A Phase II, open-label study of ponatinib, a multi-targeted oral tyrosine kinase inhibitor, in advanced non-small-cell lung cancer harboring RET translocations

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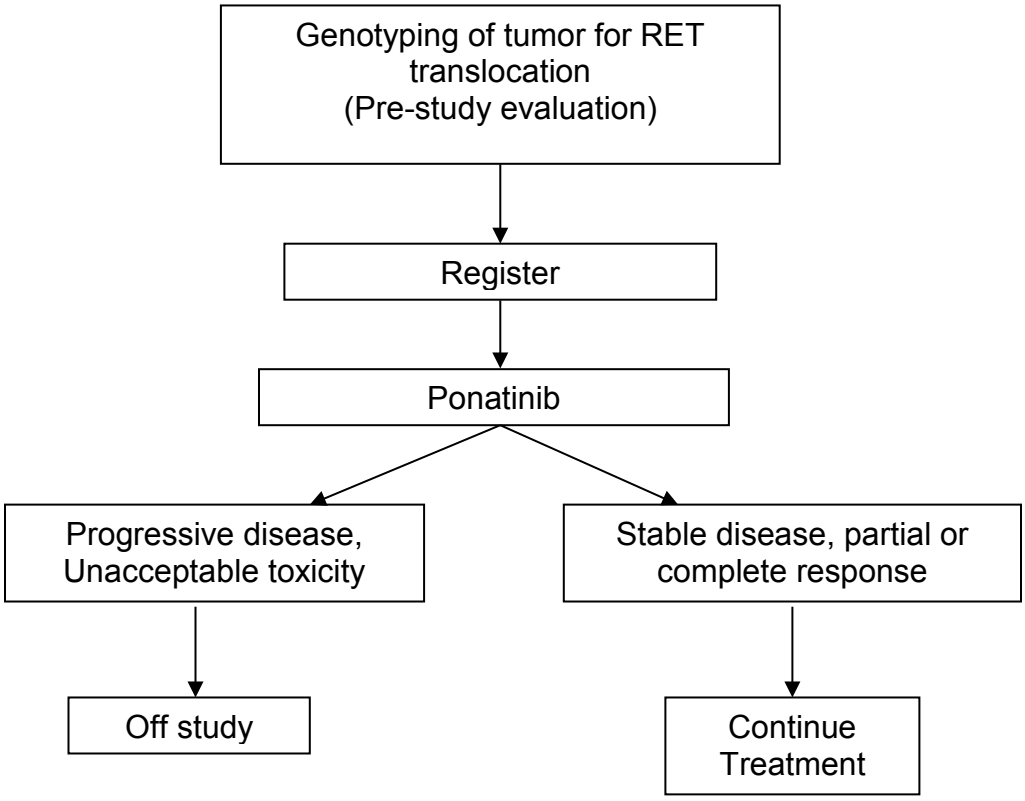
Schema


Genotyping of tumor for RET translocation (Pre-study evaluation)
Register
Ponatinib
Progressive disease, Unacceptable toxicity
Stable disease, partial or complete response
Off study
Continue Treatment

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1 Objectives

1.1 Study Design

This is a phase II, open label study evaluating ponatinib, an oral multi-target tyrosine kinase inhibitor (TKI), in patients with advanced, non-small-cell lung cancer (NSCLC) harboring translocations in RET. The purpose of this study is to investigate the efficacy, safety and tolerability of ponatinib in this molecularly-defined subpopulation. Eligible participants will have advanced, NSCLC and documented RET translocations. Eligible participants will receive ponatinib at a dose of 30 mg orally daily. Treatment will continue until disease progression, unacceptable toxicity, participant withdrawal, death or discontinuation from the study for any other reason. Participants will be allowed to continue receiving ponatinib despite progressive disease if they are deriving clinical benefit. Efficacy will be evaluated by radiographic assessments using RECIST (version 1.1) criteria at baseline and at two cycle intervals. After a participant has completed 10 cycles, disease assessments will be performed at three cycle intervals.

1.2 Primary Objective

- To evaluate the objective response rate (ORR) of ponatinib in RET-positive NSCLC as assessed by RECIST criteria.

1.3 Secondary Objectives

- To evaluate the disease control rate (DCR).
- To evaluate progression-free survival (PFS).
- To evaluate the 1-year overall survival (OS) rate.
- To determine the safety and tolerability of ponatinib in patients with RET translocation positive NSCLC.
- To determine the plasma PK profile of ponatinib.

1.4 Primary Endpoint

- The primary efficacy endpoint is ORR, defined as partial response (PR) or complete response (CR), occurring at any point post treatment according to RECIST (version 1.1) criteria.

1.5 Secondary Endpoints

- Disease control rate (DCR), defined as PR, CR, or stable disease (SD) as assessed by RECIST.
- Progression-free survival (PFS), defined as time from study entry to progression or death, whichever comes first.
- 1-year overall survival (OS) rate, defined by the number of subjects alive 1 year from the time of study entry.
- Safety parameters: Adverse drug reactions and serious adverse drug reactions. Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be used.

- Plasma PK parameters will be assessed as shown in the Schedule of Events (Table 8.1)

2 Background

2.1 Study Agent

Ponatinib (AP24534) is a novel, synthetic, orally-active tyrosine kinase inhibitor recently approved by the U.S. Food and Drug Administration (FDA) for the treatment of chronic myeloid leukemia (CML) and Philadelphia chromosome positive acute lymphoblastic leukemia (ALL). Ponatinib was initially developed as an inhibitor of the BCR-ABL fusion protein, which is formed by a reciprocal translocation involving chromosomes 9 and 22 in hematopoietic stem cells and characterizes approximately 95% of cases of chronic myeloid leukemia (Faderl S, 1999). In addition to its inhibitory activity against the BCR-ABL fusion oncoprotein, ponatinib is a potent inhibitor of a number of tyrosine kinases relevant to the treatment of human malignancies, including FLT3, KIT, VEGFR2, FGFR1, PDGFR and RET (Table 2.1).

Table 2.1 Ponatinib Kinase Screening Data

Kinase	IC_{50} (nM)
ABL	0.37
ABL^{T315I}	2.00
FLT3	12.6
KIT	12.5
RET	0.16
SRC	5.4
VEGFR2	1.5
FGFR1	2.2
PDGRFα	1.1

Two clinical trials are currently being conducted with ponatinib: phase I study AP24534-07-101 and phase 2 study AP24534-10-201. Additionally, three clinical trials examining the clinical pharmacology of ponatinib in healthy subjects have been completed (AP24534-11-102, AP24534-11-103, and AP24534-11-104).

A summary of the pharmacokinetic, safety and clinical activity data are provided below. Complete details for clinical and non-clinical studies performed with ponatinib are provided in the Investigator Brochure (Ponatinib Clinical Investigator's Brochure Version 5, Feb2013; Addendum 29Oct2013).

Preclinical Toxicology of Ponatinib

The preclinical safety profile of ponatinib was characterized in a series of *in vitro* and *in vivo* studies in mice, rats and cynomolgus monkeys. These nonclinical toxicology studies support the repeat administration of oral ponatinib to cancer patients in clinical studies.

Preclinical safety assessments of ponatinib included 6-month oral toxicology studies in rats and cynomolgus monkeys. In the 6 month oral toxicology study in rats, the no observed adverse effect level was 0.25 mg/kg/day. Higher doses of 0.75 mg/kg/day resulted in mortality in some animals. At the time of histological examination, decreased chondrocytes along the physis of the femur were observed in rats at dose levels of 0.75 mg/kg/day and 2 mg/kg/day. Moreover, lymphoid depletion was observed in the thymus at doses of 2 mg/kg/day. In the 6-month toxicology studies in cynomolgus monkeys, oral doses of 0.25, 0.75 and 2 mg/kg/day of ponatinib were well-tolerated. No ponatinib-related microscopic findings were observed at any dose level.

