Local Protocol #: 15-163

TITLE: ***Phase II Trial of Ponatinib in Patients with Bevacizumab-Refractory Glioblastoma***

Coordinating Center: Dana-Farber Cancer Institute

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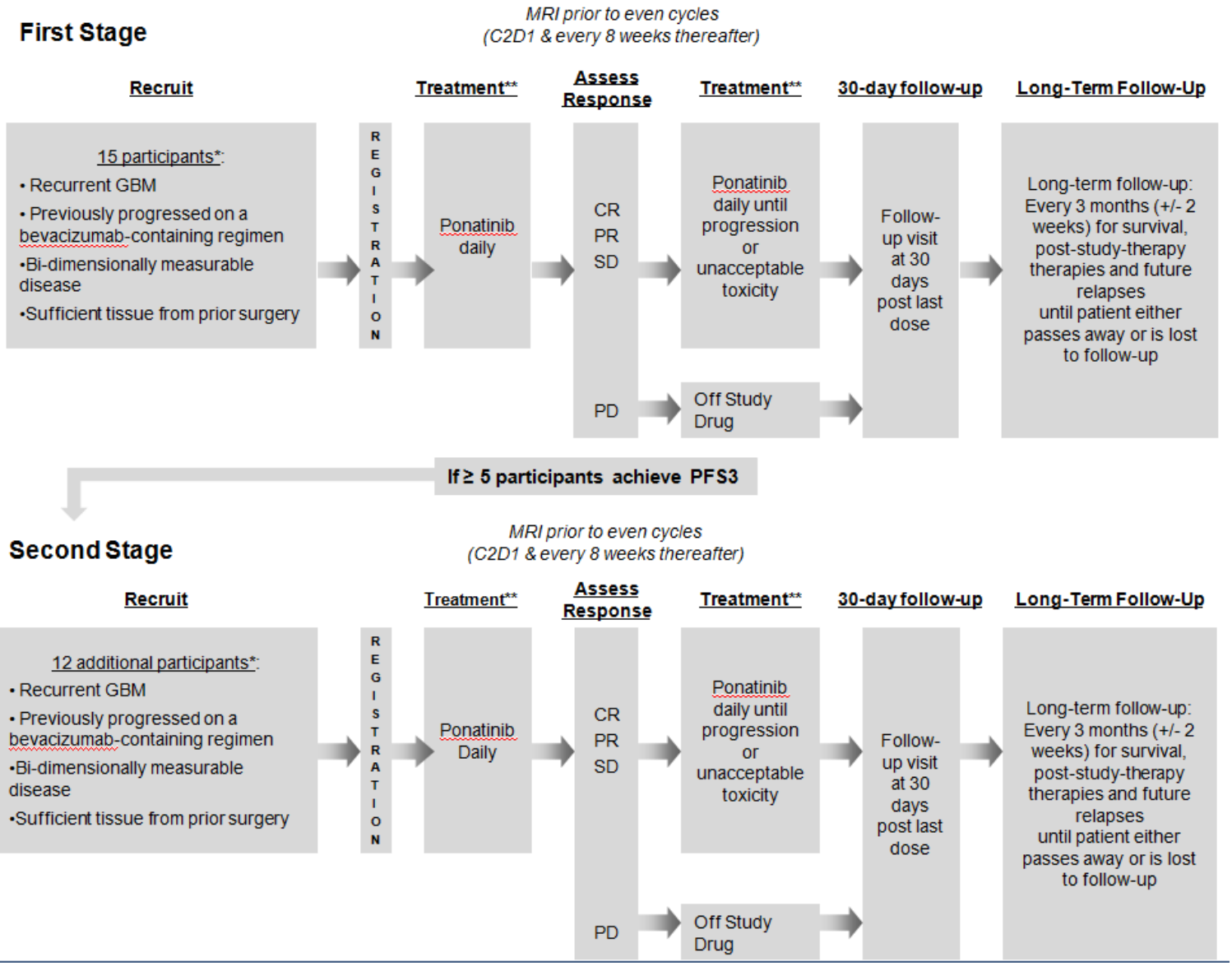
Agent: Ponatinib (AP24534); *supplied by ARIAD Pharmaceutical*

IND #: Exempt

Version # / Version Date: *Version #7.0/ 15-March-2016*

SCHEMA



Definitions:

CR – Complete Response SD – Stable Disease
PR – Partial Response PD – Progressive Disease

Footnotes:

*Total of 27 Participants

Note: To account for drop outs, 2 additional participants (up to 17 participants) may enroll in Stage 1. If at least 5 or more of the first 15 participants achieve PFS3, 12 more participants will be accrued for a total of 27 participants. To account for drop outs in the second stage, 3 more additional participants may enroll, increasing total enrollment up to 32 participants.

** Cycle Length = 28 Days

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1. OBJECTIVES

1.1 Study Design

This is a single arm, open label, Phase II trial in adult participants with recurrent glioblastoma who have progressed on bevacizumab.

1.2 Primary Objectives

- To determine the efficacy of ponatinib in participants with recurrent GBM who have progressed on bevacizumab as measured by 3-month progression-free survival (PFS3)

1.3 Secondary Objectives

- Radiographic Response (RR)
- Overall survival (OS) and progression free survival (PFS)
- Safety profile

1.4 Exploratory Objectives

- To explore the extent to which the tumor's genotype and expression profile correlate with outcome
- To explore the correlation between serum angiogenic peptides, circulating endothelial cells, and circulating progenitor cells with response to therapy
- To explore the correlation between dynamic-contrast MRI, perfusion and diffusion MRI and response to therapy.

2. BACKGROUND

2.1 Study Agent

Ponatinib (AP24534) is a novel, orally available tyrosine kinase inhibitor (TKI). In addition to targeting Breakpoint Cluster Region-Abelson (BCR-ABL), other targets of clinical interest include the kinases c-KIT (KIT), ret proto-oncogene (RET), Fms-like tyrosine kinase-3 (FLT3), vascular endothelial growth factor (VEGF), and fibroblast growth factor receptors (FGFRs).

Chemical

Ponatinib is a chemical entity prepared by chemical synthesis. The ponatinib active pharmaceutical ingredient is the mono-hydrochloride salt (AP24534 hydrochloride). Ponatinib for investigational use is supplied as white opaque capsules containing nominally 5 mg of ponatinib, or as 15 mg or 45 mg round, white, film-coated tablets. The commercial dosage form, Ponatinib, is supplied as 15 mg or 45 mg round, white film-coated tablets.

Nonclinical

A nonclinical development program was implemented to support clinical studies of ponatinib. In vitro assays demonstrated that ponatinib potently inhibits the enzymatic activity of T315I ABL kinase, 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 proliferation of cell lines expressing other major, clinically observed imatinib-, nilotinib-, and dasatinib resistant mutants of BCR-ABL. In vivo antitumor activity has been shown in tumor-bearing mouse models. Ponatinib has been shown to be 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, vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), receptor tyrosine kinase expressed on vascular endothelium (TIE2), and tyrosine kinase homologous to the Rous sarcoma virus oncogene protein PP60 (SRC). The kinase inhibition profile of ponatinib suggests potential for clinical activity in other hematologic and nonhematologic malignancies, in addition to Chronic Myeloid Leukemia (CML).

Nonclinical 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 toxicologic effects of ponatinib; in a 6-month oral toxicology study, the no-observed adverse-effect level (NOAEL) in the rat 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. 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. 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.

Clinical

Ponatinib 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 treated with ponatinib commercially. 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 Ponatinib in the US. On 20 December 2013, the FDA agreed with the revised US Prescribing Information, and commercialization of Ponatinib was resumed in the US in January 2014.

Five company-sponsored clinical studies with ponatinib have been or are being conducted in adult patients:

- A phase 1 dose-escalation study in patients with hematologic malignancies (AP24534-07-101)
- A pivotal phase 2 study in patients with refractory CML (chronic phase [CP], accelerated phase [AP], or blast phase [BP]) or Ph+ acute lymphoblastic leukemia (ALL) (AP24534-10-201; PACE)
- A pivotal randomized phase 3 study of ponatinib versus imatinib in patients with newly diagnosed CP-CML (AP24534-12-301; EPIC)
- A phase 1/2 study in Japanese patients with CML or Ph+ ALL (AP24534-11-106)
- A phase 2 study of patients with metastases and/or unresectable gastrointestinal stromal tumor (GIST; AP24534-12-202)

Seven clinical pharmacology studies in healthy subjects have been completed:

- A food-effect study (AP24534-11-102)
- A drug-drug interaction (DDI) study with ketoconazole (a cytochrome P450 [CYP]3A4 inhibitor; AP24534-11-103)
- An absorption, distribution, metabolism, and elimination (ADME) study with [14C]ponatinib (AP24534-11-104)
- A DDI study with rifampin (a CYP3A4 inducer; AP24534-12-107)
- A DDI study with lansoprazole (a proton-pump inhibitor; AP24534-12-108)
- A study of ponatinib in subjects with various degrees of hepatic impairment (matched to control subjects; AP24534-12-109)
- A bioequivalence study of ponatinib in healthy volunteers (AP24534-13-111)

In addition, ponatinib has been provided via an expanded access program through the following mechanisms:

- A company-sponsored expanded access study (AP24534-12-901 in the US; this study was closed on 14 December 2012, coinciding with the approval and commercialization of Ponatinib in the US).
- An expanded-access study (AP24534-12-903) in France in patients with refractory disease; the study is ongoing and accepting new patients.
- An expanded-access study (AP24534-12-904) in Belgium in patients with refractory disease; this study also is ongoing and enrolling new patients.
- Individual-patient treatment investigational new drug (IND) applications in the US
- Named Patient Programs (NPPs) outside the US

Multiple investigator-sponsored trials (ISTs) are underway to evaluate the response of hematologic cancers as well as solid tumors to ponatinib. Two of these have had preliminary efficacy results published:

- AP24534-11-001 (clinicaltrials.gov # NCT01424982) is a phase 2 study of ponatinib (45 mg QD) in combination with hyper-CVAD (fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone), alternating with high-dose methotrexate and cytarabine every 21 days, in patients with Ph+ ALL. As of 07 October 2013, 30 patients received ponatinib.
- AP24534-11-002 (clinicaltrials.gov # NCT01570868) is a phase 2 study of ponatinib in newly-diagnosed CP-CML patients, with 41 patients treated as of 07 October 2013.

Full descriptions of all clinical, clinical pharmacology, and investigator-sponsored studies can be found in the Investigator Brochure

2.2 Study Disease

Glioblastomas (GBMs) are the most common type of malignant primary brain tumors in adults. The annual incidence in the United States is 3-4 per 100,000, with over 10,000 new cases each year (Wen and Kesari 2008, Dolecek, Propp et al. 2012). Despite optimal treatment with surgery, radiation therapy, and chemotherapy, the prognosis remains poor. In 2005, results from a randomized Phase III trial indicated that the addition of temozolomide chemotherapy to radiation therapy for treatment of newly-diagnosed GBM prolonged median survival from 12.1 to 14.6 months (Stupp, Mason et al. 2005). For participants with recurrent GBM, treatment options are limited (Wen and Kesari 2008). The median time to tumor progression is only 9 weeks for standard cytotoxic agents (Wong, Hess et al. 1999) and 4-5 months with bevacizumab containing regimens (Friedman, Prados et al. 2009, Kreisl, Kim et al. 2009).

Tumors that progress during bevacizumab therapy often cannot be treated successfully. A retrospective series of 37 participants treated with various non-antiangiogenic approaches following bevacizumab failure reported a median overall survival of 4.5 months (Iwamoto, Abrey et al. 2009). Continuation of bevacizumab is also typically followed by progressive clinical deterioration and death. Among 54 recurrent high-grade glioma participants who

were treated with bevacizumab and cytotoxic chemotherapy, continuing bevacizumab and changing to another chemotherapy agent at recurrence was ineffective (Quant, Norden et al. 2009). The median PFS was only 6 weeks, and there were no radiographic responses. In a Phase II study of 48 recurrent GBM participants treated with bevacizumab monotherapy, 19 participants received bevacizumab and irinotecan at recurrence (Kreisl, Kim et al. 2009). The median PFS was approximately one month, and there were no radiographic responses using standard criteria (Macdonald, Cascino et al. 1990). At this time, no treatment has proven even modestly effective in the post-bevacizumab setting.

2.3 Rationale

Although anti-angiogenic approaches for GBM therapy show promise, GBMs usually develop resistance to treatment within months or even weeks of starting therapy. The predominant mechanisms of resistance to anti-angiogenic therapies are still being elucidated, but at the time of tumor progression, there are increases in plasma levels of basic fibroblast growth factor (bFGF) and stromal cell-derived factor 1α (SDF-1α) (Casanovas, Hicklin et al. 2005, Batchelor, Sorensen et al. 2007). Drugs such as ponatinib targeting not only vascular endothelial growth factor receptor (VEGFR) and platelet derived growth factor (PDGFR), but also fibroblast growth factor receptor (FGFR), may potentially help overcome some of the putative mechanisms of resistance and result in increased antitumor effects. The additional activity that ponatinib has on members of the Src family of tyrosine kinases may also contribute to a therapeutic effect since there is increasing evidence that Src is also important in glioma invasion (Stettner, Wang et al. 2005, Du, Bernasconi et al. 2009).

In addition, ponatinib is a potent pan-FGFR inhibitor and may be particularly active against patients with FGFR-driven cancers (Gozgit, Wong et al. 2012). In patients with glioblastoma, approximately 3.1% harbor oncogenic chromosomal translocations that fuse the tyrosine kinase coding domains of FGFR genes to the transforming acidic coiled-coil (TACC) coding domains (Gozgit, Wong et al. 2012). The FGFR-TACC fusion protein demonstrates oncogenic activity and inhibition of this with use of an FGFR inhibitor has shown prolonged survival in mice with intracranial glioma harboring the FGFR3-TACC3 fusion (Singh, Chan et al. 2012).

2.4 Correlative Studies Background

1.1.1 Tumor Tissue Markers

Archival tissue will be analyzed for FGFR-TACC fusion protein and correlated with clinical outcomes.

1.1.2 Plasma Markers

Serial monitoring of plasma biomarkers that reflect the effects of anti-angiogenic agents would be an ideal tool to track tumor response and elucidate tumor escape mechanisms. Since angiogenesis requires an exquisite balance of signaling from pro- and anti-angiogenic to maintain the vascular supply (Jain, di Tomaso et al. 2007), multiple biomarkers will need to be monitored. In addition to the VEGF and CXCR4 pathways

described previously, several other molecules have been implicated in tumor angiogenesis, including: placental growth factor (PlGF), angiopoietin-1 (ANG1), angiopoietin-2 (ANG2) and the soluble receptor Tie-2 (Reiss, Machein et al. 2005); the angiogenesis inhibitors tumstatin and thrombspondin-1 (Nyberg, Xie et al. 2005); and the pro-inflammatory chemokine interleukin-8 (IL-8) (Waugh and Wilson 2008).

Additionally, studies have shown that the structure of collagen IV is modified after VEGFR2 blockade (Inai, Mancuso et al. 2004, Tong, Boucher et al. 2004, Winkler, Kozin et al. 2004). Collagen IV degradation subsequently leads to release of tumstatin into the blood stream, whose levels are inversely correlated with angiogenic activity and tumor growth rate (Hamano, Zeisberg et al. 2003).

More recently, clinical studies have shown that plasma levels of angiogenic proteins change with anti-VEGF treatments. A pattern that has been described in several cancers including GBMs is an increase in VEGF and PIGF, along with reduced levels of soluble VEGFR-2 (sVEGFR-2) (Willett, Boucher et al. 2005, Motzer, Michaelson et al. 2006, Batchelor, Sorensen et al. 2007, Drevs, Siegert et al. 2007). One of these studies also demonstrated that plasma levels of circulating cytokines SDF1-α, soluble Tie-2 (sTie-2), bFGF, and collagen IV were predictive of radiographic responses and increased survival to cediranib, a pan-VEGFR inhibitor (Batchelor, Sorensen et al. 2007). Serial monitoring allowed investigators to show that treatment with cediranib elicited a reactive increase in plasma VEGF and PIGF, which reversed during treatment interruptions. These studies demonstrate the feasibility of serum angiogenic cytokines and soluble receptors as predictive and prognostic biomarkers for anti-angiogenesis treatments.

Circulating endothelial cells (CECs, with a CD31+CD45– phenotype) and circulating precursor cells (CPCs, CD34+ cells), may also be potentially useful as a surrogate angiogenesis marker. The use of CECs and CPCs as surrogate angiogenesis markers has been reported in several clinical studies of angiogenesis inhibitors. Bevacizumab, an anti-VEGF agent, decreased the number of viable CECs and CPCs in rectal carcinoma patients (Willett, Boucher et al. 2004).

