common, including URI, cough, and dyspnea. Instruct patient to report these and treat symptomatically. Monitor for effectiveness of intervention.

15.192 Common gastrointestinal symptoms seen include: anorexia, decreased appetite, abdominal pain, constipation, diarrhea, nausea, and vomiting. Treat symptomatically and monitor for effectiveness of intervention

15.193 Patients may experience arthralgias and myalgias. Treat with OTC pain relievers as allowed in protocol. Instruct patient to report any pain not relieved with these methods.

15.194 Monitor CBC w/diff. Instruct patient to report any signs or symptoms of infection and/or unusual bruising or bleeding to the health care team.

15.195 Monitor LFT's.

15.196 Warn patients of the potential for fatigue and asthenia.

15.197 Patients can experience thrombosis, cardiac/vascular events, and/or bleeding in the brain. Instruct patient to seek emergency help for any neurological or cardiac/vascular symptoms.

15.198 Oral lesions/ulcers are uncommon, but can be severe. Instruct patient on good oral hygiene. Viscous lidocaine or magic mouthwash may be helpful.

16.0 Statistical Considerations and Methodology

16.1 Overview: This protocol will assess the efficacy of ponatinib in FGFR aberrant advanced biliary cancers using a two-stage phase II study design.

16.11 Primary Endpoint: The primary endpoint of this trial is the clincal benefit rate , which includes confirmed tumor response (CR or PR) or SD for 4 or more cycle. A confirmed tumor response is defined to be either a CR or PR noted as the objective status on 2 consecutive evaluations at least 8 weeks apart. Clinical benefit rate will be evaluated using all cycles of treatment. All patients meeting the eligibility criteria who have signed a consent form, have begun treatment, and have not been deemed a major treatment violation during the first cycle of treatment will be evaulable for response.

16.2 Statistical Design

16.21 The largest clinical benefit where the proposed treatment regimen would be considered ineffective in this population is 5%, and the smallest clinical benefit rate that would warrant subsequent studies with the proposed regimen in this patient population is 20%. The following two-stage Simon Optimum design uses10 or 27 patients to test the null hypothesis that the true clinicalbenefit ratein a given patient population is at most 5%.
The null clinical benefit rate of 5% is based on response rates observed for refractory solid tumors with single agents in an unselected/empiric setting (Horstmann, E. et al., 2005).

16.211 STAGE 1: Enter 10 patients into the study. If 0 successes (i.e., patients deemed as having clinical benefit) are observed in the first 10 evaluable patients, we will consider this regimen ineffective in this patient population and terminate this study. Otherwise, if the number of successes is at least 1, we will proceed to Stage 2.

16.212 STAGE 2: Enter an additional 17 patients into the study. If 2 or fewer successes are observed in the first 27 evaluable patients, we will consider this regimen ineffective in this patient population. If 3 or more successes are observed in the first 27 evaluable patients, we may recommend further testing of this regimen in subsequent studies in this population.

16.213 NOTE: Accrual will be suspended between stages to allow patients to become evaluable for the primary endpoint.

16.211 Over Accrual: If more than the target number of patients are accrued, the additional patients will not be used to evaluate the stopping rule or used in any decision making process. Analysis involving over accrued patients is discussed in Section 16.313.

16.22 Sample Size: The two-stage study design to be utilized is fully described in Section 16.21. A minimum of 10 and a maximum of 27 evaluable patients accrued onto this study unless undue adverse events are encountered. We anticipate accruing an additional 3 patients to account for ineligibility, cancellation, major treatment violation, or other reasons. Thus, **a maximum of 30 patients will be accrued onto this study** in order to have 27 evaluable patients available for the statistical design described in Section 16.21.

16.23 Accrual Time and Study Duration: The anticipated accrual rate is approximately 3 patients per month, based on physician estimate. Therefore, the accrual period for this phase II study is expected to be 16 months (including a 6-month suspension in accrual to perform the Stage 1 analysis). The final analysis can begin approximately 22 months after the trial begins, i.e., as soon as the last patient has been observed for 6 months.

16.24 Power and Significance Level: Assuming that the number of successes is binomially distributed, the significance level is <0.15 and the probability of declaring that this regimen warrants further studies (i.e., statistical power) under various clinical benefit rates can be tabulated as a function of the true clinical benefit rate as shown in the following table.

If the true clinical benefit rate is…	0.05	0.10	0.15	0.20	0.25
Then the probability of declaring that the regimen warrants further studies is…	0.12	0.43	0.70	0.85	0.93
And the probability of stopping at Stage 1 is…	0.60	0.35	0.20	0.11	0.06

16.25 Other Considerations: Adverse events, quality/duration of response, and patterns of treatment failure observed in this study, as well as scientific discoveries or changes in standard care will be taken into account in any decision to terminate the study.