The mutagenic potential of ponatinib was investigated in three separate assays. These included assessments for the potential to reverse mutations in *S. typhimurium* and *E. coli* strains in vitro in the standard Ames assay. Additionally, human lymphocytes were assessed in vitro to assess the potential for induction of chromosomal aberrations. No evidence of mutagenic potential was observed in any of these studies.

Ponatinib has been demonstrated to be embryo-toxic in rats. Data from an embryo-fetal development study of ponatinib in rats showed maternal and developmental toxicity, including both embryo-toxicity (post-implantation loss) and teratogenicity (cleft palates). Maternal and developmental toxicity in rats occurred at a dosage of 10 mg/kg/day. Embryo and fetotoxicity occurred at 3 mg/kg/day. A teratogenic effect (cleft palate at 3 mg/kg/day) was also observed.

The cardiovascular effects of ponatinib were evaluated in conscious telemetered male dogs. Oral administration of ponatinib at doses of 2-10 mg/kg did not result in any significant changes in heart rate or blood pressure. Increases in the QTc of 11 and 14% were observed in dogs treated with the 10 mg/kg dose of ponatinib but the magnitude of this increase is not thought to be biologically relevant.

The potential for phototoxicity was also evaluated in a study involving pigmented rats. Animals treated with high doses of ponatinib (5 and 10 mg/kg) showed minimal ocular phototoxicity. Specifically, animals showed microscopic signs of inflammation of the cornea.

Safety of Ponatinib in Clinical Studies

Two clinical trials with ponatinib are currently being conducted: the phase 1 study AP24534-07-101 and the phase 2 registration study AP24534-10-201.

AP24534-07-101

AP24534-07-101 is a phase 1 dose escalation trial to determine the safety, tolerability and maximum tolerated dose (MTD) of ponatinib in patients with refractory chronic myeloid leukemia (CML) or Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL). Enrollment in the United States was completed at 81 patients as of October 2010. The primary objective of the trial was to determine the MTD of daily oral ponatinib. Secondary

objectives included safety and pharmacokinetics (PK), anti-tumor activity, and pharmacodynamic activity.

Following oral administration, maximum plasma levels of ponatinib occurred between 4 and 6 hours after dosing. The steady-state terminal elimination half-life ($t_{1/2}$) was 20-28 hours for doses exceeding 15mg. Initial ponatinib dosing was 2 mg orally once daily, escalating up to 60 mg once daily. At the 45 mg dose level, 1 dose limited toxicity (DLT) of grade 3 rash was observed. At the 60 mg dose level, 4 patients experienced DLTs of clinical pancreatitis or elevation of pancreatic enzymes. At this dose level, 1 patient also experienced grade 3 fatigue and an additional patient experienced grade 3 elevated AST and ALT. Based upon these findings, the recommended ponatinib dose was 45 mg once daily.

Eighty-one patients (100%) experienced at least one adverse event (AE) during the study period. Sixty-seven (83%) experienced at least one treatment-related AE (TRAE). The most common TRAEs included: rash (32%); thrombocytopenia (27%); arthralgia (17%); lipase increased (15%); fatigue, nausea, dermatitis acneiform, dry skin (14%); and headache, elevated triglycerides, myalgia, neutrophil count decreased, and pancreatitis (12%).

During this phase 1 trial, ponatinib was found to have anti-leukemic activity. Among 43 patients with chronic phase CML, 42 patients (98%) achieved or maintained a complete hematologic response. Major cytogenetic responses were seen in 72%, and complete cytogenetic responses were observed in 63%.

AP24534-10-201

AP24534-10-201 is a phase 2 registration trial of ponatinib in patients with refractory CML and Philadelphia chromosome-positive ALL. The primary objective of the trial is to determine the efficacy of ponatinib at a dose of 45 mg once daily in this population of patients. As of December 2011, 449 patients have enrolled and 301 remain on therapy.

Adverse events have been documented in 441 patients (98.2%). TRAEs were seen in 409 (89.3%) patients. Ninety-seven (21.6%) patients experienced at least 1 treatment-related AE. The most common TRAEs were: rash (32.1%), thrombocytopenia (31.2%), dry skin (23.8%), abdominal pain (18.5%), headache (16.7%), neutrophil count decreased (15.1%), fatigue (14.5%), myalgia (14.0%), lipase increased (13.6%), arthralgia (13.6%), constipation (12.2%), anemia (11.6%), and nausea (10.5%). Please see Table 2.2 for a listing of additional TRAEs.

Table 2.2 Treatment-Related Adverse Events Occurring in >5% of Patients in Phase 2 Clinical Trial AP24534-10-201, Safety Population (n = 449)

Preferred Term	Total, n (%)	Grade 3 and 4, n (%)
Patients with at least 1 TRAE	401 (89.3)	255 (56.8)
Rash	144 (32.1)	14 (3.1)
Platelet count decreased	140 (31.2)	110 (24.5)
Dry skin	107 (23.8)	5 (1.1)
Abdominal pain	83 (18.5)	23 (5.1)
Headache	75 (16.7)	5 (1.1)
Neutrophil count decreased	68 (15.1)	61 (13.6)
Fatigue	65 (14.5)	4 (0.9)
Myalgia	63 (14.0)	3 (0.7)
Lipase increased	61 (13.6)	35 (7.8)
Arthralgia	61 (13.6)	5 (1.1)
Constipation	55 (12.2)	4 (0.9)
Anaemia	52 (11.6)	31 (6.9)
Nausea	47 (10.5)	0
Asthenia	35 (7.8)	4 (0.9)
Pyrexia	30 (6.7)	1 (0.2)
Pain in extremity	29 (6.5)	3 (0.7)
Vomiting	28 (6.2)	0
Bone pain	28 (6.2)	1 (0.2)
Pancreatitis	26 (5.8)	21 (4.7)
Diarrhoea	25 (5.6)	2 (0.4)
Muscle spasms	24 (5.3)	0
Erythema	23 (5.1)	1 (0.2)
Alanine aminotransferase increased	23 (5.1)	8 (1.8)
Back pain	23 (5.1)	2 (0.4)

*Source: Ponatinib Clinical Investigator's Brochure, 10Apr2012.
**Database cutoff date 02 December 2011.

Five treatment-related deaths were reported during the study period following grade 5 SAEs of pneumonia, sudden death, fungal pneumonia, pancytopenia and gastritis hemorrhagic, and cardiac arrest. Grade 3 or 4 AEs occurring in ≥5% of patients include: platelet count decreased (24.5%), neutrophil count decreased (13.6%), lipase increased (7.8%), anemia (6.9%), and abdominal pain (5.1%). In the phase 1 study AP24534-07-101, pancreatic events were the DLT. In the phase 2 study AP24534-10-201, Grade 3 or 4 pancreatitis was observed in 4.7% of patients.

Among patients with chronic phase CML, 248/271 (92%) achieved or maintained a complete hematologic response. Major cytogenetic responses were seen in 116/248 (47%). At the time of study entry, 64 patients with chronic phase CML possessed the T315I resistance mutation, a known target of ponatinib. In this subpopulation of patients, 55/64 (86%) experienced a complete hematologic response and 37/64 (65%) had a major cytogenetic response.

Among the study population of 449 patients, 94 patients were enrolled with blast phase CML or Philadelphia chromosome-positive ALL. In this subpopulation, major hematologic responses were observed in 33 (37%). Major cytogenetic responses were experienced in 35%.

Adverse Events of Special Concern

Vascular Occlusion

Arterial and venous thrombosis and occlusions, including fatal myocardial infarction, stroke, stenosis of large arterial vessels of the brain, severe peripheral vascular disease, and the need for urgent revascularization procedures have occurred in at least 27% of ponatinib-treated patients from the phase 1 and phase 2 trials conducted in CML/ALL patient populations (Ponatinib Package Insert, Accessed 4/17/2014). Ponatinib has been associated with fatal and life-threatening vascular occlusion within 2 weeks of starting treatment. Ponatinib has also been associated with recurrent or multi-site vascular occlusion.