In patients with recurrent glioblastoma treated with cediranib, progression during treatment with this pan-VEGF receptor tyrosine kinase inhibitor was associated with an increase in viable CEC counts whereas progression during drug interruptions correlated with elevations in circulating progenitor cell counts (Batchelor, Sorensen et al. 2007). These findings may suggest a differential role for viable CECs versus CPCs in assessment of clinical outcomes in recurrent GBM. In addition, preclinical and clinical evidence show that certain CD45+ CD11b+ myelomonocytic cells may have a particularly important role in tumor vasculogenesis and their influx into tumors can be prevented by plerixafor (Kioi, Vogel et al. 2010). Serial monitoring of CECs, CD34+ CPCs, and VEGFR2+CD11b+CD45+ myelomonocytic cells will be measured concomitantly by 8-color flow cytometry. The following biomarkers will be obtained from serial plasma samples of patients treated with plerixafor and bevacizumab: SDF1α, collagen IV, sTie2 and G-CSF (using ELISA kits), and VEGF, PlGF, sVEGFR1, and bFGF (growth factor 1 array plate, Meso-Scale Discovery) and IL-1b, TNF-a, IL-6 and IL-8 (cytokine array plate, Meso-Scale Discovery).

3. PARTICIPANT SELECTION

3.1 Eligibility Criteria

Within 14 days of registration except where otherwise noted, participants must meet the following criteria on screening examination to be eligible to participate in the study:

1.1.3 Age ≥ 18 years

1.1.4 Karnofsky performance status ≥ 60 (see Appendix A)

1.1.5 Participants must have histologically confirmed glioblastoma or variants. Subjects with initial diagnosis of a lower grade glioma are eligible if a subsequent biopsy is determined to be glioblastoma or variants.

1.1.6 Patients must have an unequivocal progression by magnetic resonance imaging (MRI) or computed tomography (CT) scan. A scan must be performed within 14 days prior to registration and on a steroid dose that has been stable or decreasing for at least 5 days. If the steroid dose is increased between the date of imaging and initiation of study treatment, a new baseline MRI/CT is required.

1.1.7 Participants must have bi-dimensionally measurable disease with a minimum measurement of 1 cm per dimension on MRI performed within 14 days prior to registration. If receiving corticosteroids, participants must be on a stable or decreasing dose of corticosteroids for at least 5 days prior to baseline MRI.

1.1.8 There is no limit on the number of prior relapses but the most recent relapse must be the first relapse on a bevacizumab-containing regimen.

1.1.9 Participants must have normal organ and marrow function as defined below:

- Leukocytes ≥ 3,000/mcL (≥ 3,000/mm^3)
- Absolute neutrophil count ≥ 1,500/mcL (≥ 1,500/mm^3)
- Platelets ≥ 100,000/mcL (≥ 100,000/ mm^3)
- Total bilirubin ≤ 1.5 X institutional upper limit of normal, unless due to Gilbert's syndrome.
- AST (SGOT)/ALT (SGPT) ≤ 2.5 X institutional upper limit of normal
- Serum Creatinine ≤ 1.5 X institutional upper limit of normal or or creatinine clearance > 60 mL/min/1.73 m^2 (per 24 hour urine collection or calculated according to the Cockcroft-Gault formula) for subjects with creatinine levels above the institutional normal
- Serum lipase and amylase ≤ 1.5 X institutional upper limit of normal.

1.1.10 Participants must have fully recovered (grade ≤ 1 or baseline or deemed irreversible) from any clinically significant acute toxicity related to prior therapy (with the exception of lymphopenia, which is common after therapy with temozolomide). Patients who discontinued bevacizumab previously due to a bevacizumab-related toxicity will not be allowed to participate.

1.1.11 The following time periods must have elapsed prior to the planned start date of study treatment:

- ≥2 weeks or 6 half lives from any approved TKIs or investigational agent, whichever is shorter
- ≥4 weeks from prior cytotoxic therapy, except ≥ 3 weeks from last dose of temozolomide and ≥6 weeks from nitrosoureas or mitomycin C
- ≥2 weeks from non-cytotoxic agents
- ≥ 3 weeks from bevacizumab

1.1.12 Participants must have developed progressive disease after receiving prior radiation therapy and must have an interval of at least 12 weeks from the completion of any radiation therapy to study entry (unless progressive tumor growth is outside the radiation field or there is histopathological confirmation of recurrent tumor).

1.1.13 Participants may not have received prior therapy with any other Src, PDGFR, or FGFR inhibitor. Prior treatment with an anti-VEGFR or anti-VEGF agent is also allowed but only one relapse following a bevacizumab-containing regimen is allowed.

1.1.14 For women of childbearing potentia (defined as women with menses within the past 2 years) l, a negative serum pregnancy test must be documented prior to registration.

NOTE: In addition to screening, serum pregnancy test must be performed on females of childbearing potential within 72 hours before the start of investigational product. When possible, these tests can be one-in-the-same (if screening pregnancy test was performed within 72 hours of first ponatinib dose, no need to repeat).

1.1.15 The effects of ponatinib on the developing human fetus are unknown. For this reason and because ponatinib is known to be teratogenic in animal models, women of child-bearing potential (defined as women with menses within the past 2 years) and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry, for the duration of study participation, and through 4 months after the end of treatment. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

1.1.16 Ability to understand and the willingness to sign a written informed consent document.

NOTE: Consent documents can be signed up to 30 days prior to registration. If >30 days has elapsed since patient signed the consent document, s/he must re-consent (new signature) before proceeding to register onto study.

1.1.17 Participants must have sufficient tissue from prior surgery revealing glioblastoma or variants for confirmation of diagnosis and correlative studies. The following amount of tissue is required:

- 15 (5 μm thick) unstained formalin fixed paraffin embedded (FFPE) sections
- 1-2 H&E stained slides, or additional unstained 5 μm slide(s) for staining
-

NOTE: The Overall PI will allow for up to 2 participants to enroll with insufficient tissue. If a site is hoping to enroll a patient with less than the tissue required per 3.1.15, prospective approval by the Overall PI is required.

1.1.18 Protocol treatment plan must include beginning therapy within 5 consecutive days after registration.

3.2 Exclusion Criteria

Participants who exhibit any of the following conditions at screening will not be eligible for admission into the study.

1.1.19 Participants may not be receiving any other investigational agents.

1.1.20 History of allergic reactions attributed to compounds of similar chemical or biologic composition to ponatinib.

1.1.21 Participants who have received prior treatment with interstitial brachytherapy, stereotactic radiosurgery, or implanted chemotherapy sources, such as wafers of polifeprosan 20 with carmustine

1.1.22 Participants with poorly controlled diabetes defined as a HgbA1c ≥ 7.0%

1.1.23 Participants with grade ≥ 3 peripheral motor or sensory neuropathy.

1.1.24 Participants receiving any medications or substances that are moderate and strong inhibitors or inducers of CYP3A4, including enzyme-inducing anti-epileptic drugs (EIAEDs) within 14 days before the first dose of ponatinib will be excluded. This category includes phenobarbital, phenytoin, fosphenytoin, primidone, carbamazepine, and oxcarbazepine. Lists including medications and substances known or with the potential to interact with CYP3A4 isoenzymes are provided in Appendix B.

NOTE: Participants must avoid consumption of Seville orange (and juice), grapefruit or grapefruit juice, grapefruit hybrids, pummelos and exotic citrus fruits

from 7 days prior to the first dose of study drug and during the entire study treatment period due to potential CYP3A4 interaction.

1.1.25 Participants taking medications that are known to be associated with Torsades de Pointes or QT prolongation within 14 days of starting treatment. Refer to Tables C-1 and C-2 of Appendix C for a list of prohibited drugs.

1.1.26 Participants cannot take any herbal preparations/medications on study or within 7 days prior to first dose of study drug, including but not limited to: St. John‘s wort, Kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, ginseng.

1.1.27 Participants who underwent major surgery (including craniotomy) or significant traumatic injury within 28 days prior to initiating therapy. Baseline MRIs for participants who underwent salvage surgery must be obtained within 14 days of registration (similar to other patients who do not have surgery) and there must be measurable disease.

1.1.28 Participants who underwent minor surgical procedure within 7 days prior to initiating therapy.

1.1.29 History of a bleeding disorder.

1.1.30 Patients with gastrointestinal bleeding or any other hemorrhage/bleeding event CTCAE Grade ≥ 3 within 30 days prior to study entry.

1.1.31 Patients whose screening MRI scan demonstrates intratumoral hemorrhage or peritumoral hemorrhage are not eligible for treatment if deemed significant by the treating physician. If there are questions, the treating physician should contact the study’s Overall PI, Dr. Lee at 617.632.2166.

1.1.32 History of acute pancreatitis within 1 year of study treatment or a history of chronic pancreatitis.

1.1.33 History of alcohol abuse.

1.1.34 Uncontrolled hypertriglyceridemia (triglycerides >450 mg/dL)

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

- Any history of myocardial infarction
- Any history of clinically significant (as determined by the treating physician) atrial arrhythmia
- Any history of ventricular arrhythmia
- Any history of Cerebrovascular accident or transient ischemic attack (TIA)

- Any history of peripheral arterial occlusive disease requiring revascularization
- Unstable angina within 6 months prior to enrollment
- Congestive heart failure within 6 months prior to enrollment
- Venous thromboembolism including deep venous thrombosis or pulmonary embolism within 6 months prior to enrollment
- Unacceptable Screening Baseline Cardiovascular Assessment:
    - Baseline MUGA (to be done within 30 days of registration) or Echocardiogram demonstrating LVEF < 50 %
    - QTc $\geq$ 480 msec on screening ECG (using the QTcF formula)

1.1.36 Uncontrolled hypertension (diastolic blood pressure >90 mm Hg; systolic >140 mm Hg). Patients with hypertension should be under treatment on study entry to effect blood pressure control.

1.1.37 Ongoing or active infection. The requirement for intravenous (IV) antibiotics is considered active infection.

1.1.38 Known history of human immunodeficiency virus (HIV). Testing is not required in the absence of prior documentation or known history.

1.1.38.1 HIV-positive individuals on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with ponatinib. In addition, these individuals are at increased risk of lethal infections when treated with marrow-suppressive therapy. Appropriate studies will be undertaken in participants receiving combination antiretroviral therapy when indicated.

1.1.39 Pregnant or breastfeeding.

1.1.39.1 Pregnant women are excluded from this study because ponatinib has potential for teratogenic or abortifacient effects in animal models. Because there is an unknown but potential risk of adverse events in nursing infants secondary to treatment of the mother with ponatinib, breastfeeding should be discontinued if the mother is treated with ponatinib. These potential risks may also apply to other agents used in this study.

1.1.40 Malabsorption syndrome or other gastrointestinal illness that could affect oral absorption of study drugs.

1.1.41 Individuals with a history of a different malignancy, other than cervical cancer in situ, basal cell or squamous cell carcinoma of the skin, are ineligible, except if they have been disease-free for at least 5 years, and are deemed by the investigator to be at low risk for recurrence of that malignancy OR if the other primary malignancy is neither currently clinically significant nor requiring active intervention.

1.1.42 Any condition or illness that, in the opinion of the Investigator, would compromise patient safety or interfere with the evaluation of the drug.

3.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

4. REGISTRATION PROCEDURES

4.1 General Guidelines for DF/HCC Institutions

Institutions will register eligible participants in the Clinical Trials Management System (OnCore) . Registrations must occur prior to the initiation of protocol therapy. Any participant not registered to the protocol before protocol therapy begins will be considered ineligible and registration will be denied.

An investigator will confirm eligibility criteria and a member of the study team will complete the protocol-specific eligibility checklist.

Following registration, participants may begin protocol therapy. As noted in 3.1.16, protocol treatment must begin within 5 consecutive days after registration. Issues that would cause treatment delays should be discussed with the Overall Principal Investigator (PI). If a participant does not receive protocol therapy following registration, the participant's registration on the study must be cancelled. Registration cancellations must be made in OnCore as soon as possible.

4.2 Registration Process for DF/HCC Institutions

DF/HCC Standard Operating Procedure for Human Subject Research Titled *Subject Protocol Registration* (SOP #: REGIST-101) must be followed.

5. TREATMENT PLAN

5.1 Treatment Regimen and Agent Administration

Treatment will be administered on an outpatient basis. Expected toxicities and potential risks as well as dose modifications for ponatinib are described in Section 6 (Expected Toxicities and Dosing Delays/Dose Modification). No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy.

Protocol treatment must begin within 5 consecutive days after registration. The starting dose of ponatinib will be 45 mg taken orally once-daily. Patients will take the prescribed number of tablets with water, with or without food, at approximately the same time each day. Patients will be provided a medication diary (Appendix D) where administration specifics will be recorded (dose, date, time). The medication diary will be returned to clinic staff at the end of each cycle and a new one will be given to the participant for the next cycle. Participants are to return all ponatinib pill bottles and unused ponatinib pills.

Patients who forget to take their dose more than 6 hours after it is due should not make up the missed dose. Patients who vomit after taking their dose should not make up that dose, but take the next dose at the planned time, if clinically indicated. Any missing doses should be recorded, and subsequent training of patients should be documented in the appropriate source record. Pills must not be crushed, chewed, or dissolved in water.

Treatment cycles are 28 days in length; days are counted continuously, even if treatment is held for toxicity. During dose interruptions, continue to observe the study schedule as planned. All study evaluations and treatments should continue as if study treatment is not being held. Following a dose delay which resumes mid cycle, day 1 procedures not associated with the adverse event do not need to be repeated. If study drug is held across a time point which requires collection of a research blood sample, please contact Dr. Eudocia Quant Lee to confirm whether or not the sample should be collected or if the drug hold will negate the value of collection of the sample in question. If you anticipate the occurrence of such a scenario, please contact the DFCI Coordinating Center as soon as possible in order to establish a plan prior to the time point in question. If a participant requires a treatment hold > 28 days, then the participant must be discontinued from study treatment.

Criteria for dose modifications and delays apply to intracycle administration and Day 1 administrations; **there are no separate 'start of cycle' criteria. However Day 1 treatments may not begin until the respective results of the Day 1 procedures are reviewed**. Required assessments and windows for assessments are detailed in Section 9.

All patients are to be started at a 45-mg dose once daily. For patients with stable disease or better at the end of Cycle 6, as determined by RANO (Wen, Macdonald et al. 2010), the dose of ponatinib must be reduced to 30 mg QD, if not already dose-reduced for other reasons.

5.2 General Concomitant Medication and Supportive Care Guidelines

An analysis of baseline risk factors in patients from the PACE study assessed the impact of hypertension, hypercholesterolemia, diabetes, and obesity, and revealed several risk factors that pre-dispose patients to vaso-occlusive events (VOEs) on ponatinib. Based on an analysis of odds ratios (OR), the leading risk factors for serious arterial VOEs are cardiovascular disorders such as any history of MI (OR = 6.86), coronary artery disease (OR = 7.14), and coronary revascularization (OR = 6.19). The OR for serious arterial VOEs is 3.53 for history of ischemic cerebrovascular disease, 3.78 for diabetes mellitus, 2.49 for hypertension, and 2.07 for hypercholesterolemia. Based on this analysis, the following supportive care recommendations are provided to decrease the risk of VOEs for patients taking ponatinib.

Anti-diabetic Treatment

Patients with diabetes are at increased risk of experiencing arterial thrombotic events while being treated with ponatinib. Therefore, as a part of the assessment and management of the patient's cardiovascular risk factors, initiation of or modifications to diabetic care should be considered in patients being treated with ponatinib who have elevated glucose levels. The American Diabetes Association guidelines should be followed, and anti-diabetic treatment and lifestyle intervention (includes but are not limited to weight loss, decreased fat intake, calorie restriction, increased physical activity, and smoking cessation) should be started in any patient with fasting glucose >130 mg/dL (7.2 mM/L) and/or HbA1c ≥7% {Knowler, 2002 #129}{American Diabetes, 2003 #131}.

Hypertension Treatment

Hypertension (HTN) may contribute to risk of arterial thrombotic events. Patients who have HTN should be managed appropriately before initiating treatment. During ponatinib treatment, blood pressure elevations should be monitored and managed. Hypertension should be treated to achieve a goal of <150/90 mmHg. Initial antihypertensive treatment should generally include a thiazide-type diuretic, calcium channel blocker (CCB), angiotensin-converting enzyme inhibitor (ACEI), or angiotensin receptor blocker (ARB){James, 2014 #132}. Ponatinib treatment should be temporarily interrupted if HTN is not medically controlled (refer to Section 6.2.5below for additional management recommendations). Patients may require urgent clinical intervention for HTN associated with confusion, headache, chest pain, or shortness of breath.

OTHER CONCOMITANT MEDICATIONS

Participants must be instructed not to take any additional medications (including over-the-counter products) during the trial without prior consultation with the investigator. All medications taken within 30 days of screening should be recorded. If concomitant therapy must be added or changed, including over-the-counter medications or alternative therapies, the reason and name of the drug/therapy should be recorded.