16.3 Analysis Plan: The analysis for this trial will commence at planned time points (see Section 16.23) and at the time the patients have become evaluable for the primary endpoint. Such a decision will be made by the Statistician and Study Chair, in accordance with Mayo Clinic Cancer Center (MCCC) Standard Operating Procedures, availability of data for secondary endpoints (e.g., laboratory correlates), and the level of data maturity.

16.31 Primary Endpoint

16.311 Definition: The primary endpoint of this trial is the clinical benefit rate as defined in Section 16.11.

16.312 Estimation: The proportion of clinical benefit rate will be estimated by the number of patients with clinical benefit (confirmed CR, confirmed PR, or SD for 4 or more cycles) divided by the total number of evaluable patients. A confidence interval for the true clinical benefit rate will be calculated using the approach of Duffy and Santner

16.313 Over Accrual: If more than the target number of patients are accrued, the additional patients will not be used to evaluate the stopping rule or used in any decision making processes; however, they will be included in final point estimates and confidence intervals.

16.32 Definitions and Analyses of Secondary Endpoints

16.321 Progression-free survival time is defined as the time from registration to the earliest date of documentation of disease progression. If a patient dies without a documentation of disease progression the patient will be considered to have had disease progression at the time of their death. In the case of a patient starting treatment and then never returning for any evaluations, the patient will be censored for progression 1 day post-registration. The distribution of progression-free survival time will be estimated using the method of Kaplan-Meier (1958).

16.322 Survival time is defined as the time from registration to death due to any cause. The distribution of survival time will be estimated using the method of Kaplan-Meier (1958).

16.323 CA 19-9 response is defined to be a ≥50% reduction from baseline. The CA 19-9 response rate will be estimated by the number of CA 19-9 responses divided by the total number of evaluable patients. A confidence interval will be calculated based on the binomial distribution.

16.324 Adverse Events: All eligible patients that have initiated treatment will be considered evaluable for assessing adverse event rate(s). The maximum grade for each type of adverse event will be recorded for each patient, and frequency tables will be reviewed to determine patterns. Additionally, the relationship of the adverse event(s) to the study treatment will be taken into consideration.

16.33 Translational Analyses

Rate of FGFR fusions and ctDNA mutations will be described, and association with confirmed tumor response and/or clinical benefit will be investigated using a Fisher's exact test. Given the small sample size, all translational analyses are

considered exploratory and no adjustment for multiplicity will be employed. One-sided p-values ≤0.10 are considered statistically significant throughout.

16.34 Analysis of Patient-Reported Outcomes (Quality of Life and Symptoms)

Patient-reported outcomes (quality of life and symptoms) will be assessed prior to review of treatment response and discussions of patient's general health since last treatment evaluation. Patient-reported outcomes will include the EORTC QLQ-C30, a 30-item patient-reported questionnaire about patient ability to function, symptoms related to the cancer and its treatment, overall health and quality of life, and perceived financial impact of the cancer and its treatment. 28 of the 30 items are measured on a 1-4 scale (1=not at all; 4=very much) with the remaining two items (overall health and overall quality of life) scored on a 1-7 numeric analogue scale (1=very poor; 7=excellent). The recall period for the EORTC QLQ-C30 is one week. The EORTC QLQ-C30 is the product of more than a decade of collaborative research and to date, more than 2200 studies using the EORTC QLQ-C30 have been registered with the EORTC (Fayers et al, 2001 [EORTC Scoring Manual]). In addition, patients will complete the newly developed EORTC QLQ-BIL21. This EORTC module assessed quality of life domains specific to biliary cancers using 21 items on the same 1-4 scale as the core questionnaire. This questionnaire is in the process of being validated (data form this study may be used to provide validation information). Skin and bowel symptoms will be assessed using the Skindex-16 and Bowel Function Questionnaire (BFQ). The Skindex-16 contains 16 questions each on a 0-10 scale (0=never bothered, 10=always bothered) assessing skins problems and has previously been validated (Chren et al, 2001). The BFQ, developed and created by Mayo Clinic physicians, identifies patient-reported problems with various aspects of bowel function (yes or no response) to help evaluate how bowel dysfunction affects normal activities and quality of life (QOL). Content validity of this instrument has been previously reported (Atherton et al, 2013). We will use the Uniscale assessment of overall quality of life (Sloan, O'Fallon et al, 1998) on a scale of 0-10 (0=as bad as it can be, 10=as good as it can be). This single item is one of the most widely used quality of life measures and has been shown to be prognostic for survival above and beyond performance status and other common prognostic factors in a range of cancer types. The Was It Worth It (WIWI) questionnaire is minimalist and efficient, asking only five key questions with trichotomous responses about the patient's satisfaction with the study and likelihood of recommending it to other patients. This tool has been pilot tested in a recent clinical trial looking at the QOL of patients participating in phase I clinical trials at Mayo Clinic Rochester and has demonstrated to be easy to complete, understandable, and important to patients. It has also been used to assess patient satisfaction as a companion protocol (N0392) to North Central Cancer Treatment Group cancer treatment phase II and III clinical trials.