In the dose-escalation (phase 1) clinical trial, 48% (31/65) of patients with CML or Ph+ ALL developed vascular occlusive events. The median time to onset of the first vascular occlusion event was 5 months. Ponatinib can cause fatal and life threatening vascular occlusion in patients treated at dose levels as low as 15 mg per day.

Patients with and without cardiovascular risk factors, including patients age 50 years or younger, experienced these events. Vascular occlusion adverse events were more frequent with increasing age and in patients with prior history of ischemia, hypertension, diabetes, or hyperlipidemia (see Table 2.3).

Table 2.3: Vascular Occlusion Incidence in Ponatinib-Treated Patients in Phase 2 Trial According to Risk Categories

	Prior history of ischemia, hypertension, diabetes, or hyperlipidemia	**No history of ischemia, hypertension, diabetes, or hyperlipidemia**
Age: 49 or younger	18% (6/33)	12% (13/112)
Age: 50 to 74 years	33% (50/152)	18% (20/114)
Age: 75 and older	56% (14/25)	46% (6/13)
All age groups	33% (70/210)	16% (39/239)
Total	24% (109/449)	

Arterial Occlusion and Thrombosis

Arterial occlusion and thrombosis occurred in at least 20% (91/449) of ponatinib-treated patients with some patients experiencing events of more than one type. Patients have required

revascularization procedures (cerebrovascular, coronary, and peripheral arterial) due to vascular occlusion from ponatinib.
Cardiac vascular occlusion, including fatal and life-threatening myocardial infarction and coronary artery occlusion has occurred in 12% (55/449) of ponatinib-treated patients. Patients have developed heart failure concurrent or subsequent to the myocardial ischemic event.

Cerebrovascular occlusion, including fatal stroke, has occurred in 6% (27/449) of ponatinib-treated patients. Iclusig can cause stenosis over multiple segments in major arterial vessels that supply the brain (e.g., carotid, vertebral, middle cerebral artery).

Peripheral arterial occlusive events, including fatal mesenteric artery occlusion and life-threatening peripheral arterial disease, have occurred in 8% (36/449) of ponatinib-treated patients. Patients have developed digital or distal extremity necrosis and have required amputations.

Venous Thromboembolism

Venous thromboembolic events occurred in 5% (23/449) of ponatinib-treated patients, including deep venous thrombosis (8 patients), pulmonary embolism (6 patients), superficial thrombophlebitis (3 patients), and retinal vein thrombosis (2 patients).

Human Clinical Pharmacology Studies of Ponatinib

Three separate studies of ponatinib have been performed in healthy subjects to examine the clinical pharmacology of ponatinib.

AP24534-11-102

Trial AP24534-11-102 compared the effects of either a high fat meal, low fat meal, or fasting conditions on the bioavailability and pharmacokinetics of a single oral dose of ponatinib administered to healthy subjects. A total of 24 subjects enrolled, each receiving a single dose of 45 mg of ponatinib. Independent of diet or fasting conditions, mean ponatinib plasma concentrations reached a maximum at approximately 5-6 hours after ingestion of ponatinib. Similarly, no differences were observed across the three groups in terms of maximum time (t_{max}), maximum concentration (C_{max}), and $AUC_{0-\infty}$.

AP24534-11-103

Trial AP24534-11-103 investigated potential drug-drug interactions of ponatinib. The objective of this study was to determine the effects of concomitant ketoconazole administration on the pharmacokinetic profile of single-dose ponatinib in 22 healthy subjects. Ketoconazole is a strong inhibitor of CYP3A4. This study demonstrated a statistically significant effect of ketoconazole co-administration on the relative bioavailability of ponatinib along with its

CYP3A4/5 metabolite, AP24567. Specifically, ketoconazole co-administration increased the C_{max} and AUC of ponatinib by 47% and 78%, respectively.

AP24534-11-104

In study AP24534-11-104, the absorption and excretion of ^{14}C-labeled ponatinib was evaluated in 6 healthy subjects. The median time to achieve maximal [^{14}C] radioactivity concentrations (T_{max}) in plasma and whole blood was 5 and 8 hours, respectively. Geometric mean ponatinib C_{max} was 58.4 ng/mL. Geometric mean ponatinib $AUC_{0-\infty}$ was 1861 h*ng/mL. The mean half-life for ponatinib was 38.1 hours. A majority of radioactivity (86.6%) was recovered in feces, while 5.4% was recovered in urine. This study confirms that hepatic elimination is the major excretory route for ponatinib in humans.

2.2 Study Disease

Lung cancer is the leading cause of cancer-related mortality in the United States (Jemal, et al 2008). The disease is traditionally divided into non-small-cell and small-cell variants, with non-small-cell lung cancer (NSCLC) accounting for approximately 85% of cases (Herbst, et al 2008). NSCLCs can be further distinguished based upon histologic subtypes, which include adenocarcinoma, squamous cell carcinoma, and large cell carcinoma (West, et al 2009). Despite advances, a majority of patients with NSCLC present with locally advanced or metastatic disease, at which time the disease is considered incurable (Pfister, et al 2004).

Platinum-based doublets with or without bevacizumab have become the standard of care for the first-line management of advanced or metastatic NSCLC (Bunn, 2002; Azzoli, 2009; Sandler, 2006). At the time of disease progression, second-line therapies include docetaxel, pemetrexed, and erlotinib (Azzoli, 2009). While these agents are superior to best supportive care, their clinical activity is quite modest with response rates of less than 10% (Shepherd, 2000; Shepherd, 2005; Hanna, 2004). Given these limited results, additional effective therapies or treatment strategies are needed.

Recently, a new paradigm has emerged in the management of NSCLC based upon stratification of patients into molecularly-defined subgroups. Broad genotyping efforts have revealed that approximately 50% of lung adenocarcinomas possess at least one mutation in a driver oncogene (Sequist, 2011). Importantly, recognition of these driver mutations may have implications for therapy. In NSCLC, this approach was initially established with the identification of activating mutations in the epidermal growth factor receptor (EGFR). Mutations in EGFR are identified in approximately 10% of unselected NSCLC patients, but the incidence of EGFR mutations increases to nearly 50% in never-smokers (Pham, 2006). Multiple randomized phase III trials have demonstrated the superior efficacy of EGFR tyrosine kinase inhibitors (TKIs) compared to first line cytotoxic chemotherapy in this molecularly defined subpopulation of patients (Mok, 2009; Maemondo, 2010; Zhou, 2011; Rossell; 2012). As a result, EGFR testing has now become an established clinical practice in order to guide clinical decision making in NSCLC (Keedy, 2011).

The success of EGFR-directed therapies in NSCLC has led to the recognition of additional driver mutations or translocations involving oncogenes such as ALK, ROS, HER2, and BRAF (Pao, 2011). Like patients with EGFR mutations, patients harboring ALK translocations derive substantial clinical benefit from targeted tyrosine kinase inhibition with crizotinib (Kwak, 2010). In light of these successes and given the limited efficacy of cytotoxic chemotherapy in NSCLC, efforts are underway to identify novel therapies directed at molecularly-defined subpopulations of patients.

2.3 Study Rationale

Chromosomal translocations involving the RET oncogene have recently been identified as potential new driver mutations in NSCLC, occurring in approximately 1-2% of patients (Kohno et al, 2012, Takeuchi et al, 2012, Lipson et al, 2012). Specifically, pericentric chromosomal inversion results in a fusion transcript of KIF5B and RET, leading to aberrant activation of the RET kinase (Ju et al, 2012). Recently, CCDC6 has been identified as an alternative RET fusion partner in NSCLC (Li et al, 2012; Taekeuchi et al, 2012). In the setting of these translocations, RET signaling promotes cell survival and proliferation through the RAS-MAPK and PI3K-AKT pathways (Li et al, 2012). In cell lines, the KIF5B-RET fusion gene leads to oncogenic transformation (Lipson et al, 2012; Kohno et al, 2012). The presence of RET fusion genes also leads to the formation of subcutaneous tumors in a nude mouse tumorigenicity assay (Takeuchi et al, 2012), lending support to the idea that RET fusions may represent a new independent oncogenic driver. Clinically, this is supported by the finding that among patients with KIF5B-RET or CCDC6-RET fusion positive tumors, specimens were negative for concomitant mutations such as EGFR, KRAS, ALK, ROS or Her2 (Kohno et al, 2012).