In general, the use of any concomitant medication/therapies deemed necessary for the care of the participant are allowed, including drugs given prophylactically (e.g., antiemetics) with the following exceptions:

5.2.1 Moderate and strong CYP3A inhibitors and CYP3A inducers are **prohibited**. In vitro studies suggest that ponatinib is a sensitive CYP3A4 substrate. Co-administration of ponatinib with strong and moderate CYP3A4 inhibitors is predicted to increase the systemic exposure to ponatinib; likewise CYP3A inducers can be expected to decrease systemic exposure to ponatinib, possibly resulting in sub-therapeutic drug levels. Refer to Appendix B for a list of CYP3A inhibitors and inducers.

5.2.2 QT interval prolonging medications known to induce Torsades de Pointes (TdP) or to promote QT prolongation are prohibited at study entry.

5.2.2.1 If a participant, after initiating study drug, requires the concomitant use of a drug known to prolong the QT interval, then investigators, at their discretion may co-administer such medications with appropriate monitoring; however, participants must **not** initiate any medication known to induce TdP. Refer to Appendix C (Table C-1) for a list of prohibited drugs on study.

5.2.2.2 Concomitant use of QT prolonging medications that have a conditional or possible risk to induce Torsades de Pointes is allowed with caution and monitoring. Please refer to Appendix C (Table C-2) for a list of drugs.

5.2.3 Herbal preparations/medications are not allowed throughout the study. These herbal medications include, but are not limited to: St. John‘s wort, Kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, ginseng. Participants should stop using any herbal medications 7 days prior to first dose of study drug.

5.2.4 Anti-seizure medications should be used as indicated. Only participants receiving non-EIAEDs are eligible. If for unavoidable clinical reasons (emergency department visit, severe allergies, toxicities, etc.) a participant‘s AED is switched to another AED, the participant should be started on another non-EIAED if at all possible. Participants who need to permanently change anticonvulsant, but who cannot change to another non-EIAED, must be discussed with the PI.

5.2.5 Prophylactic use of aspirin and/or statins will be left to the discretion of the prescribing physician.

5.2.6 Febrile neutropenia should be managed according to NCCN guidelines or the local institution's guidelines. Measures may include appropriate laboratory testing, including blood and urine cultures and the institution of broad-spectrum antibiotics. If a source for the fever is not identified or the fever resolves when the neutrophil count recovers, antibiotics may be discontinued and the participant observed. If a patient’s individual risk factors place them at high risk of developing febrile neutropenia, primary prophylaxis use of colony-stimulating growth factors for the prevention or reduction of febrile neutropenia is recommended according to the published NCCN guidelines

5.2.7 Antiemetics: The use of antiemetics will be left to the investigators‘ discretion. The preferred antiemetic is metoclopramide which is not known to prolong QTc. Prophylactic anti-emetic is not recommended as it is not necessary.

5.3 Criteria for Taking a Participant Off Protocol Therapy

Duration of therapy will depend on individual response, evidence of disease progression and tolerance. In the absence of treatment delays due to adverse event(s), treatment may continue indefinitely, until one of the following criteria applies:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Participant demonstrates an inability or unwillingness to comply with the oral medication regimen and/or documentation requirements,
- Participant has a confirmed positive serum pregnancy test,
- Participant decides to withdraw from the protocol therapy, or
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the opinion of the treating investigator.

Participants will be removed from the protocol therapy when any of these criteria apply. The reason for removal from protocol therapy, and the date the participant was removed, must be documented in the case report form (CRF). Alternative care options will be discussed with the participant.

A QACT Treatment Ended/Off Study Form will be filled out when a participant is removed from protocol therapy. This form can be found on the QACT website or obtained from the QACT registration staff.

In the event of unusual or life-threatening complications, treating investigators must immediately notify the Overall PI, Eudocia Quant Lee, MD, at DFCI Page: 617-632-3352, ID # 49318.

5.4 Duration of Follow Up

Participants removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event. All participants will be followed until resolution or stabilization of any serious adverse events occurring during treatment or starting within 30 days of last study drug.

30-Day Follow-Up: A 30-day post-treatment evaluation is to be performed at 30 days (+/- 5 days) after last dose of study drug; these may be performed by documented clinician telephone call, if a physical visit is not feasible.

Long Term Follow-Up: After the 30-day post-treatment evaluation, participants will be followed every 3 months (+/- 1 month) for survival, post-study-therapy therapies and future relapses until patient either passes away or is lost to follow-up.

5.5 Criteria for Taking a Participant Off Study

Participants will be removed from study when any of the following criteria apply:

- Lost to follow-up
- Withdrawal of consent
- Death

The reason for study removal and the date the participant was removed must be documented in the study-specific case report form (CRF). Alternative care options will be discussed with the participant.

A QACT Treatment Ended/Off Study Form will be filled out when a participant comes off study. This form can be found on the QACT website or obtained from the QACT registration staff.

6. EXPECTED TOXICITIES AND DOSING DELAYS/DOSE MODIFICATIONS

Table 6.0: Ponatinib Dose Levels

Dose Level	Ponatinib
0 (starting dose)	45 mg daily
-1	30 mg daily
-2	15 mg daily
-3	15 mg every other day

All patients are to be started at a 45-mg dose QD. For patients with stable disease or better at the end of Cycle 6, as determined by RANO (Wen, Macdonald et al. 2010), the dose of ponatinib must be reduced to 30 mg QD, if not already dose-reduced for other reasons.

For participants who are unable to tolerate the protocol-specified dosing schedule, dose adjustments are permitted in order to keep the participant on study drug. If administration of ponatinib must be interrupted because of unacceptable toxicity, drug dosing will be interrupted or modified according to rules described in Table 6.2.

Dose delays and modifications will be made using the following recommendations. Toxicity assessments will be done using the CTEP Active Version (version 4.0) of the NCI Common Terminology Criteria for Adverse Events (CTCAE) which is identified and located on the CTEP website at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

If possible, symptoms should be managed symptomatically. In the case of toxicity, appropriate medical treatment should be used (including anti-emetics, anti-diarrheals, etc.).

All adverse events experienced by participants will be collected from the time of the first dose of study treatment until the 30-day post-treatment evaluation. Participants continuing to experience toxicity at the 30-day post-treatment evaluation may be contacted for additional assessments until the toxicity has resolved or is deemed irreversible.

6.1 Anticipated Toxicities

In order for an event to be considered expected (known correlation to study drug) for the purposes of adverse event reporting, the event must be included in this section.

1.1.43 A list of adverse events of all grades suspected to be ponatinib related, organized by CTCAE v4.0 category, includes:

- BLOOD and LYMPHATIC SYSTEM DISORDERS –
  - anemia, bone marrow hypocellular, febrile neutropenia, neutropenia, spleen disorder, & thrombocytopenia
- CARDIAC DISORDERS –
  - acute coronary syndrome, atrial fibrillation, atrial flutter, atrioventricular block, cardiac arrest*, heart failure, left ventricular systolic dysfunction, myocardial infarction (this may include: cardiogenic shock, cardiopulmonary failure, myocardial ischemia)*, paroxysmal atrial tachycardia, pericardial effusion, restrictive cardiomyopathy, right ventricular dysfunction, sick sinus syndrome, sinus bradycardia, & supraventricular tachycardia,
  - cardiac disorders, other - specify: arrhythmia, coronary artery disease, coronary artery stenosis, & superventricular tachycardia
- EYE DISORDERS –
  - blurred vision, dry eye, eye pain, eyelid edema, & retinal vascular disorder
  - eye disorders, other - specify: visual acuity reduced, visual disturbance, & visual impairment
- GASTROINTESTINAL DISORDERS –
  - abdominal distention, abdominal pain, ascites, constipation, diarrhea, dry mouth, dyspepsia, gastric hemorrhage*, gastric perforation, hemorrhoidal hemorrhage, ileal fistula, intra-abdominal hemorrhage, mucositis oral, nausea, oral pain, pancreatitis, pharyngeal mucositis rectal hemorrhage, stomach pain, upper gastrointestinal hemorrhage, vomiting
  - gastrointestinal disorders, other - specify: hematemesis & lip blister
- GENERAL DISORDERS and ADMINISTRATION SITE CONDITIONS –
  - chills, edema (face, limbs, and trunk), fatigue, ,fever, generalized muscle weakness, non-cardiac chest pain, pain, & wound complication
- HEPATOBILIARY DISORDERS –
  - hepatic failure*, SGOT elevation, SGPT elevation, & viral hepatitis
  - hepatobiliary disorders, other - specify: portal vein thrombosis
- IMMUNE SYSTEM DISORDERS –
  - allergic reaction

- INFECTIONS and INFESTATIONS –
  - lung infection*, pharyngitis, sepsis, skin infection, upper respiratory tract infection, & urinary tract infection
  - infections and infestations, other - specify: folliculitis & influenza
- INVESTIGATIONS –
  - alanine aminotransferase increased, alkaline phosphatase increased, aspartate aminotransferase increased, blood bilirubin increased, CPK increased, creatinine increased, electrocardiogram QT corrected interval prolonged, GGT increased, hypophosphatemia, lipase increased, lymphocyte count decreased, neutrophil count decreased, pancreatic enzymes increased, platelet count decreased, serum amylase increased, weight loss, white blood cell decreased
- METABOLISM and NUTRITION DISORDERS –
  - acidosis, anorexia, dehydration*, hypercalcemia, hyperkalemia, hyperglycemia, Hypernatremia, hypertriglyceridemia, hyperuricemia, hypocalcemia, hypokalemia, hypoalbuminemia, hypoglycemia, hypophosphatemia, tumor lysis syndrome
- MUSCULOSKELETAL and CONNECTIVE TISSUE DISORDERS –
  - arthralgia, back pain, bone pain, myalgia, neck pain, pain in extremity
  - musculoskeletal and connective tissue disorder, other - specify: muscle spasms
- NERVOUS SYSTEM DISORDERS –
  - dizziness, dysesthesia, edema cerebral*, headache, intracranial hemorrhage, neuralgia, peripheral motor neuropathy, peripheral sensory neuropathy, stroke
  - nervous system disorders, other - specify: transient ischemic attack
- PSYCHIATRIC DISORDERS –
  - insomnia
- REPRODUCTIVE SYSTEM and BREAST DISORDERS –
  - erectile dysfunction
- RESPIRATORY, THORACIC, and MEDIASTINAL DISORDERS –
  - cough, dyspnea, epistaxis, hoarseness, pleural effusion, pulmonary edema, pulmonary fibrosis
- SKIN and SUBCUTANEOUS TISSUE DISORDERS –
  - alopecia, bullous dermatitis, dry skin, erythema multiforme, hyperhidrosis, pruritus, rash acneiform, rash maculo-papular, Stevens Johnson syndrome
  - skin and subcutaneous tissue disorders, other - specify: hyperkeratosis & night sweats
- VASCULAR DISORDERS –
  - flushing, hot flashes, hypertension, peripheral ischemia, thromboembolic event
  - vascular disorders, other - specify: aortic thrombosis, carotid artery stenosis, cerebral artery stenosis, extremity necrosis, femoral artery occlusion, peripheral arterial occlusive disease, peripheral artery stenosis, peripheral vascular disease, subclavian artery stenosis, vertebral artery stenosis

Asterisked events include fatal outcome

6.2 Dose Modifications/Delays

Criteria for disrupting treatment, dose modification, or discontinuation are found below and in Table 6.2. Toxicity will be assessed using the NIH-NCI Common Terminology Criteria for Adverse Events, version 4.0 (CTCAEv4.0). These guidelines should be followed by clinical investigators; however, for an individual patient, dose interruptions, reductions, and treatment discontinuation should also be based on the clinical circumstance. Deviation from these guidelines must be documented and communicated with the study's Overall PI, Dr. Eudocia Quant Lee (prospectively whenever possible).

NOTE: Section 6.3 provides additional guidance for management of selected AEs for ponatinib.

Comprehensive assessments of any AEs (adverse events) experienced by the patient will be performed throughout the course of the study. Anticipated study-drug related adverse drug reactions that may be experienced are described in section 6.1.1 above. The severity of the event, as well as clinical judgment, will be utilized to determine appropriate management of the patient for any AE experienced while participating in this study.

Any medication, including those administered for therapy of symptoms considered associated with study drug administration, should be reported on the appropriate concomitant medication page of the patient's eCRF. The symptoms should be reported on the AE page.

NOTE: When choosing medications to manage toxicities per the instructions below (Sections 6.2 & 6.3), please refer to sections 5.2.1 – 5.2.7 for a list of prohibited and discouraged concomitant medication/therapies.

No dose re-escalation will be allowed.

No dose reduction below 15 mg every other day is permitted for ponatinib. If the patient cannot tolerate a minimum dose of 15 mg every other day of ponatinib, despite any allowed interruptions, the patient must be discontinued from study treatment. Doses may be interrupted for study-drug related toxicities for up to 28 days. If a nonhematologic study-drug related toxicity does not resolve to ≤ grade 1 or baseline after dose interruption for more than 28 days, the patient must be discontinued from study treatment. If a hematologic study-drug related toxicity does not resolve to ≤ grade 1 or baseline after dose interruption for more than 28 days, the study's Overall PI, Dr. Eudocia Quant Lee, must be contacted. Additionally, the Overall PI must be contacted if any adverse event deemed unrelated to treatment requires dose interruption for more than 28 days.

Cycle length will be 4 weeks (28 days), even if treatment is held for toxicity. During dose interruptions, continue to observe the study schedule as planned. All study evaluations and treatments should continue as if study treatment is not being held.

Following a dose delay which resumes mid cycle, day 1 procedures not associated with the adverse event do not need to be repeated.

If study drug is held across a time point which requires collection of a research blood sample, please contact Dr. Eudocia Quant Lee to confirm whether or not the sample should be collected or if the drug hold will negate the value of collection of the sample in question. If you anticipate the occurrence of such a scenario, please contact the DFCI Coordinating Center as soon as possible in order to establish a plan prior to the time point in question.

Participants who experience an adverse event that requires a treatment delay or dose reduction should be monitored with appropriate laboratory testing or other clinical evaluation at least weekly until resolution.

> Participants whose treatment is interrupted or permanently discontinued due to an adverse event or clinically significant laboratory value, must be followed as outlined in Table 6.2, at least once a week for 4 weeks, and subsequently at 4-week intervals, until resolution or stabilization of the event, whichever comes first. All participants must be followed for adverse events and serious adverse events up to the 30-day post treatment evaluation (section 5.4). All SAEs must be reported as detailed in Table 11.3.

When treatment must be held pending resolution of toxicity to grade 1 or return to baseline, and the toxicity is a lab abnormality, in cases where participant had a pre-existing laboratory abnormality at baseline, the toxicity can be considered "resolved" from a hold perspective when it has resolved to within 1 grade of the baseline value.

> NOTE: For the purposes of data entry, values from screening assessments should be entered in as 'baseline' values. However, true "baseline values" - for the purpose of dose modifications on study, etc. - will be considered the last assessments/tests performed prior to initiation of study therapy.
>
> Exception: In instances where the value within 1 grade of the baseline value would still require a hold, continue to hold until resolution of toxicity to grade 1 or return to baseline.

Interrupt ponatinib for at least 1 week prior to any major surgery. Contact Dr. Lee to determine when participant may resume treatment ponatinib after his/her surgery.

Table 6.2: Ponatinib Dose Modifications for Adverse Drug Reactions Attributed to Ponatinib

Ponatinib dose modifications listed below are to be followed for adverse events considered at least possibly related to Ponatinib.

NOTE: In the event of a grade 4 toxicity deemed *unrelated* to treatment, Investigator Team can hold drug in patient's best interest after discussion with and approval from the study's Overall PI, Dr. Eudocia Quant Lee.