A paper booklet containing all the patient-reported outcomes will be administered in clinic at baseline and every cycle, and each PRO will be scored according to the published scoring algorithm. Scale score trajectories over time will be examined using stream plots and mean plots with standard deviation error bars overall. Changes from baseline at each cycle will be statistically tested using paired t-tests, and standardized response means (mean of the change from

baseline scores at a given cycle, divided by the standard deviation of the change scores) will be interpreted (after applying Middel's (2002) adjustment) using Cohen's (1988) cut-offs: <0.20 = trivial; 0.20-<0.50 = small; 0.50-<0.80 = moderate; and >=/0.80 = large. Correlation between outcomes will employ Pearson and/or Spearman correlations at individual time points.

16.4 Data & Safety Monitoring

16.41 The principal investigator(s) and the study statistician will review the study at least twice a year to identify accrual, adverse event, and any endpoint problems that might be developing. The Mayo Clinic Cancer Center (MCCC) 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 MCCC Statistical Office.

16.42 Adverse Event Stopping Rule: The stopping rule specified below is 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.

Accrual will be temporarily suspended to this study 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 the following:

- if 4 or more patients in the first 20 treated patients (or 20% after 20 patients have been accrued) experience a Grade 4 or higher non-hematologic adverse event.

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.

16.5 Results Reporting on ClinicalTrials.gov: At study activation, this study will have been registered within the "ClincialTrails.gov" website. The Primary and Secondary Endpoints (ie, "Outcome Measures") along with other required information for this study will be reported on ClinicalTrials.gov. For purposes of timing of the Results Reporting, the initial estimated completion date for the Primary Endpoint of this study is 22 months after the study opens to accrual. The definition of "Primary Endpoint Completion Date" (PECD) for this study is the time that every patient has either completed 4 cycles of treatment or ended active treatment (whichever occurs first).

16.6 Inclusion of Women and Minorities

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

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

16.63 Based on prior MCCC studies involving similar disease sites, we expect about 4% of patients will be classified as minorities by race and 50% of patients will be women. Expected sizes of racial by gender subsets are shown in the following table:

Accrual Targets			
Ethnic Category	**Sex/Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	1	1	2
Not Hispanic or Latino	14	14	28
Ethnic Category: Total of all subjects	15	15	**30**
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	14	14	28
Racial Category: Total of all subjects	15	15	**30**

Ethnic Categories: **Hispanic or Latino** – a person of Cuban, Mexican, Puerto Rican, 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

17.1 Summary Table of Research Tissue Specimens to be Collected for this Protocol

Correlative Study (Section for more information)	Mandatory or Optional	Type of Tissue to Collect	Block, Slides, Core, etc. (# of each to submit)	Baseline	Just prior to Cycle 2, Day 1[1]	At Progression[1]	Process at site? (Yes or No)	Temperature Conditions for Storage /Shipping
Whole Exome Sequencing (WES); Whole Methylome Profiling (RRBS)	Optional	Fresh or Frozen	3-6 cores	X	X	X	No	Freeze.
IHC biomarkers	Optional	Formalin Fixed Paraffin Embedded or fresh	10 of slides	X	X	X	No	Ambient,

1. only if archival specimen was available

17.2 Correlative Tissue Collection

17.31 Tissue Kits will not be provided for this protocol.

17.32 Paraffin Embedded Tissue

17.321 10 slides per table 17.1

17.322 Shipping and Storage
All samples will be kept at Mayo Clinic Scottsdale campus until lab is ready for processing.

Shipping Specimens
Verify ALL sections of the Specimen Submission Forms are completed and filled in correctly.

Ship specimens via Priority Overnight service, **Monday – Thursday ONLY,** to:

Mayo Clinic
[redacted]

Do not send samples the day before, the day of, or the observed day of a national holiday.

All specimens must be shipped Monday – Thursday ONLY.

17.33 Frozen or Fresh Tissue

17.331 3-6 Cores per section 17.1 timepoints

17.332 Shipping and Storage

All samples will be kept at Mayo Clinic Scottsdale campus until lab is ready for processing.

Shipping Specimens
Verify ALL sections of the Specimen Submission Forms are completed and filled in correctly.

Ship specimens via Priority Overnight service, **Monday – Thursday ONLY,** to:

Mayo Clinic
[redacted]

[redacted]

Do not send samples the day before, the day of, or the observed day of a national holiday.

All specimens must be shipped Monday – Thursday ONLY.