Preclinical data suggests that RET is a viable target for tyrosine kinase inhibition. Indeed, cell lines expressing KIF5B-RET are sensitive to multi-target kinase inhibitors possessing RET activity, including sunitinib, sorafenib, and vandetanib (Lipson et al, 2012; Kohno et al, 2012). Conversely, gefitinib and crizotinib, multi-targeted TKIs without known RET activity, were ineffective at inhibiting proliferation in these same cell lines possessing RET translocations (Lipson et al, 2012; Kohno et al, 2012).

Clinically, RET has served as a therapeutic target in the treatment of other malignancies, such as medullary thyroid cancer (Wells et al, 2010). Germline mutations in RET underlie multiple endocrine neoplasia type 2 (MEN 2) and familial medullary thyroid carcinoma, while somatic mutations in RET are seen in approximately 50% of sporadic medullary thyroid carcinomas (Romei et al, 1996; Marsh et al, 1996). Given the central oncogenic role of RET in medullary thyroid carcinoma, recent efforts have focused on targeting this oncogene through targeted tyrosine kinase inhibition. Vandetanib is an oral TKI that selectively targets RET, vascular endothelial growth factor (VEGF), and EGFR. In a phase III randomized trial in patients with locally advanced or metastatic medullary thyroid carcinoma, vandetanib resulted in improved response rates and progression-free survival compared to placebo, suggesting that RET can be a viable novel target (Wells et al, 2010).

In this phase II, open label study, we propose use of the orally available TKI ponatinib in the treatment of patients with NSCLC harboring translocations in RET. Ponatinib has broad activity against a range of tyrosine kinases, including extremely potent inhibition of RET. In vitro, ponatinib inhibits RET kinase activity with an IC_{50} of 0.16 nM (Ponatinib Clinical Investigator's Brochure, 10Apr2012). Given its favorable toxicity profile and potent RET inhibition, there is strong rationale for the use of ponatinib in this molecularly-defined subpopulation of patients with NSCLC.

Participants will receive ponatinib at a dose of 30 mg orally once daily, which is below the maximum tolerated dose (45 mg once daily). This is based upon available pharmacokinetic, safety, and efficacy data from CML patients treated with ponatinib. In prior studies of ponatinib in the CML population, rates of adverse events (e.g. thrombocytopenia, neutropenia, rash, ALT/AST elevation, pancreatitis, and lipase elevation) appeared to correlate with increasing doses of ponatinib (http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/203469Orig1s000ClinPharmR.pdf. Accessed 10/13/2013). In addition, larger doses of ponatinib were associated with higher grades of ischemia (http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/203469Orig1s000ClinPharmR.pdf. Accessed 10/13/2013). We have chosen a ponatinib dose of 30 mg once daily in order to reduce the risk of adverse events. Participants will also be required to receive concomitant thromboprophylaxis as detailed in Section 6.11. Since ponatinib is an extremely potent inhibitor of RET, we expect to achieve adequate target inhibition at this dose. However, in patients who do not achieve an objective response response within the first 2-4 cycles of treatment, dose escalation to a ponatinib dose of 45 mg once daily may be permitted provided certain criteria are met (Section 7.4) and after discussion with the Sponsor.

Patients will be eligible for participation regardless of prior treatment with TKIs known to have anti-RET activity (e.g. vandetanib, sorafenib, XL-184). The rationale for including RET-positive patients with prior RET TKI exposure in the study population is based upon recent experience in other subtypes of oncogene-driven NSCLC, namely ALK-positive NSCLC. Among patients with ALK rearrangements, the ALK TKI crizotinib is associated with response rates of approximately 60% (Kwak et al, 2010). However, in a preliminary report of the second generation ALK TKI LDK378, response rates were greater than 80% in patients who had previously progressed on crizotinib (Mehra et al, 2012), suggesting that use of more potent TKIs may still be effective in patients with acquired resistance. This has yet to be examined in a RET-positive patient population.

3 Participant Selection

3.1 Eligibility Criteria

Patients must meet the following criteria on screening examination to be eligible to participate in this study:

3.1.1 Signed informed consent.

3.1.2 Age ≥ 18 years.

3.1.3 Histologically or cytologically confirmed advanced (stage IIIB or IV) NSCLC.

3.1.4 Molecular confirmation of a RET translocation is required to begin protocol therapy. Methods of acceptable molecular confirmation include RET FISH and next-generation sequencing performed in a CLIA certified lab.

3.1.5 At least one measurable lesion as defined by RECIST v1.1 criteria. Previously irradiated lesions are not measurable unless the lesion has demonstrated clear progression after radiation. See Section 9.0 for the evaluation of measurable disease.

3.1.6 Eligible participants must have received at least one line of prior therapy. Note: Patients will be eligible for participation despite prior treatment with known RET TKIs (e.g. vandetanib, sorafenib, XL-184).

3.1.7 Performance status score of 0-2 according to the Eastern Cooperative Group (ECOG) scale.

3.1.8 Estimated life expectancy ≥ 12 weeks.

3.1.9 Able to swallow and retain orally administered medication. Does not have any clinically significant gastrointestinal abnormalities, such as malabsorption syndrome or major resection of the stomach or small bowel that may alter absorption of the medication.

3.1.10 Adequate bone marrow function as defined by the following criteria:
- Absolute neutrophil count (ANC) ≥ $1.5x10^9$/L
- Hemoglobin ≥ 9 g/dL
- Platelets ≥ $100x10^9$/L

3.1.11 Adequate hepatic function as defined by the following criteria:
- Total serum bilirubin ≤ 1.5 x upper limit of normal (ULN), unless due to Gilbert's syndrome.
- Alanine aminotransferase (ALT) ≤ 2.5 x ULN
- Aspartate aminotransferase (AST) ≤ 2.5 x ULN

3.1.12 Adequate renal function as defined by the following criteria:
- Serum creatinine < 1.5 x ULN

3.1.13 Adequate pancreatic function as defined by the following criterion:
- Serum lipase and amylase ≤ 1.5 x ULN

3.1.14 Women of childbearing potential must have a negative pregnancy test.

3.1.15 Female and male patients who are of childbearing potential must agree to use an effective form of contraception with their sexual partners from enrollment through 30 days after the end of treatment.

3.1.16 Willingness and ability to comply with scheduled visits and study procedures.

3.2 Exclusion Criteria

Patients who exhibit any of the below findings at the time of screening will not be eligible for admission into the study.

3.2.1 Major surgery within 28 days prior to initiating therapy.

3.2.2 History of CNS disease. Note: Patients with brain metastases will be eligible if treated appropriately and if they remain clinically stable neurologically. For asymptomatic brain metastases, appropriate clinical treatment may include observation with serial imaging.

3.2.3 Participants who have received systemic chemotherapy within 3 weeks of starting study drug.

3.2.4 Participants who have received treatment with a TKI within 7 days of the first dose of study treatment. An alternative appropriate wash-out period based upon the known half-life of the agent and reversibility of drug-related adverse events may be considered after consultation with the study sponsor.

3.2.5 Participants who have received radiation therapy within 2 weeks of starting study drug. Note: Participants who have received radiation therapy to a small volume (e.g. stereotactic radiosurgery to the CNS) will be eligible if completed > 1 week prior to starting study drug.