SOC	Toxicity	Dose Modifications for Ponatinib
Non-Hematologic Toxicity		
General (not otherwise specified)	**General (not otherwise specified)**	
	General (not otherwise specified), Grade 1 or transient grade 2	Maintain ponatinib at current dose
	General (not otherwise specified), Grade 2 lasting ≥7 days with optimal care	First occurrence at any dose level: Hold ponatinib Resume at current dose level after recovery to ≤ grade 1 or return to baseline Recurrence* at 45 mg, 30 mg, or 15 mg daily: Hold ponatinib Resume after recovery to ≤ grade 1 or return to baseline; reduce dose by one dose-level Recurrence at 15 mg every other day: Discontinue ponatinib
	General (not otherwise specified), Grade 3 or 4	Occurrence** at 45 mg, 30 mg, or 15 mg daily: Hold ponatinib Resume after recovery to ≤ grade 1 or return to baseline; reduce dose by one dose-level Occurrence at 15 mg every other day: Discontinue ponatinib
Cardiac Disorders	**Myocardial Infarction**	
	Serious Myocardial Infarction (Any Grade)	Discontinue ponatinib
	Urgent Revascularization (Cardiac Disorders, Other)	
	Cardiac Disorders, Other: Specify: Urgent Revascularization (Any Grade)	Discontinue ponatinib
	LV systolic dysfunction/Heart Failure (CHF)	

SOC	Toxicity	Dose Modifications for Ponatinib
	Grade 2 LV systolic dysfunction: *N/A* Heart failure: *Symptoms with mild to moderate activity or exertion*	First occurrence at any dose level: Hold ponatinib Resume at current dose level after recovery to ≤ grade 1 or return to baseline Recurrence at 45 mg, 30 mg, or 15 mg daily: Hold ponatinib Resume after recovery to ≤ grade 1 or return to baseline; reduce dose by one dose-level Recurrence at 15 mg every other day: Discontinue ponatinib
	Grade 3 LV systolic dysfunction: *Symptomatic due to drop in ejection fraction responsive to intervention* Heart failure: *Severe with symptoms at rest or with minimal activity or exertion; intervention indicated*	Occurrence at 45 mg, 30 mg, or 15 mg daily: Hold ponatinib Resume after recovery to ≤ grade 1 or return to baseline; reduce dose by one dose-level Occurrence at 15 mg every other day: Discontinue ponatinib
Cardiac Disorders	Grade 4 LV systolic dysfunction: *Refractory or poorly controlled heart failure due to drop in ejection fraction; intervention such as ventricular assist device, intravenous vasopressor support, or heart transplant indicated* Heart failure: *Life-threatening consequences; urgent intervention indicated (e.g., continuous IV therapy or mechanical hemodynamic support)*	Hold ponatinib Consult Overall PI (Dr. Lee) about how to proceed with treatment

SOC	Toxicity	Dose Modifications for Ponatinib
GI Disorders / Investigations	**Pancreatitis and Elevation of Lipase**	
	Asymptomatic grade 1 or 2 elevation of serum lipase	Consider interruption or dose reduction of ponatinib
	Asymptomatic grade 3 or 4 elevation of lipase (>2 × ULN) or asymptomatic radiologic pancreatitis (grade 2 pancreatitis)	Occurrence at 45 mg, 30 mg, or 15 mg daily: Hold ponatinib Resume after recovery to ≤ grade 1 (≤ 1.5 x ULN) or return to baseline; reduce dose by one dose-level Occurrence at 15 mg every other day: Discontinue ponatinib
	Symptomatic grade 3 pancreatitis [severe pain, vomiting, medical intervention indicated (eg, analgesia, nutritional support)]	Occurrence at 45 mg, 30 mg, or 15 mg daily: Hold ponatinib Resume after complete resolution of symptoms and after recovery of lipase elevation to ≤ grade 1 or return to baseline; reduce dose by one dose-level Occurrence at 15 mg every other day: Discontinue ponatinib
	Grade 4 pancreatitis (life-threatening consequences; urgent intervention indicated)	Discontinue ponatinib

SOC	Toxicity	Dose Modifications for Ponatinib
Investigations	**Serum Amalyse Increased**	
	Serum amylase increased, Grade 1 or 2	Continue ponatinib without dose reduction, and monitor closely with serial enzyme level determinations
	Serum amylase increased, Grade 3 or 4	First occurrence at any dose level: Hold ponatinib Resume at current dose level after recovery to ≤ grade 1 or return to baseline Recurrence at 45 mg, 30 mg, or 15 mg daily: Hold ponatinib Resume after recovery to ≤ grade 1 or return to baseline; reduce dose by one dose-level Recurrence at 15 mg every other day: Discontinue ponatinib
	Hepatic Toxicity	
	Elevation of liver transaminase >3 × ULN (grade 2 or higher)	Occurrence at 45 mg, 30 mg, or 15 mg daily: Hold ponatinib and monitor hepatic function Resume after recovery to ≤ grade 1 (≤3 × ULN) or return to baseline; reduce dose by one dose-level Occurrence at 15 mg every other day: Discontinue ponatinib
	Elevation of AST or ALT ≥3 × ULN concurrent with an elevation of bilirubin >2 × ULN and alkaline phosphatase >2 × ULN	Discontinue ponatinib
General disorders and	**Edema (limbs, trunk, face, localized)**	
	Edema, Grade 1	Maintain ponatinib at current dose
	Edema, Grade 2 lasting ≥7 days with optimal care	First occurrence at any dose level: Hold ponatinib Resume at current dose level after recovery to ≤ grade 1 or return to baseline Recurrence* at 45 mg, 30 mg, or 15 mg daily: Hold ponatinib Resume after recovery to ≤ grade 1 or return to baseline; reduce dose by one dose-level Recurrence at 15 mg every other day: Discontinue ponatinib

SOC	Toxicity	Dose Modifications for Ponatinib
	Edema, Grade 3	First occurrence at any dose level: Hold ponatinib Resume at current dose level after recovery to ≤ grade 1 or return to baseline Recurrence at 45 mg, 30 mg, or 15 mg daily: Hold ponatinib Resume after recovery to ≤ grade 1 or return to baseline; reduce dose by one dose-level Recurrence at 15 mg every other day: Discontinue ponatinib

Metabolism and	**Hyperglycemia**	
	Hyperglycemia, All Grades	Maintain ponatinib at current dose The American Diabetes Association guidelines should be followed
Nervous System Disorders	**Peripheral Neuropathy (motor or sensory)**	
	Peripheral Neuropathy (motor or sensory), Grade 1 or 2	Maintain ponatinib at current dose
	Peripheral Neuropathy (motor or sensory), Grade 3 or 4	Occurrence at 45 mg, 30 mg, or 15 mg daily: Hold ponatinib Resume after recovery to ≤ grade 1 or return to baseline; reduce dose by one dose-level Occurrence at 15 mg every other day: Discontinue ponatinib
	Stroke	
	Serious Stroke (Any Grade)	Discontinue ponatinib

Skin and subcutaneous tissue disorders	**Skin rash (Any type of rash)**	
	Skin rash, Grade 1 or 2 or tolerable Grade 3	Maintain ponatinib at current dose. Consider initiating therapy (e.g. antihistamine, steroid, emmolient) as per section 6.3.12.
	Skin rash, Grade 4 or Intolerable Grade 3 despite optimal symptomatic therapy	Occurrence at 45 mg, 30 mg, or 15 mg daily: Hold ponatinib Resume after recovery to ≤ grade 1 or return to baseline; reduce dose by one dose-level Occurrence at 15 mg every other day: Discontinue ponatinib
Vascular Disorders	**Hypertension**	
	Hypertension, Grade 1	Maintain ponatinib at current dose
	Hypertension, Grade 2 or 3	See Section 6.3.5 for HTN management. If unable to control hypertension (<150/100 mmHg) within 28 days, discontinue ponatinib
	Hypertension, Grade 4	Discontinue ponatinib

Vascular Disorders	**Thromboembolic Event**	
	Thromboembolic Event, Grade 1 or 2	Maintain ponatinib at current dose
	Thromboembolic Event, Grade 3 Thromboembolic Event, Asymptomatic Grade 4	**1st event and not with a post inferior vena cava filter and not on fully therapeutic anticoagulation therapy**: Hold ponatinib. Treatment may resume at pre-hold dose as soon as the patient is considered clinically stable and is on full dose anticoagulation therapy and has not had a Grade 3 or 4 hemorrhagic event since initiating anticoagulation therapy. For anticoagulation therapy, the patient may only receive low molecular weight heparin or a Factor Xa inhibitor; Warfarin is not permitted. As an alternative to anticoagulation therapy, the patient may resume treatment as soon as clinically stable and is status post inferior vena cava filter placement; however anticoagulation therapy is preferred over IVC filter placement. (Since patients must be on anticoagulation therapy or have an IVC filter in order to resume, no second event shall occur). **Event with a post inferior vena cava filter and not on fully therapeutic anticoagulation therapy**: Hold ponatinib. Treatment may resume at pre-hold dose as soon as the patient is considered clinically stable and is on full dose anticoagulation therapy and has not had a Grade 3 or 4 hemorrhagic event since initiating anticoagulation therapy. For anticoagulation therapy, the patient may only receive low molecular weight heparin or a Factor Xa inhibitor; Warfarin is not permitted. **Event while on therapeutic anticoagulation therapy**: Discontinue ponatinib.
	Thromboembolic Event, Symptomatic Grade 4	Discontinue ponatinib
	Arterial Thromboembolic Event, Any Grade (New onset, worsening, or unstable angina, myocardial infarction, transient ischemic attack, cerebrovascular accident, and any other arterial thromboembolic event)	Discontinue ponatinib
Multiple System Organ Classes	**Hemorrhage of any kind**	
	Non-CNS event, Grade 1	Maintain ponatinib at current dose
	Non-CNS hemorrhage, Grade > 1	Discontinue ponatinib
	New CNS hemorrhage, Grade ≥ 1	Discontinue ponatinib

Hematologic Toxicity		
Investigations	***Drug-Related* ANC/platelets**	
	Grade 1 or 2 Neutrophil count decreased o <LLN - 1000/mm^3; o <LLN - 1.0 x $10e^9$ /L Platelet count decreased o <LLN - 50,000/mm^3; o <LLN - 50.0 x $10e^9$ /L	Maintain ponatinib at current dose
	Grade 3 or 4 Neutrophil count decreased o < 1000/mm^3; o < 1.0 x $10e^9$ /L Platelet count decreased o < 50,000/mm^3; o < 50.0 x $10e^9$ /L	First occurrence at any dose level: Hold ponatinib Resume at current dose level after recovery to ≤ grade 1 or return to baseline Recurrence at 45 mg, 30 mg, or 15 mg daily: Hold ponatinib Resume after recovery to ≤ grade 1 or return to baseline; reduce dose by one dose-level Recurrence at 15 mg every other day: Discontinue ponatinib
General (not otherwise specified)	**General (not otherwise specified)**	
	General (not otherwise specified), Grade 1 or transient grade 2	Maintain ponatinib at current dose
	General (not otherwise specified), Grade 2 lasting ≥7 days with optimal care	First occurrence at any dose level: Hold ponatinib Resume at current dose level after recovery to ≤ grade 1 or return to baseline Recurrence at 45 mg, 30 mg, or 15 mg daily: Hold ponatinib Resume after recovery to ≤ grade 1 or return to baseline; reduce dose by one dose-level Recurrence at 15 mg every other day: Discontinue ponatinib
	General (not otherwise specified), Grade 3 or 4	Occurrence** at 45 mg, 30 mg, or 15 mg daily: Hold ponatinib Resume after recovery to ≤ grade 1 or return to baseline; reduce dose by one dose-level Occurrence at 15 mg every other day: Discontinue ponatinib

* "Recurrence" means the second time an AE is encountered by a patient at a given dose level.
** "Occurrence" means the first time an AE is encountered by a patient at a given dose level.

Definitions: ANC = absolute neutrophil count; CHF = congestive heart failure; CT = computed tomography; LV = left ventricular.

6.3 Toxicity Management

Criteria for disrupting treatment, dose modification, or discontinuation are found in Section 6.2 above, including Table 6.2. This section provides additional guidance for management of selected AEs for ponatinib.

1.1.44 Vascular Occlusion

Serious arterial and venous thrombotic and occlusive adverse events, 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 ponatinib-treated patients. Patients with and without cardiovascular risk factors, including patients age 50 years or younger, experienced these events. Vascular occlusive adverse events were more frequent with increasing age and in patients with prior history of ischemia, hypertension, diabetes, or hyperlipidemia.

1.1.44.1 Arterial Occlusion and Thrombosis

Serious arterial thrombotic adverse events occurred in ponatinib-treated patients with some patients experiencing events of more than one type. Serious cardiovascular thrombotic adverse events included myocardial infarction and coronary artery disease. Some patients developed congestive heart failure concurrent or subsequent to the myocardial ischemic event.

Serious cerebrovascular adverse events were also reported in ponatinib-treated patients. There were patients who developed stenosis of large arterial vessels of the brain (eg, carotid, vertebral, middle cerebral artery).

Serious peripheral arterial adverse events were reported in ponatinib-treated patients; some patients developed digital or distal extremity necrosis with complications of diabetes mellitus and peripheral arterial disease that required amputations.

Monitor and aggressively treat factors that increase cardiovascular risk, such as hypertension, cigarette smoking, hypercholesterolemia, and hyperglycemia. Interrupt and consider discontinuation of study drug in patients who develop arterial thrombotic adverse events. Any patient who experiences a serious adverse event of myocardial infarction, stroke, or urgent revascularization while on trial must be discontinued from the trial unless, for that individual patient, the investigator believes the potential benefits of ponatinib treatment are likely to exceed the risks of continued treatment and the patient has no other treatment options.

1.1.44.2 Venous Thromboembolism

Serious venous thromboembolic adverse events occurred in ponatinib-treated patients, including deep venous thrombosis, pulmonary embolism, superficial thrombophlebitis, and retinal vein thrombosis. Consider dose modification or discontinuation of ponatinib in patients who develop serious venous thromboembolic adverse events.

Ponatinib should not be restarted in patients with serious venous occlusive adverse events unless the potential benefit outweighs the risk of recurrent venous occlusions and the patient has no other treatment options.

1.1.45 Neuropathy

Serious peripheral and cranial neuropathic adverse events have occurred in ponatinib-treated patients. In clinical trials, serious peripheral neuropathic adverse events reported included the following: peripheral neuropathy, paresthesia, hypoesthesia, and hyperesthesia. Of the patients who developed neuropathy, many 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 ponatinib and evaluate if neuropathy is suspected.

1.1.46 Hepatotoxicity

Hepatotoxicity, most commonly manifested by reversible transaminase and alkaline phosphatase elevation and hyperbilirubinemia, has been observed with ponatinib. Monitoring of hepatic function is recommended and management of laboratory abnormalities should be managed with dose interruption and/or dose reduction according to Table 6.2.

1.1.47 Congestive Heart Failure and Left Ventricular Dysfunction

Severe congestive heart failure (CHF) and left ventricular (LV) dysfunction have been reported in patients taking ponatinib. Patients with cardiac disease or risk factors for cardiac disease should be monitored carefully and any patient with signs or symptoms consistent with cardiac failure should be evaluated and treated. In patients who develop severe CHF (grade 4 left ventricular dysfunction), ponatinib should be held and the overall PI (Dr. Lee) should be consulted to determine how/if to proceed with treatment.

1.1.48 Hypertension

Blood pressure should be monitored at each visit. Hypertension (HTN) by at least 2 blood pressure measurements should be graded according to CTCAE version 4.0, which defines HTN as a disorder characterized by a pathological increase in blood pressure; a repeated elevation in the blood pressure exceeding 140 mm Hg for systolic over 90 mm Hg for diastolic. For patients who develop HTN or worsening HTN during study treatment, aggressive 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, or if grade 4 HTN develops, dose interruption and reduction is recommended according to Dose Modification Guidelines in Table 6.2.

1.1.49 Ocular Toxicity

Serious ocular adverse event toxicities leading to blindness or blurred vision have occurred in ponatinib-treated patients. Retinal toxicities including macular edema, retinal vein occlusion, and retinal hemorrhage have also occurred in ponatinib-treated patients. Other ocular toxicities include cataracts, glaucoma, iritis, iridocyclitis, and ulcerative keratitis. Conduct comprehensive eye exams at baseline and when clinically indicated. See the 'Non-Heme: General (not otherwise specified)' category of Table 6.2 for dose modification details.

1.1.50 Pancreatitis and Lipase or Amylase Elevations

Pancreatitis (symptomatic abdominal pain associated with pancreatic enzyme elevation) and/or elevations in lipase and amylase are known AEs associated with ponatinib. Most cases of pancreatitis or elevated pancreatic enzymes occur within the first 2 months of treatment with ponatinib. The events are generally uncomplicated and reversible and can be managed with a brief interruption of treatment and standard medical therapies. Almost all patients are able to continue on with ponatinib treatment at the same or a reduced dose once the event has improved to grade 1 or resolved. Patients with low-grade (1 or 2) elevation in amylase can be continued without dose reduction but should be monitored closely with serial enzyme level determinations. See Table 6.2 for details.

1.1.51 Hemorrhage

Hemorrhagic events have occurred in patients receiving ponatinib. Most hemorrhagic events occurred in patients with grade 4 thrombocytopenia. Maintain or discontinue ponatinib as outlined in Table 6.2.

1.1.52 Fluid Retention and Edema

Ponatinib is associated with edema and occasionally serious fluid retention. Patients should be weighed and monitored regularly for signs and symptoms of fluid retention. An unexpected rapid weight gain should be carefully investigated and appropriate treatment provided. Interrupt, reduce the dose of, or discontinue ponatinib as outlined in Table 6.2.

1.1.53 Cardiac Arrhythmias

Supraventricular tachyarrhythmias were reported in patients treated with ponatinib. Advise patients to report signs and symptoms of rapid heart rate (palpitations, dizziness). Symptomatic bradyarrhythmias have also been reported. Advise patients to report signs and symptoms suggestive of slow heart rate (fainting, dizziness, or chest pain, see Table 6.2).