18.0 Records and Data Collection Procedures

18.1 Submission Timetable

Initial Material(s)

CRF	**Active-Monitoring Phase** (Compliance with Test Schedule Section 4.0)
On-Study	≤14 days after registration
Adverse Event - Baseline	
RECIST Measurement – Baseline	
Concomitant Medication - Baseline	
Hematology Laboratory	
Chemistry Laboratory	
Other Laboratory	
Patient Questionnaire Booklet[1]	
Booklet Compliance [2]	
OP and Path Reports (see Section 17.0)	
Research Blood Submission	
Research Tissue Submission	≤30 days after registration
End of Active Treatment/Cancel Notification	Submit ≤2 weeks after registration if withdrawal/refusal occurs prior to beginning protocol therapy

1. Patient questionnaire booklet **must** be used; copies are not acceptable for this submission.
2. This form must be completed only if the patient questionnaire booklet contains absolutely NO patient provided assessment information.

Test Schedule Material(s)

CRF	**Active-Monitoring Phase** (Compliance with Test Schedule Section 4.0)
	At each evaluation during treatment
Evaluation/Treatment	X[1]
Adverse Event	X

CRF	**Active-Monitoring Phase** (Compliance with Test Schedule Section 4.0)
	At each evaluation during treatment
RECIST Measurement	X
Concomitant Medication	X
Other Laboratory	X (see Section 4.0)
Hematology Laboratory	X (see Section 4.0)
Chemistry Laboratory	X (see Section 4.0)
Research Tissue Submission	X (see Section 17.0)
Research Blood Submission	X (see Section 14.0)
Patient Questionnaire Booklet	X[2]
Booklet Compliance	X[3]
End of Active Treatment/Cancel Notification	X
Notification Form – Grade 4 or 5 Non-AER Reportable Events/Hospitalization	At each occurrence (see Section 10.0)
ADR/AER	At each occurrence (see Section 10.0)

1. Complete at each evaluation during Active Treatment (see Section 4.0).
2. Patient questionnaire booklet **must** be used; copies are not acceptable for this submission. To be completed prior to treatment every cycle.
3. This form must be completed only if the patient questionnaire booklet contains absolutely NO patient provided assessment information.

Follow-up Material(s)

CRF	**Event Monitoring Phase**[1]				
	q. _6_ months until PD	At PD	After PD q. __6__ mos.	Death	New Primary
Event Monitoring	X[2]	X[2]	X	X	At each occurrence

1. If a patient is still alive 2 years after registration, no further follow-up is required.
2. Submit copy of documentation of response or progression to the MCCC Operations Office, Attention: [redacted].

19.0 Budget

19.1 Costs charged to patient: routine clinical care

19.2 Tests to be research funded: amylase and lipase blood tests, Electrocardiograms, ECHOs, Optional Cycle 2, Day 1 tissue biopsy and study drug, ponatinib.

19.3 Other budget concerns: none

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Appendix I

ECOG Performance Status Scale

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

Name _____

Mayo Clinic No_____

Study Name/Number_____

Appendix II: MEDICATION DIARY

Patient 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 check "**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.

Medication(s)	Dose
Ponatinib	MG

Study Drug	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**
Date							
Ponatinib							

Study Drug	**Day 8**	**Day 9**	**Day 10**	**Day 11**	**Day 12**	**Day 13**	**Day 14**
Date							
Ponatinib							

Study Drug	**Day 15**	**Day 16**	**Day 17**	**Day 18**	**Day 19**	**Day 20**	**Day 21**
Date							
Ponatinib							

Study Drug	**Day 22**	**Day 23**	**Day 24**	**Day 25**	**Day 26**	**Day 27**	**Day 28**
Date							
Ponatinib							

Date:_____ Participants Signature:_____

Area Below Only To Be Completed only by Coordinator

Number of pills returned_____ Study Coordinator Initials_____

Date_____ Discrepancy Yes____ No_____

Appendix III – Patient Information Sheet

To order booklets please e-mail [redacted]

PATIENT INFORMATION SHEET
Patient Completed Quality of Life Booklet

You have been given a booklet to complete for this study. The booklet contains some questions about your 'quality of life' as a patient receiving treatment for cancer. Your answers will help us to better understand how the treatment you are receiving is affecting the way you feel.

1. This booklet contains six sets of questions:
    - EORTC QLQ-C30 (30 questions)
    - EORTC QLQ-BIL21 (21 questions)
    - Skindex-16 (16 questions)
    - Bowel Function Questionnaire (10 questions)
    - Uniscale (1 question)
    - Was It Worth It (WIWI) (5 questions)

2. Directions on how to complete each set of questions are written on the top of each set.

3. Please complete the booklet during your scheduled clinical visit and return it to your nurse, physician, or research coordinator.

Thank you for taking the time to help us.