3.2.6 History of significant bleeding disorder unrelated to cancer.

3.2.7 History of acute pancreatitis within 1 year of study entry or history of chronic pancreatitis.

3.2.8 History of or ongoing alcohol abuse that, in the opinion of the Investigator, would compromise compliance or impart excess risks associated with study participation.

3.2.9 Uncontrolled hypertriglyceridemia (triglycerdies > 450 mg/dL). If a patient is excluded solely based upon a non-fasting triglyceride level, a fasting test should be performed to determine eligibility.

3.2.10 Study participants must have had prior EGFR and ALK testing. Participants with sensitizing mutations in EGFR or ALK rearrangements will be excluded.

3.2.11 History of arterial thrombotic disease, specifically including, but not restricted to:
- Myocardial infarction or unstable angina.
- Cerebrovascular event (CVA) or transient ischemic attack (TIA).
- Peripheral vascular disease or claudication.

3.2.12 Significant uncontrolled or active cardiovascular disease, specifically including, but not restricted to:
- History of clinically significant (as determined by the treating physician) atrial arrhythmia; or any ventricular arrhythmia.
- History of congenital long QT syndrome.
- Abnormal QTcB ($\geq$ 450 msec in males and $\geq$ 470 msec in females)
- Ejection fraction $\leq$ 50% as assessed by echocardiogram.

3.2.13 Uncontrolled hypertension (Diastolic blood pressure > 100 mmHg; Systolic blood pressure > 150 mmHg).

3.2.14 History of venous thromboembolism (e.g. deep venous thrombosis or pulmonary embolism) within 6 months of study entry. Note: Participants enrolled after this window must be on appropriate therapeutic anticoagulation.

3.2.15 Taking medications that are known to be associated with Torsades de Pointes. Medications include but are not limited to:
- Quinidine, procainamide, disopyramide
- Amiodarone, sotalol, ibutilide, dofetilide
- Erythromycins, clarithromycin
- Chlorpromazine, haloperidol, mesoridazine, thioridazine, pimozide
- Zyprasidone, cisapride, bepridil, droperidol, methadone, arsenic
- Chloroquine, domeperidone, halofantrine, levomethdyl, pentamidine
- Sparfloxacin, lidoflazine

Note: Participants who have taken a medication associated with Torsades de Pointes will still be eligible for participation if the medication is discontinued at least 14 days before the initiation of study treatment.

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

3.2.17 Known history of human immunodeficiency virus (HIV). Testing is not required in the absence of history.

3.2.18 Pregnant or breastfeeding.

3.2.19 Diagnosed with or received anti-cancer therapy for another primary malignancy within 3 years prior to entry (except for non-melanoma skin cancer or in situ cancers).

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

4 Registration Procedures

4.1 General Guidelines for DF/HCC and DF/PCC Institutions

Institutions will register eligible participants with the DF/HCC Quality Assurance Office for Clinical Trials (QACT) central registration system. Registration must occur prior to the initiation of therapy. Any participant not registered to the protocol before treatment 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 treatment. Issues that would cause treatment delays should be discussed with the Principal Investigator (PI). If a participant does not receive protocol therapy following registration, the participant's registration on the protocol may cancelled. Registration cancellations must be made in OnCore as soon as possible.

4.2 Registration Process for DF/HCC and DF/PCC Institutions

DF/HCC Standard Operative Procedure for Human Subject Research titled "Subject Protocol Registration (SOP #: REGIST-101) must be followed.

4.3 General Guidelines for Other Participating Institutions

Eligible participants will be entered on study centrally at Massachusetts General Hospital by the Coordinating Center. All sites should contact the Coordinating Center to verify treatment availability.

Following registration, participants should begin protocol treatment within 72 hours or as soon as possible. Issues that would cause treatment delays should be discussed with the Principal Investigator/Sponsor. If a participant does not receive protocol therapy following registration, the participant's protocol status must be changed. The Coordinating Center should be notified of participant status changes as soon as possible.

Except in very unusual circumstances, each participating institution will order the study agent(s) directly from the supplier. A participating site may order the agent(s) only after

the initial IRB approval for the site has been forwarded by the Coordinating Center to the supplier.

4.4 Registration Process for Other Participating Institutions

Refer to section 3.7 of Appendix D (Data and Safety Monitoring Plan) of protocol for instructions on registration process.

5 Study Procedures

5.1 Study Procedures Descriptions

See the Schedule of Events (Table 8.1) for the required assessments at each visit. The following list describes the procedures/tests required for this study.

1. **Informed consent:** Informed consent, documented by a signed consent form, must be obtained prior to any screening activities not otherwise part of the participant's care. A note documenting the informed consent procedure should be included in the participant's medical record.

2. **Demographics:** Demographic information consists of the participant's age, gender, race, and ethnicity (as allowed by local law and regulations).

3. **Medical and Surgical History:** Medical and surgical history includes diagnoses, therapies, medical and surgical treatments, and current medications.

4. **Prior Cancer Therapy:** Prior cancer therapy history consists of the specific oncologic regimens a patient has received, the dates of the regimen and the best response to the regimen, and the reason for failure or intolerance to each regimen. Stem cell transplant or experimental or investigational therapy history must also be recorded.

5. **Diagnosis:** The initial cancer diagnosis and the current cancer diagnosis at the time of screening (if different), along with dates of diagnosis need to be recorded.

6. **Mutation Status:** Any previously identified RET translocations, method of identification and the dates of identification must be recorded. If available, the presence of additional mutations such as KRAS, EGFR, ALK or ROS should be recorded.

7. **Physical Exam:** A complete physical examination will be performed, the extent of which should be consistent with the medical history and the participant's underlying disease.

8. **Vital Signs:** Vital signs include temperature, pulse, respiratory rate, and blood pressure (when patient is seated). In addition, the screening assessment should include height and weight.

9. **ECOG Performance Status:** The participant's performance status must be assessed using the ECOG performance scale (Appendix A).

10. **Hematology:** Hematology measurements include complete blood count (CBC) with differential and platelet count.

11. **Serum Chemistry:** Serum chemistry (either fasting or non-fasting) consists of a peripheral blood draw with the following assessments: sodium, potassium, chloride, bicarbonate, blood urea nitrogen (BUN, or urea), albumin and total protein, creatinine, total bilirubin (direct and indirect), ALT (SGPT), AST (SGOT), alkaline phosphatase, magnesium, phosphorous, calcium, amylase and lipase. Triglycerides will only be obtained at baseline.

12. **Pharmacokinetics:** Plasma PK samples will be obtained on cycle 1, day 1 and cycle 2, day 1. Please refer to the Schedule of Events (Table 8.1). Samples will be sent to Advion Bioanalytical Labs for analysis. Refer to the study-specific laboratory manual for details.

13. **Electrocardiogram (ECG):** All ECGs must be 12-lead ECGs. Please refer to the Schedule of Events (Table 8.1) for the required ECG schedule. Additional ECGs may be performed at the investigator's discretion to ensure patient safety. In particular, ECG monitoring should be performed during the study if a patient is taking medications that can potentially prolong the QT interval (other than medications explicitly prohibited). For consistency, the Bazett correction (QTcB) method must be used for calculating all QTc intervals.

14. **Echocardiogram:** An echocardiogram to establish left ventricular ejection fraction (EF) is required at screening to determine eligibility. An additional echocardiogram may be performed at C4D1 at the discretion of the investigator based upon participant symptoms.

15. **Safety Assessments – Adverse Events:** Participants must be followed for all adverse events (AEs) from the start of study treatment until at least 30 Days After the End of Treatment, and for all serious or study drug-related toxicities until the AEs are resolved or are considered chronic or stable or until patient contact discontinues. Serious adverse events (SAEs) should be monitored and reported as described in Section 10.0.

    Type, incidence, severity (graded in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] Version 4.0), timing, seriousness and relatedness, outcome, action taken with study drug, and treatment will be assessed and documented by the investigator throughout the study.