1.1.54 Myelosuppression

Neutropenia, anemia, and thrombocytopenia have been observed in clinical studies of ponatinib in patients with CML. While myelosuppression can occur at any time during treatment, its onset in CML patients most commonly occurs within the first month on treatment. Myelosuppression can partially be attributed to the CML itself; however, treatment with ponatinib could also contribute. These events can typically be managed with supportive care and, if felt to be treatment-related, either a reduction or interruption of treatment with ponatinib should occur. Rarely, one or more cytopenias can lead to permanent discontinuation of treatment. The use of hematopoietic growth factors such as granulocyte colony-stimulating factor, and granulocyte-macrophage colony-stimulating factor is permitted on study; these agents may be used to support blood counts as clinically indicated to minimize treatment interruptions or repeated dose reductions.

The important clinical AE of febrile neutropenia falls under the broad category of myelosuppression. If a patient's individual risk factors place them at high risk of developing febrile neutropenia, primary prophylaxis use of colony-stimulating growth factors for the prevention or reduction of febrile neutropenia is recommended according to the published NCCN guidelines [NCCN Guidelines Version 1.2012 – Myeloid Growth Factors].

1.1.55 Rash and/or Pruritus

Skin rashes have been commonly reported to be associated with ponatinib. The vast majority of the skin events are nonserious, either self-limiting or manageable with antihistamines or topical steroids, and do not result in discontinuation. In more severe cases, a short course of oral corticosteroids may be used until the rash has improved or resolved.

In patients treated with ponatinib, the most common skin manifestations are a diffuse maculo-papular rash that is non-pruritic or an acneiform dermititis. Occasionally, patients treated with ponatinib have been reported to have a dry, flaky or exfoliative type of rash or a psoriasiform dermatitis. Rarely, an erythema multiforme type of rash has been associated with ponatinib.

Most patients can be maintained on the current dose of ponatinib, uninterrupted, and if necessary their symptoms can be managed with antihistamines, emollients, or topical steroids. Follow the dose modification guidelines for 'Skin rash' in Table 6.2.

1.1.56 Diarrhea, Nausea, and Vomiting

Diarrhea is a common side effect of ponatinib. The use of anti-diarrhea medications is permitted. Patients who experience ≥grade 2 diarrhea may begin loperamide at its standard treatment schedule (4 mg orally x 1, than 2 mg orally after each loose stool, up to a maximum of 16 mg/day).

Nausea and vomiting are also reported as side effects of ponatinib. The use of an antiemetic prophylactically is not recommended. However, if a patient is symptomatic, appropriate antiemetic medications may be used as clinically indicated.

1.1.57 Constitutional Symptoms/Joint Pain

Certain constitutional symptoms such as myalgia, arthralgia, headache, weakness, fatigue, asthenia, and low grade fever have been very commonly reported with ponatinib. These symptoms have been reported mainly at the initiation of treatment, are typically short lived (<2 weeks), and are seldom, if ever, reported beyond the first month of treatment. These AEs are most commonly low grade (grade 1 and 2) and are self-resolving without the need for dose interruption or dose reduction when they do occur. Most patients can be maintained on the current dose of ponatinib, uninterrupted, and their symptoms can be managed with a short course of oral analagesics, corticosteroids, and/or anti-pyretics as clinically indicated. If dose interruption is indicated, patients can resume the same dose of ponatinib typically without recurrence of symptoms once the original episode has improved or resolved.

1.1.58 Compromised Wound Healing and Gastrointestinal Perforation

Based on its mechanism of action, ponatinib may compromise wound healing. Interrupt ponatinib for at least 1 week prior to major surgery. Contact Dr. Lee to determine when participant may resume treatment ponatinib after his/her surgery.

1.1.59 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 Table 6.2 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 treatment, or more frequently as clinically indicated.

7. DRUG FORMULATION AND ADMINISTRATION

7.1 Ponatinib

1.1.60 Description

The drug substance ponatinib (laboratory code AP24534) HCl is the mono-hydrochloride salt of the active moiety ponatinib free base.

Chemical International Union of Pure and Applied Chemistry (IUPAC) name: 3-(imidazo[1,2-b]pyridazin-3-ylethynyl)-4-methyl-N-{4-[(4-methylpiperazin-1-yl)methyl]-3-(trifluoromethyl)phenyl} benzamide, hydrochloride salt

Chemical Abstracts Service (CAS) Index name: Benzamide,3-(2-imidazo[1,2-b]pyridazin-3-ylethynyl)-4-methyl-N-[4-[(4-methyl-1-piperazinyl)methyl]-3-(trifluoromethyl)phenyl]-, hydrochloride (1:1)

International Non-Proprietary Name (INN): ponatinib

CAS Registry number: 1114544-31-8 (HCl salt), 943319-70-8 (free base)

Ponatinib HCl is an off-white to yellow crystalline, anhydrous solid. The molecular formula of ponatinib HCl is C29H28ClF3N6O, and the molecular weight is 569.02. A single crystal form of ponatinib HCl has been identified by X-ray powder diffraction. The melting point by differential scanning calorimetry (DSC) is in the range of 250°C to 265°C. Ponatinib HCl has a thermodynamic solubility in hydrochloric acid-potassium chloride of 2.64 mg/mL at pH 1.7. The free base ponatinib has a solubility in hydrochloric acid-potassium chloride at pH 1.7 of 2.64 mg/mL, and has an aqueous solubility of less than 0.0001 mg/mL at pH 7.5; it can exist in polymorphic forms. Ponatinib free base has been observed in amorphous and 4 crystalline forms. Ponatinib has no chiral centers.

1.1.61 **Form**

Ponatinib for investigational use is supplied as off-white opaque capsules containing nominally 5 mg of ponatinib, or as 15 mg and 45 mg round, white, film-coated tablets. On this trial, ponatinib will be provided as 15 mg tablets in 90-count bottles. Inactive ingredients in the capsule blend are colloidal silicon dioxide, lactose anhydrous, magnesium stearate, microcrystalline cellulose, and sodium starch glycolate. The capsule shell contains gelatin and titanium dioxide. The tablet formulation includes inactive ingredients lactose monohydrate, microcrystalline cellulose, sodium starch glycolate, colloidal silicon dioxide, and magnesium stearate; tablet film coating is comprised of polyethylene glycol, talc, polyvinyl alcohol, and titanium dioxide.

All excipients used in the manufacture of ponatinib tablets and capsules are of compendial grade. Lactose anhydrous, lactose monohydrate, and gelatin comply with applicable regulatory guidelines regarding materials of animal origin. No other excipients of human or animal origin are used in the formulation of ponatinib tablets or capsules.

1.1.62 **Storage and Handling**

Ponatinib drug product is recommended for storage below 30°C.

1.1.63 **Availability**

Ponatinib is an investigational agent and will be supplied free-of-charge from Ariad Pharmaceuticals.

1.1.64 **Ordering**

The initial shipment of ponatinib will be ordered by ARIAD upon receipt of IRB approval and other required documentation. Ponatinib re-supplies will be ordered from each institution's individual pharmacy (or designee) using an ARIAD Investigational Product Re-Supply Request Form. This form will be supplied to each institution's pharmacy by the coordinating center once the study meets the requirements for activation. The number of requested bottles and the shipping address to where the drug should be sent are detailed on the Re-Supply Request Form. All sites should anticipate 3-5 business days to receive drug after the order is placed.

1.1.65 **Accountability**

The investigator, or a responsible party designated by the investigator, should maintain a careful record of the inventory and disposition of the agent using the NCI Drug Accountability Record Form (DARF) or another comparable drug accountability form. (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.)

Ponatinib dispensing record/inventory logs and copies of signed packing lists should be maintained at the investigational site. Batch numbers for ponatinib should be recorded in the drug accountability records.

1.1.66 **Destruction and Return**

Participating sites will follow their institutional policy regarding destruction of returned empty and partially used investigational drug.

8. CORRELATIVE/SPECIAL STUDIES

8.1 Plasma Biomarkers

NOTE: Given the large number of samples to be processed, please notify Anna Khachatryan and Julia Kahn (annak@steele.mgh.harvard.edu; julia@steele.mgh.harvard.edu) two days prior to each blood sample collection.

NOTE: Each site is responsible for providing tubes.

NOTE: The submitting institution is responsible for the costs of shipping and handling.

NOTE: For all submissions, please notify the Dana Farber NeuroOncology Coordinating Center Team by e-mail at NeuroOnc_Coor@dfci.harvard.edu regarding shipment (date mailed, mail carrier, tracking number, participant case numbers).

Blood samples will be obtained for protein analysis of potential biomarkers for anti-angiogenic therapy and for cell collection at the following time points:

Blood Collection Timepoints:

- Cycle 1, Day 1: prior to the first ponatinib dose
- Cycle 1, Day 2: 24 hours (+/- 4 hrs) following the first ponatinib dose but prior to the second ponatinib dose
- Subsequent Cycles, Day 1 pre-ponatinib (+/- 3 days)
- Off Treatment

1.1.67 Sample Collecting and Processing

At the time points specified above, TWO blood samples (~8 ml each) will be collected using either SARSTEDT Monovette® EDTA KE (9 ml), Part # 02.1333.001 or Becton-Dickinson VacutainerTM K2E (10 ml), Part # 367525 or Greiner Bio-One Vacuette® K3E EDTA K3 (9 ml), Part 455036. Tubes must be processed within 2 hours after collection*. Each site is responsible for providing tubes.

Sample processing:

- Collect 2 tubes of ~8 ml each of blood. The tubes must be pre-cooled in an ice bath.
- Gently invert five to six times to ensure adequate mixing and prevent coagulation.
- Cool the tubes immediately in an ice bath.
- Place tubes on wet ice and send to Steele Laboratory (see Section 8.2.3)
- Call courier for pick-up and delivery of specimen

* Should a sample be drawn without sufficient time to be processed at the Steele Lab within 2 hours of collection, (e.g. in the event patient is drawn at 4 pm), please refer to processing instructions provided in Appendix E. This alternative should be avoided whenever possible.

1.1.68 Sample Labeling

Each site is responsible for providing tubes and labels. The vial is to be labeled with the following information:

Patient study number
Patient Initials
Military time sample was obtained
Date sample was obtained
Cycle #/Day# of sample

If a paper labels are used, protective tape, such as Scienceware* Protective Lab Labeling Tape > 1-1/2 in. x 108 ft.; (Fisher catalog # 11-867B; Bel-Art No.:134530015), should cover the label in its entirety to prevent the label from degrading. Otherwise, indelible marker is to be used directly on the tube.

1.1.69 Shipment and Packaging of the Samples

Each site is responsible for providing shipping of the samples. The tubes should remain on wet ice and delivered to the Steele Laboratory using a courier.

Dan G. Duda, DMD, PhD
Attn: Anna Khachatryan and Julia Kahn
Steele Laboratory
Massachusetts General Hospital, Cox-734
100 Blossom Street
Boston, MA 02114
Phone (617) 724-1352
Partners pager 14082
Email: annak@steele.mgh.harvard.edu; julia@steele.mgh.harvard.edu

1.1.70 Plasma Sample Analysis

Analyses will be performed in the laboratory of Rakesh K. Jain, PhD, and Dan G. Duda, DMD, PhD, in the Department of Radiation Oncology at Massachusetts General Hospital per established protocols (Batchelor, Sorensen et al. 2007).

8.2 Tissue Submissions

NOTE: The submitting institution is responsible for the costs of shipping and handling.

NOTE: For all submissions, please notify the Dana Farber NeuroOncology Coordinating Center Team by e-mail at NeuroOnc_Coor@dfci.harvard.edu regarding shipment (date mailed, mail carrier, tracking number, participant case numbers).

1.1.71 Pathology Review (mandatory for all patients)

a. Following registration, slides from the prior surgery/biopsy revealing glioblastoma or variants must be submitted for review. The purpose of this review is to verify the histologic diagnosis.

The materials are to be submitted within approximately 60 days of registration to:

Keith L. Ligon, M.D., Ph.D.
c/o Sarah Gaffey

b. Pathology Materials Required for Review:
   1. One to two representative H&E stained slides from a pre-registration biopsy or resection demonstrating lesion (ideally from patient's most recent surgery/biopsy)
      - or additional unstained 5 μm slide(s) for staining
   2. A copy of the corresponding pathology report and operative report.
   3. A printout of The Central Path Review Study eCRF

1.1.72 Archival Tissue for Tissue Biomarker Analysis

Paraffin slides will be used for DNA isolation and immunohistochemistry to evaluate molecular pathways such as the VEGFR, FGFR, and PDGFR pathways. We will attempt to correlate tumor genotype and vascularity with response to treatment.

At the completion of the study, any unused/remaining material will be stored for future research according to the patient consent permission. Potential future research may include immunohistochemistry (IHC) analyses, DNA extraction, and/or tissue microarray (TMA) construction to analyze predictive biomarkers, changes in expression pattern with therapy, and correlation with response and/or adverse events.

The following will be submitted to the Steele Laboratory for tissue biomarker analysis:

- 15 (5 µm thick) unstained formalin fixed paraffin embedded (FFPE) sections from archival surgery/biopsy

The materials are to be submitted within approximately 60 days of registration to:

Dan G. Duda, DMD, PhD
Attn: Anna Khachatryan and Julia Kahn
Steele Laboratory
Massachusetts General Hospital, Cox-734
100 Blossom Street
Boston, MA 02114
Phone (617) 724-1352
Partners pager 14082
Email: annak@steele.mgh.harvard.edu; julia@steele.mgh.harvard.edu

Pathology Materials Required for Review:

1. Slides as specified above
2. A copy of the applicable pathology reports and operative reports
3. A printout of The Tissue Biomarker Study eCRF

9. STUDY CALENDAR

Baseline evaluations (including MRI/CT scan) are to be conducted within 14 days prior to registration, unless otherwise noted. In the event that the participant's condition is deteriorating, laboratory evaluations should be repeated within 72 hours prior to initiation of the next cycle of therapy.

All study labs and assessments:

- Must be resulted prior administration of any study medication on Day 1 of each Cycle, unless otherwise specified (e.g., plasma biomarkers).
- And can be performed within 3 days prior to Day 1 of each Cycle, including Cycle 1

	Pre-Study[a]	Cycle 1, Day 1[b]	Subsequent Cycles, Day 1[b,c]	Off Treatment	30 Days After Study Drug Visit[d]	Long-Term Follow Up[e]
Ponatinib		X[m] ----------X				
Informed consent[q]	X					
Documentation of tumor diagnosis	X					
History and Height	X					
Concurrent Medications[r]	X	X----------X			X	
Physical exam (weight, vital signs including blood pressure)[n]	X	X	X	X		
KPS	X	X	X	X	X	
Neurologic Exam	X	X	X	X		
Comprehensive Eye Exam[s]	X	*If clinically indicated*	*If clinically indicated*	*If clinically indicated*	*If clinically indicated*	
EKG[f]	X	X	X[f]			
CBC w/differential	X	X	X	X		
Serum Chemistry[g] (2- hours Fasting)	X	X	X	X		
Serum Beta-HCG[h]	X	X	X			
Lipid Panel and HgbA1c	X[o]					
MUGA or ECHO	X[t]					
Adverse Events[i]		X----------X			X	
Submission of Tissue		X[p]				
Tumor measurement[j,k]	X[j]		Prior to every even-numbered cycle[j,]	X[k]		
Plasma Biomarkers[l]		X	X	X		
Survival, post-study-therapies, future relapses					X	X

a. Screening labs and assessments may be used for C1D1, provided they are taken within 3 days prior to day 1 of study drug.
b. All Day 1 evaluations must be performed within 3 days of Day 1.
c. A window of +/- 2 day is permitted for Day 1 starts for Cycle 2 and beyond.
d. 30-day off-study evaluation is to be performed at 30 days (+/- 5 days) after last dose of study drug; these may be performed by documented clinician telephone call, if a physical visit is not feasible.

e. Participants will be followed every 3 months (+/- 1 month) for survival, post-study-therapy therapies and future relapses until patient either passes away or is lost to follow-up.

f. EKG at screening and prior to every odd cycle.
   - NOTE: For participants who develop prolonged QTcF as described in section 6.3.16, participants should be monitored with weekly EKG x 4 weeks, then monthly EKG x 6 months, then EKG every 3 months for remainder of the study treatment, or more frequently as clinically indicated.

g. Chemistry: Creatinine or creatinine clearance, total bilirubin (if total bilirubin is greater than the upper limit of normal, direct and indirect bilirubin should be performed), SGOT [AST], SGPT [ALT], LDH, alkaline phosphatase, albumin, total protein, BUN, calcium, fasting plasma glucose (2 hours fasting), phosphorus, potassium, sodium, bicarbonate, chloride, magnesium. GGT, amylase, and lipase.

h. Serum pregnancy test (women of childbearing potential) must be performed at screening and again within 72 hours before the start of investigational product. When possible, these tests can be one-in-the-same (if screening pregnancy test was performed within 72 hours of first ponatinib dose, no need to repeat); otherwise, pregnancy test must be repeated within 72 hours prior to first ponatinib dose.

i. Adverse events will be collected from the time of the first dose of study treatment until the 30-day post-dose evaluation. Participants continuing to experience toxicity at the 30-day post-dose evaluation may be contacted for additional assessments until the toxicity has resolved or is deemed irreversible.

j. Brain MRI (standard contrast enhanced MRI of the head) will be performed at baseline, prior to Cycle 2, and then prior to every even-numbered cycles (approximately every 8 weeks) thereafter. Perfusion and diffusion MRI should be performed at baseline and prior to Cycle 2. The baseline scan must be performed within 14 days prior to registration. Each scan should be performed on a steroid dose that has been stable or decreasing for at least 5 days. If the steroid dose is increased within 5 days from the date of scheduled imaging or if it is increased between the date of imaging and initiation of study treatment, a new baseline MRI/CT is required. The same type of scan (i.e., MRI or CT) must be used throughout the period of protocol treatment for tumor measurement. A patient who develops a contraindication to undergo an MRI scan during study treatment may remain on study and undergo contrast enhanced CT scans.

k. Off-Treatment MRI/CT is to be performed within 14 days of the last dose of study drug administration.

l. Details regarding collection of plasma biomarkers are available in Section 8.1. These do not need to be resulted prior to study drug administration.

m. Protocol treatment must begin within 5 consecutive days after registration.

n. Vital signs: weight, heart rate, blood pressure, respiration rate, temperature, and oxygen saturation. Repeat BP if systolic > 140 mm Hg or if diastolic > over 90 mm Hg.

o. Lipid panel to screen for possible hypercholesterolemia (to include HDL, LDL, triglycerides and VLDL) ; HgbA1c to screen for possible diabetes

p. Submission of tissue is to occur within approx 60 days after registration (please see Section 8.2).

q. Consent documents can be signed up to 30 days prior to registration. If > 30 days has elapsed since patient signed the consent document, s/he must re-consent (new signature) before proceeding to register on study.

r. All medications taken within 30 days of screening should be recorded. If concomitant therapy must be added or changed, included over-the-counter medications or alternative therapies, the reason and name of the drug/therapy should be recorded.

s. A comprehensive eye exam must be performed at screening. Additional exams should be performed as clinically indicated. The eye exam should test visual acuity, refraction, pupillary function, ocular motility, visual fields, and introcular pressure.

t. MUGA or ECHO to be done within 30 days of registration in order to screen for possible cardiovascular issues.