Appendix IV
EORTC QLQ - C30 (Version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
16. Have you been constipated?	1	2	3	4
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4

19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you.

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Appendix V
EORTC QLQ – BIL21

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
31. Have you had trouble with eating?	1	2	3	4
32. Have you felt full up too quickly after beginning to eat?	1	2	3	4
33. Have you had problems with your sense of taste?	1	2	3	4
34. Were you restricted in the types of food you can eat as a result of your disease or treatment?	1	2	3	4
35. Have your skin or eyes been yellow (jaundiced)?	1	2	3	4
36. Have you had itching?	1	2	3	4
37. Have you been worried about your skin being yellow?	1	2	3	4
38. Have you been less active than you would like to be?	1	2	3	4
39. Have you felt 'slowed down'?	1	2	3	4
40. Have you felt lacking energy?	1	2	3	4
41. Did you have pain during the night?	1	2	3	4
42. Have you had pain in your stomach area?	1	2	3	4
43. Have you had pain in your back?	1	2	3	4
44. Did you have a bloated feeling in your abdomen?	1	2	3	4
45. Have you felt stressed?	1	2	3	4
46. Have you felt less able to enjoy yourself?	1	2	3	4
47. Have you worried about your health in the future?	1	2	3	4
48. Have you worried about your family in the future?	1	2	3	4
49. To what extent have you been troubled with side effects from your treatment?	1	2	3	4
50. Have you had difficulties with drainage tubes/bags?	1	2	3	4
51. Have you worried about losing weight?	1	2	3	4

Appendix VI
SKINDEX-16

Directions: Please circle the number (0-6) best reflecting your response to the following that describes **during the past week**, how often have you been bothered by:

1. **Your skin itching:**

0 1 2 3 4 5 6 7 8 9 10
Never bothered Always bothered

2. **Your skin burning or stinging:**

0 1 2 3 4 5 6 7 8 9 10
Never bothered Always bothered

3. **Your skin hurting:**

0 1 2 3 4 5 6 7 8 9 10
Never bothered Always bothered

4. **Your skin being irritated:**

0 1 2 3 4 5 6 7 8 9 10
Never bothered Always bothered

5. **The persistence/recurrence of your skin condition:**

0 1 2 3 4 5 6 7 8 9 10
Never bothered Always bothered

6. **Worry about your skin condition (for example, that it will spread, get worse, scar or be unpredictable, etc.):**

0 1 2 3 4 5 6 7 8 9 10
Never bothered Always bothered

7. **The appearance of your skin:**

0 1 2 3 4 5 6 7 8 9 10
Never bothered Always bothered

8. Frustration about your skin:

0 1 2 3 4 5 6 7 8 9 10
Never bothered Always bothered

9. Embarrassment about your skin:

0 1 2 3 4 5 6 7 8 9 10
Never bothered Always bothered

10. Being annoyed about your skin:

0 1 2 3 4 5 6 7 8 9 10
Never bothered Always bothered

11. Feeling depressed about your skin:

0 1 2 3 4 5 6 7 8 9 10
Never bothered Always bothered

12. The effects of your skin on your interactions with others (for example, interactions with family, friends, close relationship, etc.):

0 1 2 3 4 5 6 7 8 9 10
Never bothered Always bothered

13. The effects of your skin on your desire to be with people:

0 1 2 3 4 5 6 7 8 9 10
Never bothered Always bothered

14. Your skin making it hard for you to show your affection:

0 1 2 3 4 5 6 7 8 9 10
Never bothered Always bothered

15. The effects of your skin condition on your daily activities:

0 1 2 3 4 5 6 7 8 9 10
Never bothered Always bothered

16. Your skin making it hard to work or do what you enjoy:

0 1 2 3 4 5 6 7 8 9 10
Never bothered Always bothered

Appendix VII
Bowel Function Questionnaire

Directions: Each of the statements or questions below describe symptoms or problems which sometimes occur in patients with your type of cancer. Questions 2-10 can be answered by circling "yes" or "no".

1. How many bowel movements do you have each day on average? _____

2. Do you sometimes have to get up at night to have a bowel movement? yes no

3. Do you sometimes lose control of your bowel movements? yes no

4. Do you sometimes have another bowel movement within 30 min of the previous one? yes no

5. Do you sometimes wear protective clothing or a pad in case you lose control of a bowel movement? yes no

6. Are you sometimes unable to tell the difference between stool and gas? yes no

7. Are your bowel movements sometimes liquid in consistency? yes no

8. Once you feel the urge to have a bowel movement, do you find that you must do so within 15 min to avoid an accident? yes no

9. Do you ever have cramping with bowel movements? yes no

If yes, is your cramping:
☐ mild
☐ moderate
☐ severe

10. Do you ever have blood in your bowel movement? yes no

If yes, check the description that best describes the amount of blood in your bowel movement:
☐ on toilet tissue only
☐ mixed with or coating bowel movement
☐ enough to turn water in toilet bowl red

Appendix VIII
Uniscale

Please circle the number (0-10) best reflecting your response to the following that describes your feelings **during the past week, including today.**

1. How would you describe your overall Quality of Life?

0	1	2	3	4	5	6	7	8	9	10
As bad as it can be										As good as it can be

If you have not started treatment on this study, please stop here. Thank you for taking the time to help us.