    Malignancy-related signs and symptoms noted at study entry will be recorded as AEs during the trial if they worsen in severity or increase in frequency.

16. **Concomitant Medications:** Concomitant medications for all ongoing medical history conditions or AEs must be reported from the date the informed consent is signed until at least 30 Days After the End of Treatment, and for all concomitant medications related to

serious or study drug-related toxicities until the medication is no longer taken or until patient contact discontinues.

17. **Pregnancy Test:** The pregnancy test must be a beta-human chorionic gonadotropin (β-HCG) test and either urine or serum can be used. Women who are not of childbearing potential (status post-hysterectomy, status post-bilateral oophorectomy, or post-menopausal [defined as amenorrhea for at least 12 months]) and men do not need to have the test performed. The test must be known to be negative prior to the study drug administration and be performed within 7 days prior to first study drug administration.

18. **Disease Assessment:** At screening, disease assessment must include imaging of the chest, abdomen, pelvis and brain using appropriate radiological procedures (computed tomography [CT] scan, MRI scan) and physical examination (for palpable lesions). Brain imaging is required at entry. Follow-up brain imaging need not be routinely performed in the absence of findings. Target and non-target lesions must be selected at study start and followed throughout the course of treatment for response assessment according to RECIST guidelines (See Section 9). Imaging assessment is also required to be performed at the End of Treatment. Note: RECIST-defined responses will be confirmed with an imaging assessment ≥4 weeks later.

19. **Survival:** All participants should be followed for survival every 3 months, up to 2 years after the initial dose of ponatinib.

5.2 Screening Period

The screening period begins when the informed consent form is signed, and continues until the first dose of ponatinib is administered. Screening physical examination, vital signs, and ECOG assessments can be used as the Day 1 assessment, without the need for having to repeat the tests, if these screening assessments are accomplished within 7 days prior to Day 1**.**

Assessments required at screening are shown on the Schedule of Events (Table 8.1). A detailed description of procedures is provided in Section 5.1.

5.3 Screen Failures

Patients who have signed informed consent and subsequently fail to meet the inclusion and/or exclusion criteria are defined as screen failures. For all screen failures, the Investigator is to maintain a screening log that documents the patient initials and reason(s) for screen failure. A copy of the log should be retained in the Investigator's study files.

5.4 Active Study Period

The active study period begins when the participant receives the first dose of ponatinib. Assessments required during the active study period are shown on the Schedule of Events (Table 8.1). A detailed description of procedures and timing is provided in Section 5.1.

Note: Clinical laboratory assessments do not need to be repeated on Cycle 1 Day 1 if they were performed for screening within 7 days prior to Cycle 1 Day 1.

Note: Cycle 1 day 1 labs must be reviewed prior to initiation of study treatment. See Table 7.1 for administration criteria and dose modifications for cycle 1 day 1.

5.5 End of Treatment

The End of Treatment is defined as the point when the participant receives the last dose of ponatinib or the participant discontinues taking ponatinib. Study procedures at the End of Treatment must be conducted within 14 days following the last dose of study drug.

Assessments required at the End of Treatment are shown on the Schedule of Events (Table 8.1). A detailed description of procedures and timing is provided in Section 5.1.

5.6 30 Days After End of Treatment

Participants are required to complete all post treatment discontinuation assessments 30 Days After End of Treatment. Study procedures at 30 Days After End of Treatment must be conducted within 30 days (± 7 days) following the last dose of study drug.

Assessments required at 30 Days After End of Treatment are shown on the Schedule of Events. A detailed description of procedures and timing is provided in Section 5.1.

5.7 Follow-up Period

The follow-up period for a participant begins after the last completed assessment during the active study period. Any participant who discontinued study treatment for any reason other than disease progression, death or withdrawal of consent will continue to have tumor assessments every 12 weeks (±14 days) until the participant starts another anti-cancer therapy.

All participants should be followed for PFS and survival at least every 3 months (± 14 days), up to 2 years after the initial dose of ponatinib.

5.8 Duration of Therapy / Subject Discontinuation

Duration of therapy will depend on individual response, evidence of disease progression and tolerance. Treatment will continue until one of the following:

- Intolerable toxicity as determined by the Investigator.
- Progression of disease requiring an alternative therapy. Note: In some cases, despite disease progression by RECIST criteria, participants may be continued on study drug if deemed beneficial by the participant and investigators as well as approval from the Principal Investigator/Sponsor.
- Entry into another therapeutic clinical trial or implementation of another anti-cancer therapy.

- Significant deviation from the protocol or eligibility criteria, in the opinion of the Investigator.
- Noncompliance with study or follow-up procedures.
- Withdrawal of participant consent.
- Termination of the trial by the Principal Investigator/Sponsor.
- Any other reason that, in the opinion of the Investigator, would justify removal of the participant from the study.

In the event that a participant is withdrawn from the study, every effort will be made by the Investigator to document and report the reason(s) for withdrawal as thoroughly as possible. The reason(s) for withdrawal must be clearly reported on the appropriate page of the participant's electronic case report form (eCRF). An eCRF must be completed for any participant who receives study drug. An End-of-Treatment reason must be recorded for any participant who receives study medication.

If a participant is discontinued from the trial for any reason, every effort must be made to perform all End of Treatment assessments per the schedule of events. In the event that the participant fails to return for the necessary visit(s), an effort must be made to contact the participant to determine the reason, and this information should be recorded in the appropriate source record and reported as a deviation. All participants who discontinue prematurely from the active study period will be followed for PFS and survival at least every 3 months (± 14 days), up to 2 years after the initial dose of ponatinib.

6 Treatment Plan

Treatment will be administered on an outpatient basis. Expected toxicities and guidelines for dose modifications for ponatinib are described in Section 7 (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.

Treatment Description					
Agent	**Pre-medication / Precautions**	**Dose**	**Route**	**Schedule**	**Cycle Length**
Ponatinib	Anti-thrombotic therapy (e.g. aspirin), Lipid-lowering therapy (e.g. statin)	30 mg daily	Orally	Daily	28 days

6.1 Study Drug

Ponatinib is a novel, orally-available TKI with potent activity against mutant forms of RET.

6.2 Selection of Starting Dose

The starting dose of ponatinib is 30 mg per day (see Section 2.3 for more details on the starting dose rationale).

6.3 Treatment Administration

Participants will self-administer ponatinib at home at a dose of 30 mg by mouth daily. Ponatinib will be taken on a continuous daily basis. Each 28-day dosing period is referred to as 1 cycle. Dose adjustments will be made as necessary as outlined in Section 7. Participants will be instructed to keep a study diary of drug administration. In addition, participants will be provided with a copy of the FDA's medication guide on ponatinib. This guide can be accessed at:

http://www.fda.gov/Drugs/DrugSafety/ucm085729.htm

Participants will be instructed to take ponatinib at approximately the same time of day. Participants have a +6 hour window. There must be a minimum of 18 hours between doses. Participants who forget to take their scheduled dose of study drug will be instructed not to make up the missed dose. Ponatinib can be taken with or without food.

Missed doses should be recorded in the appropriate source record (e.g. clinic chart), study diary card and study drug administration electronic case report form (eCRF). Vomited doses should not be made up.

6.4 Formulation, Packaging, and Labeling

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

All of the excipients used in ponatinib tablets 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.

6.5 Handling

Procedures for proper handling and disposal of anticancer drugs should be considered.

If tablets are crushed or broken, pharmacy and clinical personnel should wear disposable chemotherapy gloves. Personnel who are pregnant should avoid exposure to crushed and/or broken tablets.

The Investigator (or assigned designee, i.e., study pharmacist) will dispense the proper number of each strength tablet to the participant to satisfy dosing requirements for the study. The

containers provided to the participant should be labeled with proper instructions for use. The lot numbers, dosing start dates and the number of tablets for each dosage strength must be recorded on the drug accountability pages of record for the site. The participant must be instructed to return all unused ponatinib in the provided packaging at each subsequent visit.