10. MEASUREMENT OF EFFECT

10.1 Antitumor Effect

For the purposes of this study, patients should be reevaluated for response prior to even cycles (C2D1 and every 8 weeks thereafter). In addition to a baseline scan, confirmatory scans should also be obtained not less than 4 weeks after the initial documentation of objective response.

Response and progression will be evaluated in this study using RANO response criteria (Section 10.1.4) (Wen, Macdonald et al. 2010). Efficacy evaluations will occur every 8 weeks and will consist of imaging and clinical assessment.

1.1.73 Definitions

Evaluable for toxicity. All participants who receive at least one dose of study treatment will be evaluable for toxicity from the time of their first treatment.

Evaluable for objective response. Only those participants who have measurable disease present at baseline, have received at least one dose of ponatinib, and have had their disease re-evaluated will be considered evaluable for response. These participants will have their response classified according to the definitions stated below. (Note: Participants who exhibit objective disease progression or die prior to the end of cycle 1 will also be considered evaluable.)

1.1.74 Disease Parameters

Measurable disease. Measurable disease is defined as bidimensionally contrast-enhancing lesions with clearly defined margins by CT or MRI scan, with two perpendicular diameters of at least 10 mm, visible on 2 or more axial slices which are preferably at most 5 mm apart with 0 mm skip. In the event the MRI is performed with thicker slices, the size of a measurable lesion at baseline should be two times the slice thickness. Measurement of tumor around a cyst or surgical cavity represents a particularly difficult challenge. In general such lesions should be considered non-measurable unless there is a nodular component measuring > 10 mm in diameter. The cystic or surgical cavity should not be measured in determining response.

Non-measurable disease. Non-measurable disease is defined as either unidimensionally measurable lesions, masses with margins not clearly defined, or lesions with maximal perpendicular diameters < 10 mm.

Number of lesions. If there are multiple contrast-enhancing lesions, a minimum of the two largest lesions should be measured and the sum of the products of the perpendicular diameters of these lesions determined. However, given the heterogeneity of high-grade gliomas, and the difficulty in measuring some lesions, a maximum of 5 of the largest lesions may be measured.

1.1.75 Methods for Evaluation of Measurable Disease

Neurological Examination

A neurological examination will be performed at baseline and before each 28-day course of therapy. The clinical examination will be conducted by a member of the neuro-oncology study team (neuro-oncologist or nurse practitioner). Evaluation will be based on changes in signs or symptoms compared to the prior examination and deemed unrelated to a post-ictal state or an unrelated event such as an infection or venous thrombosis. Relative changes will be graded as definitely better, possibly better, unchanged, possibly worse or definitely worse.

Radiologic Assessment

All patients will be followed with contrast-enhanced brain MRI (preferred) or contrast-enhanced head CT. All efficacy determinations will be based on RANO response criteria (Section 10.1.4) (Wen, Macdonald et al. 2010).

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 14 days prior to registration. Thereafter, tumor measurements will be obtained prior to every even cycle (approximately every 8 weeks) days after the first dose as long as the patient remains on the study drug.

1.1.76 Response Criteria

Radiographic response should be determined in comparison to the tumor measurement obtained at pretreatment baseline for determination of response, and the smallest tumor measurement at either pretreatment baseline or following initiation of therapy for determination of progression. Table 10-1 outlines the criteria for radiographic changes following therapy. Table 10-2 contains a summary of RANO response criteria. In the event that the radiographic changes are equivocal and it is unclear whether the patient is stable or has developed progressive disease, it is permissible to continue treatment and observe the patient closely, for example at 4 weekly intervals. If subsequent imaging studies demonstrate that progression has occurred, the date of progression should be the scan at which this issue was first raised.

All measurable and non-measurable lesions should be assessed using the same techniques as baseline. Ideally patients should be imaged on the same MRI, or least with the same magnet strength, for the duration of the study to reduce difficulties in interpreting changes.

Table 10.1: Criteria for Response Assessment Incorporating MRI And Clinical Factors

All measurable and non-measurable lesions must be assessed using the same techniques as baseline.

Complete Response:

Requires all of the following:

a) Complete disappearance of all enhancing measurable and non-measurable disease sustained for at least 4 weeks.
b) No new lesions.
c) Stable or improved non-enhancing (T2/FLAIR) lesions.
d) Patients must be off corticosteroids (or on physiologic replacement doses only).
e) Stable or improved clinically.

NOTES:

- Patients with non-measurable disease only cannot have a complete response. The best response possible is stable disease.
- In the absence of a scan confirming sustained response 4 weeks later, best response would be considered a Non-Sustained Complete Response

Partial Response:

Requires all of the following:

a) Greater than or equal to 50% decrease compared to baseline in the sum of products of perpendicular diameters of all measurable enhancing lesions sustained for at least 4 weeks.
b) No progression of non-measurable disease.
c) No new lesions.
d) Stable or improved non-enhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared to baseline scan.
e) The corticosteroid dose at the time of the scan evaluation should be no greater than the dose at time of baseline scan.
f) Stable or improved clinically.

NOTES:

- Patients with non-measurable disease only cannot have a partial response. The best response possible is stable disease.
- In the absence of a scan confirming sustained response 4 weeks later, best response would be considered a Non-Sustained Partial Response

Stable Disease:

Requires all of the following:

a) Does not qualify for complete response, partial response, or progression.
b) Stable non-enhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared to baseline scan. In the event that the corticosteroid dose was increased for new symptoms and signs without confirmation of disease progression on neuroimaging, and subsequent follow-up imaging shows that this increase in corticosteroids was required because of disease progression, the last scan considered to show stable disease will be the scan obtained when the corticosteroid dose was equivalent to the baseline dose.
c) Stable clinically.

NOTE: In the absence of a scan confirming stable disease 4 weeks later, best response would be considered Non-Sustained Stable Disease

Progression:

Defined by any of the following:

a) Greater than > 25% increase in sum of the products of perpendicular diameters of enhancing lesions compared to the smallest tumor measurement obtained either at baseline (if no decrease) or best response, on stable or increasing doses of corticosteroids.*
b) Significant increase in T2/FLAIR non-enhancing lesion on stable or increasing doses of corticosteroids compared to baseline scan or best response following initiation of therapy,* not due to co-morbid events (e.g. radiation therapy, demyelination, ischemic injury, infection, seizures, post-operative changes, or other treatment effects).
c) Any new lesion.
d) Clear clinical deterioration not attributable to other causes apart from the tumor (e.g. seizures, medication side effects, complications of therapy, cerebrovascular events, infection, etc.) or changes in corticosteroid dose.
e) Failure to return for evaluation due to death or deteriorating condition.
f) Clear progression of non-measurable disease.

*Stable doses of corticosteroids include patients not on corticosteroids

Table 10.2: Summary of RANO Response Criteria

	CR	PR	SD	PD#
T1-Gd +	None	≥50% decrease	<50% decrease- <25% increase	≥25% increase*
T2/FLAIR	Stable or decrease	Stable or decrease	Stable or decrease	Increase*
New Lesion	None	None	None	Present*
Corticosteroids	None	Stable or decrease	Stable or decrease	NA
Clinical Status	Stable or increase	Stable or increase	Stable or increase	Decrease*
Requirement for Response	All	All	All	Any*

CR=complete response; PR=partial response; SD=stable disease; PD=progressive disease

#: Progression occurs when any of the criteria with * is present

NA: Increase in corticosteroids alone will not be taken into account in determining progression in the absence of persistent clinical deterioration

Evaluation of Best Overall Response.

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria. Complete and partial responses should be confirmed by two consecutive evaluations done at least four weeks apart. Stable disease will be accepted if it is measured at least two cycles (8 weeks) after the start of treatment and confirmed at least four weeks apart.

1.1.77 Efficacy Assessments

Progression free survival (PFS) will be defined from the time the patient enters the study until there is clinical or radiographic evidence of progressive disease (see definition of PD above).

Overall survival (OS) will be defined from the time the patient enters the study to the date of death. Patients not known to have died will be censored for survival as of the last date known alive.

PFS and overall survival will be estimated by using the Kaplan-Meier method.

The proportion of patients alive and progression free at 3 months (PFS3) is defined as the number of patients alive and progression free at 3 months divided by the total number of patients enrolled.

Radiographic response is defined as the proportion of patients with a best overall response of CR or PR divided by the total number of patients enrolled.

10.2 Response Review

Central review of MRI or CT scans is planned for participants who achieve CR, PR, or PFS3.

Central review will be performed by Dr. Lee on registered participants who have been determined by the enrolling institution as having achieved PFS3, complete radiographic response, or partial radiographic response. When a participant’s films are requested, all films of all views from pre-registration and subsequent scans must be submitted for central review. Once the Central Review is complete, the central review results will be made available to the local PI.

The submitting institution is responsible for the costs of shipping scans for central review.

11. ADVERSE EVENT REPORTING REQUIREMENTS

11.1 Adverse Event Characteristics and Definitions:

1.1.78 Adverse Event (AE) Definition:

An adverse event (AE) is any undesirable sign, symptom or medical condition or experience that develops or worsens in severity after starting the first dose of study treatment or any procedure specified in the protocol, even if the event is not considered to be related to the study.

Abnormal laboratory values or diagnostic test results constitute adverse events only if they induce clinical signs or symptoms or require treatment or further diagnostic tests.

1.1.79 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.

1.1.80 General Considerations:

- Information on all adverse events, whether reported by the participant, directly observed, or detected by physical examination, laboratory test or other means, will be collected, recorded, followed and reported as described in the following sections.
- The occurrence of adverse events should be sought by non-directive questioning of the participant at each visit during the study. Adverse events also may be detected when they are volunteered by the participant during or between visits or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:
  - the severity grade (using CTCAE v. 4.0)
  - its attribution to the study drug
  - its duration (start and end dates or if continuing at final exam)
  - action taken (no action taken; study drug dosage adjusted/temporarily interrupted; study drug permanently discontinued due to this adverse event; concomitant medication taken; non-drug therapy given; hospitalization/prolonged hospitalization)
  - whether it constitutes a serious adverse event (SAE)
- Adverse events experienced by participants will be collected and reported from **initiation of study medication**, throughout the study, and within 30 days of the last dose of study medication. Participants who experience an ongoing adverse event related to a study procedure and/or study medication beyond 30 days will continue to be contacted by a member of the study team until the event is resolved, stabilized, or determined to be irreversible by the participating investigator.

- All adverse events should be treated appropriately. Such treatment may include changes in study drug treatment including possible interruption or discontinuation, starting or stopping concomitant treatments, changes in the frequency or nature of assessments, hospitalization, or any other medically required intervention. Once an adverse event is detected, it should be followed until its resolution, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.
- Participants should be instructed to report any serious post-study-treatment event(s) that might reasonably be related to participation in this study. The investigator should notify the IRB and any other applicable regulatory agency of any unanticipated death or adverse event occurring after a participant has discontinued or terminated study participation that may reasonably be related to the study.

1.1.81 For expedited reporting purposes only:

- AEs for ponatinib should be reported only if the adverse event varies in nature, intensity or frequency from the expected toxicity information which is provided.
- Other AEs for the protocol that do not require expedited reporting are outlined in the next section (Expedited Adverse Event Reporting) under the sub-heading of Protocol-Specific Expedited Adverse Event Reporting Exclusions.

1.1.82 Expectedness of the AE: Adverse events can be 'Expected' or 'Unexpected.'

- Expected adverse event

  "Expected" adverse events are those that have been previously identified as resulting from administration of the agent. For recording and reporting purposes on this trial, an adverse event is considered expected when it appears in the Ponatinib expected adverse events list Section 6.1.1 of the protocol.
- Unexpected adverse event

  For recording and reporting purposes on this trial, an adverse event is considered "unexpected" when it varies in nature, intensity or frequency from information provided in the Ponatinib expected adverse events list Section 6.1.1 of the protocol.

1.1.83 Attribution of the AE:

- Definite – The AE *is clearly related* to the study treatment.
- Probable – The AE *is likely related* to the study treatment.
- Possible – The AE *may be related* to the study treatment.
- Unlikely – The AE *is doubtfully related* to the study treatment.
- Unrelated – The AE *is clearly NOT related* to the study treatment.

1.1.84 Serious Adverse Event (SAE) Definition:

A serious adverse event (SAE) is any adverse event, occurring at any dose and regardless of causality that:

- Results in death
- Is life-threatening. Life-threatening means that the person was at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form.
- Requires or prolongs inpatient hospitalization (i.e., the event required at least a 24-hour hospitalization or prolonged a hospitalization beyond the expected length of stay). Hospitalization admissions and/or surgical operations scheduled to occur during the study period, but planned prior to study entry are not considered SAEs if the illness or disease existed before the person was enrolled in the trial, provided that it did not deteriorate in an unexpected manner during the trial (e.g., surgery performed earlier than planned).
- Results in persistent or significant disability/incapacity. Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.
- Is a congenital anomaly or birth defect; or
- Is an important medical event when, based upon appropriate medical judgment, it may jeopardize the participant and require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

All serious adverse events, whether "reportable" as defined in this protocol or not, must be reported to ARIAD.

1.1.84.1 Protocol-Specific Expedited Adverse Event Reporting Exclusions:

Events **not** considered to be serious adverse events are:

- Hospitalization for routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, or for elective procedures
- Hospitalization for elective or pre-planned treatment for a pre-existing condition that did not worsen
- Emergency outpatient treatment for an event not fulfilling the serious criteria outlined above and not resulting in inpatient admission
- Hospitalization for respite care not associated with an adverse event attributed to the study drug
- Hospitalization for seizure, if felt related to patient's underlying disease
- Hospitalization for treatment of patient's underlying disease (e.g. admission after patient is removed from active study treatment for craniotomy)
- Lymphopenia (grades 2-4)

1.1.85 Adverse Events of Special Interest (AESIs) Definition:

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 (cross-refer to the section where the serious criteria are described and defined) 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

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.

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).

11.2 Procedures for AE and SAE Recording and Reporting

Participating investigators will assess the occurrence of AEs and SAEs at all participant evaluation time points during the study.

All AEs and SAEs whether reported by the participant, discovered during questioning, directly observed, or detected by physical examination, laboratory test or other means, will be recorded in the participant's medical record and on the appropriate study-specific case report forms (eCRFs).

11.3 Expedited Adverse Event Reporting Requirements (By Site to Overall PI and ARIAD Pharmaceuticals)

The study must be conducted in compliance with FDA regulations, local safety reporting requirements, and reporting requirements of the principal investigator.

Each adverse event will be assessed to determine if it meets the criteria for reporting. Adverse event reporting is to occur according to the site's specific IRB guidelines, and as outlined in this Section. Any serious adverse event occurring after the participant is registered in the study and until 30 days after the participant has stopped the study drug, participation must be reported. Serious adverse events must be followed until resolution.