If you have started treatment on this study, please continue to the next page.

Appendix IX
Was It Worth It (WIWI)

Participating in a clinical trial / research study is a personal choice and an individual experience. We would like to get your feedback on your experience in this research study.

Directions: Please answer each question by circling Y (for yes), N (for no), or U (for uncertain).

1. **Was it worthwhile for you to participate in this research study?** *(circle one)*

   Y N U

2. **If you had to do it over, would you participate in this research study again?** *(circle one)*

   Y N U

3. **Would you recommend participating in this research study to others?** *(circle one)*

   Y N U

4. **Overall, did your quality of life change by participating in this research study?** *(circle one)*

   It improved It stayed the same It got worse

5. **Overall how was your experience of participating in this research study?** *(circle one)*

   Better than I expected The same as I expected Worse than I expected

Thank you for taking the time to help us.

Appendix X
Child-Pugh Classification

Parameter	Points Assigned		
	1	**2**	**3**
Ascites	Absent	Slight	Moderate
Bilirubin (mg/dL)	≤2	2 to 3	>3
Albumin (g/dL)	>3.5	2.8 to 3.5	<2.8
Prothombin Time			
Seconds over control	1 to 3	4 to 6	>6
INR	<1.7	1.8 to 2.3	>2.3
Encephalopathy	None	Grade 1 to 2	Grade 3 to 4

Modified Child-Pugh Classification of the severity of liver disease according to the degree of ascites, the plasma concentrations of bilirubin and albumin, the Prothrombin time, and the degree of encephalopathy. A total score of 5 to 6 is considered Grade A (well-compensated disease); 7-9 is Grade B (significant functional compromise); and 10 to 15 is Grade C (decompensated disease). These grades correlate with one and two year survival; Grade A – 100% and 65%; Grade B: 80% and 60%; and Grade C – 45% and 35%.

Appendix XI: MEDICATION GUIDE Iclusig® (eye-CLUE-sig) (ponatinib) Tablets

What is the most important information I should know about Iclusig?

Iclusig can cause serious side effects, including:

Blood clots or blockage in your blood vessels (arteries and veins). Blood clots or blockage in your blood vessels may lead to heart attack, stroke, or death. A blood clot or blockage in your blood vessels can prevent proper blood flow to your heart, brain, bowels (intestines), legs, eyes, and other parts of your body. You may need emergency surgery or treatment in a hospital. Get medical help right away if you get any of the following symptoms:

- chest pain or pressure
- pain in your arms, legs, back, neck or jaw
- shortness of breath
- numbness or weakness on one side of your body
- trouble talking
- headache
- dizziness
- severe stomach area pain
- decreased vision or loss of vision

Blood clots or blockage in your blood vessels can happen in people with or without risk factors for heart and blood vessel disease, including people 50 years of age or younger. Talk to your healthcare provider if this is a concern for you.

Heart problems. Iclusig can cause heart problems, including heart failure which can be serious and may lead to death. Heart failure means your heart does not pump blood well enough. Iclusig can also cause irregular slow or fast heartbeats and heart attack. Your healthcare provider will check your heart function before and during your treatment with Iclusig. Get medical help right away if you get any of the following symptoms: shortness of breath, chest pain, fast or irregular heartbeats, dizziness, or feel faint.

Liver problems. Iclusig can cause liver problems, including liver failure, which can be severe and may lead to death. Your healthcare provider will do blood tests before and during your treatment with Iclusig to check for liver problems. Get medical help right away if you get any of these symptoms of liver problems during treatment:

- yellowing of your skin or the white part of your eyes (jaundice)
- dark "tea-colored" urine
- sleepiness

See **"What are the possible side effects of Iclusig?"** for information about side effects.

What is Iclusig?

Iclusig is a prescription medicine used to treat adults who have:

- a specific type of abnormal gene (T315I-positive) chronic phase, accelerated phase, or blast phase chronic myeloid leukemia (CML), or T315I-positive Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL)
- chronic phase, accelerated phase, or blast phase CML or Ph+ ALL who cannot receive any other tyrosine kinase inhibitor (TKI) medicines

It is not known if Iclusig is safe and effective in children less than 18 years of age.