6.6 Availability

Ponatinib will be provided free of charge to study participants by Ariad.

6.7 Storage

Bottles containing ponatinib tablets should be stored at room temperature.

All investigational products should be stored in a secure area according to local regulations. The investigator is responsible for ensuring that it is dispensed only to study participants and only from official study sites.

6.8 Ordering

Each investigative site will order ponatinib directly through Ariad. Shipments will be at appropriate intervals, depending on patient accrual. Each site must use an appropriate dispensing log/accountability form provided by the Sponsor, or an acceptable substitute approved by the Sponsor. Each time study medication is dispensed for a participant, the following information must be recorded: the patient's initials, the patient's study number, tablet strength (45 mg or 15 mg), the number of tablets dispensed with the corresponding lot number, and the initials of the person dispensing the drug. Ponatinib may be repackaged by the site pharmacy and is typically supplied in bottles containing 60 tablets. If repackaged, ponatinib should be placed into a high density polyethylene (HDPE) bottle. These logs are to be maintained by the study pharmacist in the pharmacy throughout the duration of the study. Logs at non-DF/HCC sites will be periodically verified by a representative of the Sponsor. The Investigator is responsible for ensuring that the patient diary card(s) and study drug provided to the participant and returned from the participant are accounted for and noted in source documentation.

6.9 Accountability

The investigator will ensure that a current record of disposition of investigational product is maintained at each study site where the investigational product is inventoried and disposed.

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

6.10 Destruction and Return

If the investigational product is to be destroyed on site, it is the investigator's responsibility to ensure that arrangements have been made for disposal, and that procedures for proper disposal

have been established according to applicable regulations, guidelines, and institutional procedures. Appropriate records of the disposal must be maintained.

Consult with the Principal Investigator for instructions on disposal of unused ponatinib tablets.

6.11 Required Concomitant Therapy

Ponatinib has been associated with an increased risk for arterial thrombotic events, such as myocardial infarction, peripheral vascular disease and cerebrovascular accident.

Thromboprophylaxis is required for all participants receiving ponatinib. It is recommend that participants receive daily aspirin (81 or 325 mg). Note: This does not apply to participants who are already receiving therapeutic anticoagulation (e.g. low molecular weight heparin), provided that these participants meet the eligibility criteria outlined in Sections 3.1 and 3.2. It is recommended that if the platelet count falls below 50,000/mm^3, thromboprophylaxis be held to minimize the risk of bleeding. It should then be resumed when platelet counts are equal to or above this level.

All patients should also be treated with a statin to reduce the risk of cardiovascular events. We recommend atorvastatin (Lipitor) administered at a minimum of 10 mg/day, but other statins and doses may be substituted if appropriate. The specific regimen should correspond with moderate-intensity or high-intensity statin therapy as defined by the recent AHA/ACC guidelines (Stone et al, Circulation 2013, http://circ.ahajournals.org/content/suppl/2013/11/07/01.cir.0000437738.63853.7a.DC1.html). High-intensity therapy should be considered in patients in high risk categories, such as those with a history of cardiovascular disease, diabetes, or LDL cholesterol greater than 190 mg/dL, but patient age and risk of side effects due to statin therapy (myopathy, elevated CPK, elevated liver enzymes) should be taken into consideration. Measurement of cholesterol and dose adjustment to meet a cholesterol target is not necessary but could be considered to ensure compliance or per physician or patient preference.

6.12 Permitted Treatment

All routine and appropriate supportive care, including blood products, will be provided during this study, as clinically indicated, and in accordance with the standard of care practices. Please see Section 7 for management of expected adverse events (AEs).

Palliative radiation therapy will be permitted for participants with symptomatic bone metastases or CNS metastases as long as they have demonstrated stability in terms of systemic disease. Disease stability for these purposes will be defined as complete response, partial response, stable disease or clinical benefit in the opinion of the Investigator. For participants undergoing radiation, ponatinib must be held for at least 72 hours before the initiation of radiation. Ponatinib may be resumed no sooner than 72 hours after the completion of radiation.

6.13 Prohibited Treatment

The following concurrent medications and treatments are prohibited:

- Any other anti-cancer therapy including, but not limited to, chemotherapeutic agents, immunotherapy, biological response modifiers, surgery and/or systemic hormonal therapy (hematopoietic growth factors are permitted).
- Use of any other investigational drug or device.
- Use of medications that are known to be associated with the development of Torsades de Pointes (see Appendix B).
- Herbal preparations or related over-the-counter preparations containing herbal ingredients either during or within 2 weeks prior to the first dose of ponatinib.
- Elective surgery requiring in-patient care.

6.14 Treatments to be Used with Caution

Medications that are potent substrates, inhibitors or inducers of P450 cytochromes, in particular CYP3A4 (see Appendix C), should be avoided when possible but are not prohibited.

Medications that prolong the QTcB interval should be avoided when possible but are not prohibited. If such medications are deemed necessary and used while a participant is on study, additional ECG monitoring should be performed as clinically indicated.

6.15 Potential Drug-Drug Interactions

In vitro and in vivo studies have demonstrated that CYP3A4 is involved in the metabolism of ponatinib. Therefore, drug-drug interactions (DDIs) are possible if ponatinib is given with substrates, inhibitors or inducers of CYP3A4 (see Appendix C). Investigators are encouraged to avoid administration of drugs that are substrates, inhibitors or inducers of CYP3A4 if clinically feasible.

Additionally, medications associated with prolongation of the QTc interval may interact with ponatinib and contribute to further QTc prolongation, which has the potential to contribute to ventricular arrhythmia. In addition, some medications associated with QTc prolongation also interact with the CYP3A4 cytochrome and an effect on the QTc interval might thus be exacerbated.

7 Expected Toxicities and Dose Modifications

The most common expected toxicities for ponatinib include rash, dry skin, thrombocytopenia, abdominal pain, elevations in amylase and lipase, pancreatitis, anemia, neutropenia, hypertension, QTc prolongation, hepatotoxicity, headache, fatigue and myalgias. Please see Table 2.2 for the frequencies of adverse events in the previous ponatinib phase II trial AP24534-10-201. For dose modifications and toxicity-specific management, please refer to Table 7.1 and Section 7.5.

7.1 Management of Adverse Drug Reactions

Comprehensive assessments of any study drug-related adverse events experienced by the participant will be performed throughout the course of the study. The severity of the event, as well as clinical judgment, will be utilized to determine appropriate management of the participant for any AE experienced while participating in this trial.

7.2 Dose Delays and Reductions

Dose delays and/or reductions will be implemented for participants who experience adverse drug reactions as indicated in the following sections.

7.3 Dose Delay and/or Reduction for Adverse Events (AEs) Attributable to the Study Drug

Table 7.1 describes suggested guidelines for dose modification due to study-drug-related toxicity, graded according to NCI CTCAE 4.0. However, for an individual participant, dose interruptions, reductions and treatment discontinuation should also be based on the clinical circumstance and investigators should use clinical judgment in deciding whether a dose reduction, delay or discontinuation is appropriate for any given clinical circumstance. In general, when the observed toxicity has resolved to ≤ grade 1, the investigator may resume full dosing if clinically indicated.

No dose reduction below 15 mg once daily is permitted for ponatinib. If the participant cannot tolerate a minimum dose of 15 mg per day of ponatinib, despite any allowed interruptions, the participant must be discontinued from study treatment. Doses may be interrupted for study-drug related toxicities for up to 28 days. If a non-hematologic study-drug related toxicity does not resolve to Grade 1 or less after dose interruption for more than 28 days, the participant must be discontinued from study treatment. If a hematologic study-drug related toxicity does not resolve to Grade 1 or less after dose interruption for more than 28 days, the Principal Investigator/Sponsor must be contacted. Additionally, the Principal Investigator/Sponsor must be contacted if any adverse event deemed unrelated to treatment requires dose interruption for more than 28 days. Lastly, for each participant, once a dose reduction has occurred, the dose level may not be re-escalated during subsequent treatment cycles of ponatinib.