Investigators **must** report to the Overall PI any serious adverse event (SAE) that occurs after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment on the local institutional SAE form.

It is the responsibility of each participating investigator to report adverse events to the Overall PIARIAD Pharmaceuticals, DF/HCC IRB, and/or others as described below. The Overall PI or representative Coordinating Center personnel will ensure the report is forwarded to the proper parties, as appropriate (FDA, etc.).

Adverse event reporting by each site is detailed in Table 11.3. Adverse event reporting by the DF/HCC Overall Principal Investigator (Dr. Eudocia Quant Lee) /or their designees follows in Sections 11.4 and 11.5.

For trials where a DF/HCC investigator is serving as the Overall Principal Investigator, each participating institution **must** abide by the reporting requirements set by the DF/HCC. This applies to any medical event equivalent to an unexpected grade 2 or 3 with a possible, probable or definite attribution, and any grade 4 toxicities or grade 5 (death) regardless of attribution.

Whenever feasible, the participating investigator should provide follow-up information on the serious adverse event within the following 24-48 hours. Follow-up information should describe whether the event has resolved or continues, if and how the event was treated, and whether the participant will continue or discontinue study participation.

Note: If the participant is in long term follow up, report the death at the time of continuing review.

Table 11.3: Reporting to the ARIAD Pharmaceuticals, Study's Overall PI, and IRB:

Adverse Event Characteristics				Notification Requirement		
Seriousness	**Toxicity**	**Known correlation**	**Attribution to study drug**	***ARIAD Pharmaceuticals*** - **Via Fax[c]** **Use Facsimile Coversheet [c] and Medwatch 3500A [d]**	**E. Lee, MD: Overall PI - Via Email [b]** **Use Facsimile Coversheet [c] and Medwatch 3500A [d]**	**DF/HCC IRB**
Serious	Any	Any (Expected or Unexpected)	Any	Within 24 hours from notification [a]	Within 24 hours from notification [a]	As needed if required per local IRB To be submitted within IRB established reporting timelines. Please ensure that Dr. Lee prospectively approves all submissions.
Any	Adverse Events of Special Interest (AESIs)[e] Vascular occlusive events, Any Grade	Any (Expected or Unexpected)	Any	Within 2 working days from notification [a]	Within 2 working days from notification [a]	
Non-Serious	Grade 4 (unless expressly noted in Section 11.1.7.1)	Any (Expected or Unexpected)	Any	– –	Within 5 working days from notification[a]	
Non-Serious	Grade 2 or 3; moderate or severe	Unexpected	Possible, probable, definite	– –	Within 7 working days from notification[a]	

a. In the event that the participating investigator does not become aware of the serious adverse event immediately (e.g., participant sought treatment elsewhere), the participating investigator is to report the event within 24 hours after learning of it and document the time of his or her first awareness of the adverse event.

b. Email the Medwatch 3500A form, facsimile coversheet, and the IRB SAE report to the DFCI Coordinating Site with the subject title as "Ponatinib SAE" to NeuroOnc_SAE@dfci.harvard.edu. All SAE reports received at this account are forwarded immediately to study's Overall PI, Dr. Eudocia Quant Leeand to the DFCI Coordinating Center personnel.

c. Facsimile Coversheet is found in Appendix F. Adverse Event Reporting Facsimile Coversheet contains all FAX numbers/e-mails and destinations.

d. Medwatch 3500A downloadable form at http://www.fda.gov/medwatch/getforms.htm

e. See section 11.1.8 of the protocol for definition of Adverse Events of Special Interest (AESIs)

11.4 Reporting to the Food and Drug Administration (FDA)

The IND has been exempt by the FDA; therefore, IND reporting requirements do not apply.

11.5 Reporting to Participating Institutions

The Overall Principal Investigator (or her designee) will circulate to all participating Investigator Teams:

- All reportable AEs occurring on this study protocol. A cover letter will indicate the protocol title, the IND#, and whether the FDA and/or DF/HCC IRB were informed.
- And all IND safety reports received on study that have not occurred directly on this protocol, within 30 days of lead site notification. A letter will accompany the report indicating whether a consent form change or protocol change is required or other actions including a statement re: whether the report has been or will be submitted to DF/HCC IRB for review.

11.6 Reporting of Pregnancy

Any pregnancy occurring during study participation (through long-term follow-up), regardless of whether or not a serious outcome occurred, will be reported to the study PI using the same procedures outlined in Table 11.3 within 7 days of learning of its occurrence.

The pregnancy is to be followed up to determine outcome, including spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defects, congenital abnormalities or maternal and newborn complications.

11.7 Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any subject safety reports or sentinel events that require reporting according to institutional policy.

11.8 Monitoring of Adverse Events and Period of Observation

All adverse events, both serious and non-serious, and deaths that are encountered from initiation of study intervention, throughout the study, and within 30 days of the last study intervention should be followed to their resolution, or until the participating investigator assesses them as stable, or the participating investigator determines the event to be irreversible, or the participant is lost to follow-up. The presence and resolution of AEs and SAEs (with dates) should be documented on the appropriate case report form and recorded in the participant's medical record to facilitate source data verification.

For some SAEs, the study sponsor, Overall PI, or designee may follow-up by telephone, fax, and/or monitoring visit to obtain additional case details deemed necessary to appropriately evaluate the SAE report (e.g., hospital discharge summary, consultant report, or autopsy report).

Participants should be instructed to report any serious post-study event(s) that might reasonably be related to participation in this study. Participating investigators should notify the DF/HCC Overall Principal Investigator and their respective IRB of any unanticipated death or adverse event occurring after a participant has discontinued or terminated study participation that may reasonably be related to the study.

12. DATA AND SAFETY MONITORING

12.1 Data Reporting

12.1.1 Method

The QACT will collect, manage, and perform quality checks on the data for this study.

12.1.2 Responsibility for Data Submission

Investigative sites within DF/HCC or DF/PCC are responsible for submitting data and/or data forms to the QACT according to the schedule set by the QACT. The schedule for completion and submission of case report forms (paper or electronic) to the QACT is as follows:

Form	Submission Timeline
Eligibility Checklist	Complete prior to registration with QACT
On Study Form	Within 14 days of registration
Baseline Assessment Form	Within 14 days of registration
Treatment Form	Within 10 days of the last day of the cycle
Adverse Event Report Form	Within 10 days of the last day of the cycle
Response Assessment Form	Within 10 days of the completion of the cycle required for response evaluation
Off Treatment/Off Study Form	Within 14 days of completing treatment or being taken off study for any reason
Follow up/Survival Form	Within 14 days of the protocol defined follow up visit date or call

12.2 Data Safety Monitoring

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this study. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Overall PI and study team.

The DSMC will review each protocol up to four times a year or more often if required to review toxicity and accrual data. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; DLT information; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring within 30 days of intervention for Phase I or II protocols; for gene transfer protocols, summary of all deaths while being treated and during active follow-up; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

12.3 Monitoring

The quality control process for a clinical trial requires verification of protocol compliance and data accuracy. The Coordinating Center, with the aid of the QACT, provides quality control oversight for the protocol.

Involvement in this study as a participating investigator implies acceptance of planned study monitoring, as well as potential audits or inspections, including both on-site and remote source data verification, by representatives designated by the DF/HCC Overall Principal Investigator (or Protocol Chair). The purpose of these reviews is to examine study-related activities and documents to determine whether these activities were conducted and data were recorded, analyzed, and accurately reported in accordance with the protocol, institutional policy, Good Clinical Practice (GCP), the Code of Federal Regulations (CFR), and any additional applicable regulatory requirements.

The Participating Institutions may be required to submit participant source documents to the Coordinating Center for monitoring. Participating Institution may also be subject to on-site monitoring conducted by the Coordinating Center.

Data will be monitored for timeliness of submission, completeness, and adherence to protocol requirements. Monitoring will begin at the time of participant registration and will continue during protocol performance and completion.

13. REGULATORY CONSIDERATIONS

13.1 Protocol Review and Amendments

This protocol, the proposed informed consent and all forms of participant information related to the study (e.g., advertisements used to recruit patients) and any other necessary documents must be submitted, reviewed and approved by a properly constituted IRB governing each study location.

Any changes made to the protocol must be submitted as amendments and must be approved by the IRB prior to implementation. Any changes in study conduct must be reported to the IRB. The DF/HCC Overall Principal Investigator (or a representative) will disseminate protocol amendment information to all participating investigator teams.

All decisions of the IRB concerning the conduct of the study must be made in writing.

13.2 Informed Consent

All patients must be provided a consent form describing this study and providing sufficient information for patients to make an informed decision about their participation in this study. The formal consent of a participant, using the IRB approved consent form, must be obtained before the participant is involved in any study-related procedure. The consent form must be signed and dated by the participant or the participant's legally authorized representative, and by the person obtaining the consent. The participant must be given a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

This study is to be conducted according to the following considerations, which represent good and sound research practice:

- US Code of Federal Regulations (CFR) governing clinical study conduct and ethical principles that have their origin in the Declaration of Helsinki
- Title 21 Part 50 – Protection of Human Subjects
  www.access.gpo.gov/nara/cfr/waisidx_02/21cfr50_02.html
- Title 21 Part 54 – Financial Disclosure by Clinical Investigators
  www.access.gpo.gov/nara/cfr/waisidx_02/21cfr54_02.html
- Title 21 Part 56 – Institutional Review Boards
  www.access.gpo.gov/nara/cfr/waisidx_02/21cfr56_02.html
- Title 21 Part 312 – Investigational New Drug Application
  www.access.gpo.gov/nara/cfr/waisidx_02/21cfr312_02.html
- State laws
- DF/HCC research policies and procedures
  http://www.dfhcc.harvard.edu/clinical-research-support/clinical-research-unit-cru/policies-and-procedures/

It is understood that deviations from the protocol should be avoided, except when necessary to eliminate an immediate hazard to a research participant. In such case, the deviation must be reported to the IRB according to the local reporting policy.

13.3 Study Documentation

The investigator (or a representative) must prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each research participant. This information enables the study to be fully documented and the study data to be subsequently verified.

Original source documents supporting entries in the case report forms include but are not limited to hospital records, clinical charts, laboratory and pharmacy records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays.

13.4 Records Retention

All study-related documents must be retained for the maximum period required by applicable federal regulations and guidelines or institutional policies.

14. STATISTICAL CONSIDERATIONS

14.1 Study Design/Endpoints

This is a single arm, open label, Phase II trial in adult participants with recurrent glioblastoma who have progressed on bevacizumab. Although anti-angiogenic approaches for GBM therapy show promise, GBMs usually develop resistance to treatment within months or even weeks of starting therapy. Drugs such as ponatinib, which target multiple receptors, may potentially help overcome some of the putative mechanisms of resistance and result in increased antitumor effects. Its additional activity may also contribute to a therapeutic effect.

Primary Endpoint:

a) To determine the efficacy of ponatinib in participants with recurrent GBM who progressed on bevacizumab as measured by 3-month progression-free survival (PFS3)

Secondary Endpoints:

- Radiographic Response (RR)
- Overall survival (OS) and progression free survival (PFS)
- Safety profile

Exploratory Endpoints:

- To explore the extent to which the tumor's genotype and expression profile correlate with outcome
- To explore the correlation between serum angiogenic peptides, circulating endothelial cells, and circulating progenitor cells with response to therapy
- To explore the correlation between dynamic-contrast MRI, perfusion and diffusion MRI and response to therapy.

14.2 Sample Size, Accrual Rate, Study Duration, and Analysis of Primary Endpoint

The primary objective of the study is to determine the efficacy of ponatinib in participants with recurrent GBM who have progressed on a bevacizumab containing regimen as measured by 3-month progression-free survival (PFS3). PFS3 was chosen since agents with anti-VEGFR activity may produce pseudoresponses, making response a less reliable endpoint. Based on retrospective data, PFS3 rate among recurrent GBM patients who received a second bevacizumab-containing regimen after failing bevacizumab treatment once is 15% (Quant, Norden et al. 2009). This trial will enroll enough patients to discriminate between a 15% and 35% PFS3 rate. A Simon optimal two-stage design will be used to permit early cessation of the study if the agent is unlikely to be effective. The first stage will accrue 15 participants. To account for drop outs, 2 additional participants (up to 15 + 2 = 17 participants) may enroll in the first stage. If at least 5 or more of the first 15 participants achieve PFS3, 12 more participants will be accrued for a total of 27 participants. To account for drop outs in the second stage, 3 more additional participants may enroll, increasing total enrollment for Stage 1 + 2 up to 32 participants. The study will be declared successful if at least 10 or more out of 27 participants achieve PFS at 3 months. This design assumes alpha error of 0.10 and beta error of 0.2. The probability of early termination if the drug is ineffective is 69%.

A total of 32 participants may be accrued. With an accrual rate of 3-4 participants per month, the anticipated enrollment period will be 8-11 months.

14.3 Analysis of Secondary and Exploratory Endpoints

Response rate will be the proportion of participants with measurable disease who experience complete or partial radiographic response determined by the RANO Criteria (Wen, Macdonald et al. 2010). Progression free survival, PFS3, and overall survival will be calculated using standard statistical methods. Safety will be summarized using descriptive statistics. Participants will not be replaced for any reason.

In general the circulating biomarker and neuro-imaging results will be summarized in a descriptive manner with comparison between pre- and post-treatment assay results when possible.

14.4 Reporting and Exclusions

1.1.86 **Evaluation of toxicity.** All participants will be evaluable for toxicity from the time of their first treatment.

1.1.87 **Evaluation of response.** Only those participants who have measurable disease present at baseline and have received at least one dose of study treatment with Ponatinib will be considered evaluable for response.

1.1.88 **Evaluation of other efficacy endpoints**. All participants who receive at least one dose of study treatment will be included in analyses of all other endpoints. Time-to-event endpoints will be measured from first dose date.

15. PUBLICATION PLAN

Participant medical information obtained by this study is confidential, and disclosure to third parties other than those noted herein is prohibited. Data generated by this study must be available for inspection upon request by representatives of the FDA, national and local health authorities, Pharmaceutical company providing the agent, and the IRB for each study site, if appropriate. The intention is to publish the results of this study in a medical journal such as Journal of Clinical Oncology or Neuro-Oncology. Results may be presented at national meetings of the American Society for Clinical Oncology and/or Society for Neuro-Oncology. Results will be made publicly available as required by law.

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Appendix A: Performance Status Criteria

Karnofsky Performance Scale	
Percent	Description
100	Normal, no complaints, no evidence of disease.
90	Able to carry on normal activity; minor signs or symptoms of disease.
80	Normal activity with effort; some signs or symptoms of disease.
70	Cares for self, unable to carry on normal activity or to do active work.
60	Requires occasional assistance, but is able to care for most of his/her needs.
50	Requires considerable assistance and frequent medical care.
40	Disabled, requires special care and assistance.
30	Severely disabled, hospitalization indicated. Death not imminent.
20	Very sick, hospitalization indicated. Death not imminent.
10	Moribund, fatal processes progressing rapidly.
0	Dead.

Appendix B: Medications and substances known or with the potential to interact with CYP3A4 isoenzymes

List of CYP3A Inhibitors and CYP3A Inducers***

Strong CYP3A4,5,7 Inhibitors	Moderate CYP3A4,5,7 Inhibitors	Other CYP3A4,5,7 Inhibitors	CYP3A4 Inducers
boceprevir	amprenavir	Alprazolam	amprenavir
clarithromycin	aprepitant	amiodarone	aprepitant
conivaptan	atazanavir	amlodipine	armodafinil
grapefruit juice	crizotinib	atorvastatin	avasimibe*
indinavir	ciprofloxacin	NOT azithromycin	barbiturates
itraconazole	darunavir	bicalutamide	bosentan**
ketoconazole	diltiazem	chloramphenicol	carbamazepine*
lopinavir	erythromycin	cilostazol	echinacea
mibefradil	fluconazole	cimetidine	efavirenz**
nefazodone	fosamprenavir	cyclosporine	etravirine**
nelfinavir	imatinib	delaviridine	esclicarbazepine
posaconazole	suboxone	diethyl-dithiocarbamate	felbamate
ritonavir	verapamil	elvitegravir	fosphenytoin
saquinavir		fluoxetine	glucocorticoids
telithromycin		fluvoxamine	modafinil**
telaprevir		gestodene	nafcillin**
voriconazole		ginkgo	nevirapine
		goldenseal	oxcarbazepine
		isoniazid	phenobarbital
		mifepristone	phenytoin*
		nilotinib	pioglitazone
		norfloxacin	prednisone
		norfluoxetine	primidone
		oral contraceptives	rifabutin
		ranitidine	rifampin*
		ranolazine	rufinamide
		starfruit	ritonavir
		tipranavir/ritonavir	St. John's Wort*
		tofisopam	talviraline
		troleandomycin	tipranavir
		zileuton	topiramate (not prohibited but to be used with caution at doses >200mg/day)
			troglitazone

This database of CYP 3A inhibitors and inducers was compiled from:

- the Indiana University School of Medicine's "Clinically Relevant" Table
- the University of Washington's Drug Interaction Database based on in vitro studies.
- the FDA's "Guidance for Industry, Drug Interaction Studies;"
- and from (Pursche et al. 2008).