What should I tell my healthcare provider before taking Iclusig? Before you take Iclusig, tell your healthcare provider if you:

- have a history of blood clots in your blood vessels (arteries or veins)
- have heart problems, including heart failure, irregular heartbeats, and QT prolongation
- have diabetes
- have a history of high cholesterol
- have liver problems
- have had inflammation of your pancreas (pancreatitis)

have high blood pressure

- have bleeding problems
- plan to have any surgical procedures
- are lactose (milk sugar) intolerant. Iclusig tablets contain lactose.
- drink grapefruit juice
- have any other medical conditions
- are pregnant or plan to become pregnant. Iclusig can harm your unborn baby. You should not become pregnant while taking Iclusig. Tell your healthcare provider right away if you become pregnant or plan to become pregnant.
- are breastfeeding or plan to breastfeed. It is not known if Iclusig passes into your breast milk. You and your healthcare provider should decide if you will take Iclusig or breastfeed. You should not do both.

Tell your healthcare provider about all the medicines you take, including prescription medicines and over-the-counter medicines, vitamins, and herbal supplements. Iclusig and other medicines may affect each other causing side effects.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I take Iclusig?

- Take Iclusig exactly as your healthcare provider tells you to take it.
- Your healthcare provider may change your dose of Iclusig or tell you to stop taking Iclusig.
- Do not change your dose or stop taking Iclusig without talking to your healthcare provider.
- Swallow Iclusig tablets whole. Do not crush or dissolve Iclusig tablets.
- You may take Iclusig with or without food.
- If you miss a dose of Iclusig, take your next dose at your regular time. Do not take 2 doses at the same time to make up for a missed dose.
- If you take too much Iclusig, call your healthcare provider or go to the nearest hospital emergency room right away.

What are the possible side effects of Iclusig? Iclusig may

cause serious side effects, including:

See **"What is the most important information I should know about Iclusig?"**

- **High blood pressure**. Your blood pressure should be checked regularly and any high blood pressure should be treated while you are taking Iclusig. Tell your healthcare provider if you get headaches, dizziness, chest pain or shortness of breath.
- **Inflammation of the pancreas (pancreatitis).** Symptoms include sudden stomach-area pain, nausea, and vomiting. Your healthcare provider should do blood tests to check for pancreatitis during treatment with Iclusig.
- **Neuropathy.** Iclusig may cause damage to the nerves in your arms, brain, hands, legs, or feet (Neuropathy). Tell your healthcare provider if you get any of these symptoms during treatment with Iclusig:
    - muscle weakness, tingling, burning, pain, and loss of feeling in your hands and feet
    - double vision and other problems with eye sight, trouble moving the eye, drooping of part of the face, sagging or drooping eyelids
- **Effects on the eye.** Serious eye problems that can lead to blindness or blurred vision may happen with Iclusig. Tell your healthcare provider if you get any of the following symptoms: perceived flashes of light, light sensitivity, floaters, dry or itchy eyes, and eye pain. Your healthcare provider will monitor your vision before and during your treatment with Iclusig.
- **Severe bleeding.** Iclusig can cause bleeding which can be serious and may lead to death. Tell your healthcare provider if you get any signs of bleeding while taking Iclusig including:
  o vomiting blood or if your vomit looks like coffee-grounds

o pink or brown urine
o red or black (looks like tar) stools
o coughing up blood or blood clots
o unusual bleeding or bruising of your skin
o menstrual bleeding that is heavier than normal
o unusual vaginal bleeding
o nose bleeds that happen often
o drowsiness or difficulty being awakened
o confusion
o headache
o change in speech

- **Fluid retention.** Your body may hold too much fluid (fluid retention). Tell your healthcare provider right away if you get any of these symptoms during treatment with Iclusig:

o swelling of your hands, ankles, feet, face, or all over your body
o weight gain
o shortness of breath and cough

- **Low blood cell counts.** Iclusig may cause low blood cell counts. Your healthcare provider will check your blood counts regularly during treatment with Iclusig. Tell your healthcare provider right away if you have a fever or any signs of an infection while taking Iclusig.
- **Tumor Lysis Syndrome (TLS). TLS** is caused by a fast breakdown of cancer cells. TLS can cause you to have:

o kidney failure and the need for dialysis treatment
o an abnormal heartbeat Your healthcare provider may do blood tests to check for TLS.

- **Possible wound healing problems.** If you need to have a surgical procedure, tell your healthcare provider that you are taking Iclusig. You should stop taking Iclusig at least 1 week before any planned surgery.
- **A tear in your stomach or intestinal wall (perforation).** Tell your healthcare provider right away if you get:

o severe pain in your stomach-area (abdomen)
o swelling of the abdomen
o high fever

The most common side effects of Iclusig include:

- skin rash
- constipation
- stomach-area (abdomen) pain
- fever
- tiredness
- joint pain
- headache
- nausea
- dry skin

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all of the possible side effects of Iclusig. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at [redacted]

How should I store Iclusig?