* Strong Inducers

** Moderate Inducers

*** Strong inhibitors are predicted to increase ponatinib AUC > 5-fold, and moderate inhibitors are predicted to increase ponatinib AUC > 2-fold but < 5-fold.

Appendix C: Medications known to be associated with Torsades de Pointes

Table C-1 **Prohibited** QT prolonging drugs with risk of Torsades de Pointes

Drug	QT risk(*)	Comment
Amiodarone	known risk for TdP	Females>Males, TdP risk regarded as low
Arsenic trioxide	known risk for TdP	
Astemizole	known risk for TdP	No longer available in US. CYP3A4 substrate with narrow therapeutic index.
Bepridil	known risk for TdP	Females>Males
Chloroquine	known risk for TdP	
Chlorpromazine	known risk for TdP	
Cisapride	known risk for TdP	Restricted availability; Females>Males. CYP3A substrate with narrow therapeutic index.
Disopyramide	known risk for TdP	Females>Males
Dofetilide	known risk for TdP	
Domperidone	known risk for TdP	Not available in the US.
Droperidol	known risk for TdP	
Halofantrine	known risk for TdP	Females>Males
Haloperidol	known risk for TdP	When given intravenously or at higher-than- recommended doses, risk of sudden death, QT prolongation and torsades increases.
Ibutilide	known risk for TdP	Females>Males
Levomethadyl	known risk for TdP	Sensitive CYP3A substrate
Mesoridazine	known risk for TdP	
Methadone	known risk for TdP	Females>Males
Pentamidine	known risk for TdP	Females>Males
Pimozide	known risk for TdP	Females>Males. Sensitive CYP3A substrate with narrow therapeutic index
Probucol	known risk for TdP	No longer available in U.S.
Procainamide	known risk for TdP	
Quetiapine	possible risk for TdP	Sensitive CYP3A substrate
Quinidine	known risk for TdP	Females>Males. Sensitive CYP3A substrate
Sotalol	known risk for TdP	Females>Males
Sparfloxacin	known risk for TdP	
Tacrolimus	possible risk for TdP	Sensitive CYP3A substrate with narrow therapeutic index
Terfenadine	Known risk for TdP	No longer available in U.S. Sensitive CYP3A substrate with narrow therapeutic index
Thioridazine	Known risk for TdP	
Vardenafil	possible risk for TdP	Sensitive CYP3A substrate
(*) Classification according to the Qtdrugs.org Advisory Board of the Arizona CERT Sensitive substrates: Drugs whose plasma AUC values have been shown to increase 5-fold or higher when co-administered with a potent inhibitor of the respective enzyme.		

Table C-2 List of QT prolonging drugs prohibited at eligibility, but allowable - **with caution and appropriate monitoring** – on study (see protocol section 5.2.2)

Drug	QT risk	Drug	QT risk
Alfuzosin	possible risk for Torsades de Pointes	Lithium	possible risk for Torsades de Pointes
Amantadine	possible risk for Torsades de Pointes	Mexiletine	conditional risk for Torsades de Pointes
Amitriptyline	conditional risk for Torsades de Pointes	Moexipril/HCTZ	possible risk for Torsades de Pointes
Azithromycin	possible risk for Torsades de Pointes	Moxifloxacin	possible risk for Torsades de Pointes
Chloral hydrate	possible risk for Torsades de Pointes	Nicardipine	possible risk for Torsades de Pointes
Citalopram	conditional risk for Torsades de Pointes	Nortriptyline	conditional risk for Torsades de Pointes
Clomipramine	conditional risk for Torsades de Pointes	Octreotide	possible risk for Torsades de Pointes
Clozapine	possible risk for Torsades de Pointes	Ofloxacin	possible risk for Torsades de Pointes
Desipramine	conditional risk for Torsades de Pointes	Ondansetron	possible risk for Torsades de Pointes
Diphenhydramine	conditional risk for Torsades de Pointes	Oxytocin	possible risk for Torsades de Pointes
Dolasetron	possible risk for Torsades de Pointes	Paliperidone	possible risk for Torsades de Pointes
Doxepin	conditional risk for Torsades de Pointes	Paroxetine	conditional risk for Torsades de Pointes
Dronedarone	possible risk for Torsades de Pointes	Perflutren lipid microspheres	possible risk for Torsades de Pointes
Felbamate	possible risk for Torsades de Pointes	Protriptyline	conditional risk for Torsades de Pointes
Flecainide	possible risk for Torsades de Pointes	Ranolazine	possible risk for Torsades de Pointes
Fluoxetine	conditional risk for Torsades de Pointes	Risperidone	possible risk for Torsades de Pointes
Foscarnet	possible risk for Torsades de Pointes	Roxithromycin*	possible risk for Torsades de Pointes
		Sertindole	possible risk for Torsades de Pointes
Galantamine	conditional risk for Torsades de Pointes	Sertraline	conditional risk for Torsades de Pointes
Gatifloxacin	possible risk for Torsades de Pointes	Solifenacin	conditional risk for Torsades de Pointes
Gemifloxacin	possible risk for Torsades de Pointes	Tizanidine	possible risk for Torsades de Pointes
Granisetron	possible risk for Torsades de Pointes	Trazodone	conditional risk for Torsades de Pointes
Imipramine	conditional risk for Torsades de Pointes	Trimethoprim-Sulfa	conditional risk for Torsades de Pointes
Indapamide	possible risk for Torsades de Pointes	Trimipramine	conditional risk for Torsades de Pointes
Isradipine	possible risk for Torsades de Pointes	Venlafaxine	possible risk for Torsades de Pointes
Levofloxacin	possible risk for Torsades de Pointes	Ziprasidone	possible risk for Torsades de Pointes
(*) Classification according to the Qtdrugs.org Advisory Board of the Arizona CERT			

Appendix D: Pill Diary

Completed by study personnel: Participant ID #_____ Participant Initials: _____ Cycle #: _____ Month & Year: _____
Ponatinib Daily Dose_____mg/day

To be completed by Participant or Guardian: # of 15 mg Pill Bottles Received: _____ # of 15 mg Capsules Received: _____

DAY:	**DAY:**	**DAY:**	**DAY:**	**DAY:**	**DAY:**	**DAY:**
Date: Time: No. of 15 mg pills _____ Participant Initials _____	Date: Time: No. of 15 mg pills _____ Participant Initials _____	Date: Time: No. of 15 mg pills _____ Participant Initials _____	Date: Time: No. of 15 mg pills _____ Participant Initials _____	Date: Time: No. of 15 mg pills _____ Participant Initials _____	Date: Time: No. of 15 mg pills _____ Participant Initials _____	Date: Time: No. of 15 mg pills _____ Participant Initials _____
Date: Time: No. of 15 mg pills _____ Participant Initials _____	Date: Time: No. of 15 mg pills _____ Participant Initials _____	Date: Time: No. of 15 mg pills _____ Participant Initials _____	Date: Time: No. of 15 mg pills _____ Participant Initials _____	Date: Time: No. of 15 mg pills _____ Participant Initials _____	Date: Time: No. of 15 mg pills _____ Participant Initials _____	Date: Time: No. of 15 mg pills _____ Participant Initials _____ I_____

DAY:	**DAY:**	**DAY:**	**DAY:**	**DAY:**	**DAY:**	**DAY:**
Date: Time: No. of 15 mg pills _____ Participant Initials _____	Date: Time: No. of 15 mg pills _____ Participant Initials _____	Date: Time: No. of 15 mg pills _____ Participant Initials _____	Date: Time: No. of 15 mg pills _____ Participant Initials _____	Date: Time: No. of 15 mg pills _____ Participant Initials _____	Date: Time: No. of 15 mg pills _____ Participant Initials _____	Date: Time: No. of 15 mg pills _____ Participant Initials _____
Date: Time: No. of 15 mg pills _____ Participant Initials _____	Date: Time: No. of 15 mg pills _____ Participant Initials _____	Date: Time: No. of 15 mg pills _____ Participant Initials _____	Date: Time: No. of 15 mg pills _____ Participant Initials _____	Date: Time: No. of 15 mg pills _____ Participant Initials _____	Date: Time: No. of 15 mg pills _____ Participant Initials _____	Date: Time: No. of 15 mg pills _____ Participant Initials _____

Participant/Guardian Signature: _____ Date: _____

To be completed by study personnel: # of 15 mg Bottles Returned: _____ # of 15 mg Capsules Returned: _____

Compare w/ drug diary entries made by participant or guardian. If discrepancy (in the # of bottles or the # of pills returned), please reconcile:

Study Personnel Signature:_____ Date: _____

Ponatinib Dosing Instruction Sheet
to Be Given to Study Participants with Participant Pill Diary

Ponatinib Description:

- Your study drug (Ponatinib) is supplied as 15 mg white, film-coated tablets.

Ponatinib Instructions – When and How:

- Take the prescribed number of Ponatinib tablets with water, with or without food.
    - Ponatinib tablets should be swallowed whole; do not crush, cut or chew them.
- Take your dose of Ponatinib once daily, at approximately the same time each day.
    - NOTE: During your first Cycle of treatment, bring your Day 2 dose with you to clinic, as you will take it after your visit that day
- If you forget to take a dose of Ponatinib, you may take it up to six hours after the scheduled dose. DO NOT make up the missed dose any more than 6 hours later than the time you usually take your study drug; simply consider that day's dose skipped. Take your next dose the following day as usual.
- If you vomit your pills, do not take more pills; you will take your next dose on the next day as usual. You should write down in your pill diary that you vomited the pills.

Additional Instructions:

- You must avoid eating or drinking any foods with Seville oranges (like marmalade), grapefruit or foods or drink with grapefruit, and any exotic fruits during the entire treatment period.
- Keep your ponatinib tablets in their original container(s) at room temperature, and keep study drug away from children, others who cannot read the label, and pets.
- Do not throw away empty pill bottles, and do not throw the study drug in the trash or flush into the toilet.
- Bring this diary, all pill bottles, and any unused pills to your next clinic visit. Your Treatment Team will collect your diary, all Ponatinib pill bottles and unused Ponatinib pills, and you will be given a new pill diary at that time.
- Contact your study doctor or nurse if you are having any new or worsening side effects.
- Do not begin any new medication, over-the-counter drug, or herbal preparation without first checking with your Study Treatment Team to determine if it is acceptable to take while on this study.

Appendix E: Instructions for Local Processing of Plasma Biomarkers

Plasma Biomarkers
Local Processing Instructions

In the event that a Plasma Biomarkers sample is drawn without sufficient time to be processed at the Steele Lab within 2 hours of collection, (e.g. in the event patient is drawn at 4 pm), please refer to the following processing instructions.

NOTE: The instructions below are provided on an as needed basis. This alternative should be avoided whenever possible, as this additional process does render samples no longer analyzable by flow cytometry.

1. Blood Draw and Centrifugation

- As noted in protocol section 8.1.1:
  - Collect 2 tubes of ~8 ml each of blood. The tubes must be pre-cooled in an ice bath.
  - Gently invert five to six times to ensure adequate mixing and prevent coagulation.
  - Cool the tubes immediately in an ice bath.

- Within 2 hours of collection, samples must be processed locally for storage. To process these samples locally:
  - Centrifuge the blood tube at 700g (2000rpm) for 20 minutes at 4°C with no break at the end of centrifugation for plasma extraction.
  - Using a sterile pipette, pipette the top clear layer (careful not to disturb the bottom red layer) and aliquot equally into 3 pre-labeled 1.8 mL Nunc cryovials.
  - Visually check the plasma for hemolysis.
    - If the plasma appears to be yellow and clear, please proceed with processing the plasma, record the observation internally per standard practice, and make the Study Team aware of any abnormality.
    - If the plasma appears to be dark red, please discard the plasma, record the event internally per standard practice, and make the Study Team aware of the event.
  - After the plasma has been extracted, check the red blood cells by sticking two wooden applicator sticks in the tube and observe the sticks for clots. Record if there was clotting observed per standard practice, and make the Study Team aware of the any abnormality.
  - Immediately store the cryovials into a -80°C freezer*.
  - Record time of freeze and location of the vials (i.e., freezer number, shelf, box number, and room #, as applicable) per standard practice.

2. Labeling and Storing Specimens

Each specimen should be labeled with the following information:

Patient study number
Patient Initials
Military time sample was obtained
Date sample was obtained
Cycle #/Day# of sample

and that label affixed to the cryvials and then covered completely with protective cryogenic freezer tape (Fisher catalogue no. 11-867B).

All cryovials should be stored in a monitored -80° C freezer.

3. SHIPPING SPECIMENS TO CORE FACILITY

Plasma samples should be shipped next day (if possible) in an isothermal container with plenty of dry ice and delivered to the Steele Laboratory using a courier.

Steele Laboratory (Dan G. Duda, DMD, PhD)
Attn: Anna Khachatryan and Julia Kahn
Massachusetts General Hospital, Cox-734
100 Blossom Street
Boston, MA 02114
Phone: (617) 724-1352; Partners pager: 14082
Email: annak@steele.mgh.harvard.edu; julia@steele.mgh.harvard.edu

Be sure to indicate/label shipment: "Notice: Keep Frozen", Upright arrows, "Diagnostic Specimens – Not restricted, Packed in Compliance with IATA Packing Instruction 650", and "Class 9 – Dry Ice".

Specimens should be shipped Monday to Wednesday only by overnight FedEx to the Testing Core Facility. On the day of shipment, the study coordinator will notify the Testing Core Facility via e-mail at annak@steele.mgh.harvard.edu; julia@steele.mgh.harvard.edu or FAX (617-724-5841, ATTN: A. Khachatryan & J. Kahn) so they know to expect the upcoming shipment. Include the estimated date of arrival and the FedEx tracking number.

NOTE: The subject line of the e-mail/FAX should include the following so that the Testing Core Facility staff can distinguish plasma specimens sent for this trial:

Notification of plasma specimen shipment for DF/HCC #15-163

Upon receipt of specimens, the Testing Core Facility will reconcile the materials and notify the site study coordinator of missing specimens, damaged specimens, or any concerns to be addressed.

Suggested packing process for dry ice shipments:

- Place all plasma tubes in storage freezer boxes, tape the sides of the boxes;
- Place one freezer box, each separately, in a large zip-locked bag;
- Pack the Styrofoam container with plenty of dry ice;
- Place the bagged freezer boxes in the middle of the bio-shipper (you can fit as many as the box allows);
- Pack the Styrofoam container with an additional dry-ice on the top of the boxes to cover the top;
- Close the lid, place any corresponding shipping forms on top of the lid, and seal the shipping container with tape.
- Maintain a copy of the transmittal log at the site.

4. Labeling Shipping Containers: FedEx shipping labeling will include the following:

1. The study coordinator's return address.
2. The Testing Core Facility address:

   Steele Laboratory (Dan G. Duda, DMD, PhD)
   ATTN: Anna Khachatryan and Julia Kahn
   MGH, Cox-734
   100 Blossom St.
   Boston, MA 02114
   Phone: (617) 724-1352; Pager: 14082
   Emails: annak@steele.mgh.harvard.edu; julia@steele.mgh.harvard.edu
3. "Notice: Keep Frozen", "Class 9 – Dry Ice" stickers or "Keep Refrigerated", Upright arrows, and "Diagnostic Specimens – Not restricted, Packed in Compliance with IATA Packing Instruction 650".

Appendix F: Study Safety Reporting Coversheet

DF/HCC Protocol No. 15-163 ARIAD Pharmaceuticals Protocol No. AP24534-13-020

Date:_____ Number of pages including cover sheet:_____

To (check off recipient of this fax):

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From:	Institution:
Phone No.:	Fax No.:

Participant # and Initials:
Date Event Met Reporting Criteria (as defined in protocol):
Type of Report: ☐Initial ☐Follow-up

Event #1 Description:	Event #2 (If Applicable) Description*: (Please use another sheet if more than 2 events being reported at this time)*
Meets Definition of Serious AE: ☐ Serious ☐ Non-serious	Meets Definition of Serious AE: ☐ Serious ☐ Non-serious
Toxicity Grade: ☐G1/mild ☐G2/moderate ☐G3/severe ☐G4/life threatening ☐G5	Toxicity Grade: ☐G1/mild ☐G2/moderate ☐G3/severe ☐G4/life threatening ☐G5
Historical/Known Correlation to **Ponatinib**: ☐Expected ☐Unexpected	Historical/Known Correlation to **Ponatinib**: ☐Expected ☐Unexpected
Attribution to **Ponatinib**: ☐Unrelated ☐Unlikely ☐Possible ☐Probable ☐Definite	Attribution to **Ponatinib**: ☐Unrelated ☐Unlikely ☐Possible ☐Probable ☐Definite
Reporting Investigator (please print):	

Signature of Investigator: _____Date:_____