Store Iclusig at room temperature between 68°F to 77°F (20°C to 25°C).

Keep Iclusig and all medicines out of the reach of children.

General information about Iclusig

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use Iclusig for a condition for which it was not prescribed. Do not give Iclusig to other people, even if they have the same symptoms you have. It may harm them.

You can ask your healthcare provider or pharmacist for information about Iclusig that is written for health professionals.

For more information, go to www.iclusig.com or call [redacted]

What are the ingredients in Iclusig?

Active ingredient: ponatinib

Inactive ingredients: lactose monohydrate, microcrystalline cellulose, sodium starch glycolate (type B), colloidal silicon dioxide and magnesium stearate. The tablet coating consists of talc, polyethylene glycol, polyvinyl alcohol and titanium dioxide.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Manufactured for: ARIAD Pharmaceuticals, Inc. 26 Landsdowne Street Cambridge, MA 02139-4234

Revised: December 2013
Reference ID: 3425782

Appendix XII: Prohibited Drugs Affecting the QT Interval

The list of drugs that can be associated with Torsades de Pointes or prolonged QT interval is shown on the table below. This can also be can be found online at http://www.azcert.org/medical-pros/drug-lists/bycategory.cfm.
Three categories of drugs are listed on this website. Concomitant use of drugs in the first category (Drugs with Risk of Torsades de Pointes) is prohibited, and these drugs are listed below. Agents in the 2 categories of lesser risk (Drugs with Possible Risk of Torsades de Pointes; and Drugs with Conditional Risk of Torsades de Pointes) should be avoided. Note: these are available on the website, but are not listed in the table below.

Table B-1 Drugs Generally Accepted by the QTDrugs.org Advisory Board of the Arizona CERT to have a Risk of Causing Torsades de Pointes and Prohibited in this Study

Generic Name	Brand Name	Class/Clinical Use
Amiodarone	Cordarone®	Anti-arrhythmic / abnormal heart rhythm
Amiodarone	Pacerone®	Anti-arrhythmic / abnormal heart rhythm
Arsenic trioxide	Trisenox®	Anti-cancer / Leukemia
Astemizole	Hismanal®	Antihistamine / Allergic rhinitis
Bepridil	Vascor®	Anti-anginal / heart pain
Chloroquine	Aralen®	Anti-malarial / malaria infection
Chlorpromazine	Thorazine®	Anti-psychotic/ Anti-emetic / schizophrenia/ nausea
Cisapride	Propulsid®	GI stimulant / heartburn
Clarithromycin	Biaxin®	Antibiotic / bacterial infection
Disopyramide	Norpace®	Anti-arrhythmic / abnormal heart rhythm
Dofetilide	Tikosyn®	Anti-arrhythmic / abnormal heart rhythm
Domperidone	Motilium®	Anti-nausea / nausea
Droperidol	Inapsine®	Sedative;Anti-nausea / anesthesia adjunct, nausea
Erythromycin	Erythrocin®	Antibiotic;GI stimulant / bacterial infection; increase GI motility
Erythromycin	E.E.S.®	Antibiotic;GI stimulant / bacterial infection; increase GI motility
Halofantrine	Halfan®	Anti-malarial / malaria infection
Generic Name	**Brand Name**	**Class/Clinical Use**

Haloperidol	Haldol®	Anti-psychotic / schizophrenia, agitation
Ibutilide	Corvert®	Anti-arrhythmic / abnormal heart rhythm
Levomethadyl	Orlaam®	Opiate agonist / pain control, narcotic dependence
Mesoridazine	Serentil®	Anti-psychotic / schizophrenia
Methadone	Dolophine®	Opiate agonist / pain control, narcotic dependence
Methadone	Methadose®	Opiate agonist / pain control, narcotic dependence
Pentamidine	Pentam®	Anti-infective / pneumocystis pneumonia
Pentamidine	NebuPent®	Anti-infective / pneumocystis pneumonia
Pimozide	Orap®	Anti-psychotic / Tourette's tics
Probucol	Lorelco®	Antilipemic / Hypercholesterolemia
Procainamide	Pronestyl®	Anti-arrhythmic / abnormal heart rhythm
Procainamide	Procan®	Anti-arrhythmic / abnormal heart rhythm
Quinidine	Cardioquin®	Anti-arrhythmic / abnormal heart rhythm
Quinidine	Quinaglute®	Anti-arrhythmic / abnormal heart rhythm
Sotalol	Betapace®	Anti-arrhythmic / abnormal heart rhythm
Sparfloxacin	Zagam®	Antibiotic / bacterial infection
Terfenadine	Seldane®	Antihistamine / Allergic rhinitis
Thioridazine	Mellaril®	Anti-psychotic / schizophrenia