Table 7.1 Ponatinib: Dose Modifications for Drug Adverse Reactions

Toxicity	Modification
Nonhematologic Toxicity	
General (Any CTCAE v4.0 nonhematologic toxicity not otherwise specified below)	
Grade 1 or transient Grade 2	No intervention
AST/ALT Elevations	
Grade 1 or transient Grade 2	No intervention
Grade 2 lasting ≥7 days with optimal care AND total bilirubin < 2 x ULN	Hold ponatinib Resume at 30 mg after recovery to ≤ grade 1 Recurrence at 30 mg: Hold ponatinib Resume at 15 mg after recovery to ≤ grade 1 Recurrence at 15 mg Discontinue ponatinib
Grade 3 or 4 AND total bilirubin < 2 x ULN	Hold ponatinib Resume at 30 mg after recovery to ≤ grade 1 Recurrence at 30 mg Hold ponatinib Resume at 15 mg after recovery to ≤ grade 1 Recurrence at 15 mg Discontinue ponatinib
Grade ≥ 2 AND total bilirubin ≥ 2 x ULN (In the absence of liver metastases)	Discontinue ponatinib
Pancreatitis	
Grade 2 (enzyme elevation or radiologic findings only)	See amylase/lipase section below
Grade 3 (severe pain, vomiting, medical intervention indicated [eg, analgesia, nutritional support])	Hold ponatinib Perform ultrasound or abdominal CT scan with contrast If imaging is positive, continue holding ponatinib and repeat according to clinical care. If imaging is negative, or after resolution by imaging, resume at 15 mg after recovery to ≤ grade 1 Recurrence at 15 mg: Repeat above Consider discontinuing ponatinib
Grade 4	Hold ponatinib Consult sponsor
Amylase/Lipase	
Grade ≤ 2	No intervention; monitor closely

Toxicity	Modification
Grade 3 with no radiologic findings	Hold ponatinib Resume at 30 mg after recovery to ≤ grade 1 Recurrence at 30 mg: Hold ponatinib Resume at 15 mg after recovery to ≤ grade 1 Recurrence at 15 mg: Discontinue ponatinib
Grade 3 with radiologic findings or Grade 4	Hold ponatinib Repeat imaging according to clinical care After resolution by imaging, resume at 15 mg after recovery to ≤grade 1 Recurrence at 15 mg: Discontinue ponatinib
LV dysfunction/CHF	
Grade 2 or 3	Hold ponatinib Resume at 30 mg after recovery to ≤ grade 1 Recurrence at 30 mg: Hold ponatinib Resume at 15 mg after recovery to ≤ grade 1 Recurrence at 15 mg: Discontinue ponatinib
Grade 4	Discontinue ponatinib
Skin rash	
Grade 2 persistent despite optimal symptomatic therapy	Hold ponatinib Resume at 30 mg after recovery to ≤ grade 1 Recurrence at 30 mg: Hold ponatinib Resume at 15 mg after recovery to ≤ grade 1 Recurrence at 15 mg: Discontinue ponatinib
Grade 3 persistent despite optimal symptomatic therapy	Hold ponatinib Resume at 30 mg after recovery to ≤ grade 1 Recurrence at 30 mg: Hold ponatinib Resume at 15 mg after recovery to ≤ grade 1 Recurrence at 15 mg: Discontinue ponatinib

Toxicity	Modification
Hematologic Toxicity	
Drug-Related ANC/platelets	
Grade 1 or 2	No dose adjustment
Grade 3 or 4	Hold ponatinib Resume at 30 mg after recovery to ≤ grade 1 Recurrence at 30 mg: Hold ponatinib Resume at 15 mg after recovery to ≤ grade 1 Recurrence at 15 mg: Discontinue ponatinib

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

7.4 Dose Escalation

Participants who do not experience an objective response within 2-4 cycles of starting treatment with ponatinib may be candidates for dose-escalation of ponatinib to a dose of 45 mg once daily, provided the following criteria are met: 1) the participant has not experienced any vascular toxicities of ***any*** grade, 2) the participant has not experienced any grade 3/4 treatment-related toxicities, and 3) the treating investigator receives approval from the study Sponsor.

In addition, participants who achieve an objective response to therapy but subsequently relapse may also be candidates for dose escalation to a ponatinib dose of 45 mg once daily, provided the same criteria above are met.

7.5 Management of Selected Adverse Events

7.5.1 Vascular Occlusion

Arterial and venous thrombosis and occlusions have occurred in at least 27% of ponatinib treated patients, including fatal myocardial infarction, stroke, stenosis of large arterial vessels of the brain, severe peripheral vascular disease, and the need for urgent revascularization procedures. Patients with and without cardiovascular risk factors, including patients less than 50 years old, experienced these events. Monitor for evidence of thromboembolism and vascular occlusion. Interrupt or stop ponatinib immediately for vascular occlusion. If a participant experiences an arterial thrombotic event while receiving ponatinib, the subject should discontinue ponatinib permanently. Please see Section 6.11 for a list of required concomitant therapy in order to minimize the risk of arterial thrombotic events. In participants with venous thrombosis or occlusion, a benefit-risk consideration should guide a decision to restart ponatinib therapy. This should be done in collaboration with the study Principal Investigator.

7.5.2 Myelosuppression

Neutropenia, anemia, and thrombocytopenia have all been commonly reported either together or individually in patients treated with ponatinib. While myelosuppression can occur any time during treatment, its onset most commonly occurs within the first month on treatment. 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 (see Table 7.1). Rarely, one or more cytopenias can lead to permanent discontinuation of treatment. The use of hematopoietic growth factors such as granulocyte colony-stimulating factor (G-CSF) or granulocyte-macrophage colony-stimulating factor (GM-CSF) 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 adverse event 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].

7.5.3 Rash and/or Pruritus

Skin rashes have been commonly reported to be associated with ponatinib. The vast majority of the skin events are 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 an acneiform dermatitis or diffuse maculo-papular rash that is non-pruritic. 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.

7.5.4 Pancreatitis and Amylase or Lipase Elevations

Pancreatitis (symptomatic abdominal pain associated with pancreatic enzyme elevation) and/or elevations in lipase and amylase are known AEs associated with ponatinib. Pancreatitis was reported in 7% of patients in the phase 2 study of ponatinib and 12% in the phase 1 dose-escalation study. Most cases of pancreatitis or elevated pancreatic enzymes occur within the first month 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.

7.5.5 Diarrhea, Nausea, and Vomiting

Diarrhea is a less-common side effect of ponatinib. The use of anti-diarrhea medications is permitted. Participants 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 not commonly seen with ponatinib. The use of an antiemetic prophylactically is not recommended. However, if a participant is symptomatic, appropriate antiemetic medications may be used as clinically indicated.

7.5.6 Constitutional Symptoms / Joint Pain

Certain constitutional symptoms such as myalgia, arthralgia, headache, weakness, fatigue, asthenia, and low grade fever have been commonly reported with ponatinib. For patients treated with ponatinib, these symptoms have been reported mainly at the initiation of treatment. They 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.

7.5.7 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 7.1.

7.5.8 Severe 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.

7.5.9 Hypertension

Blood pressure should be monitored at each visit. Hypertension (HTN) by at least two blood pressure measurements should be graded according to CTCAE version 4.0. For participants who develop HTN or worsening HTN during study treatment, anti-hypertensive 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-hypertensive therapy including titration of anti-hypertensive medication or introduction of additional anti-hypertensive medications, or if grade 4 HTN develops, dose interruption and reduction is recommended according to Dose Modification Guidelines for general non-hematologic AEs in Table 7.1.

7.5.10 Prolonged QTcB

If a prolongation of QTcB 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 participant is on and discontinue medications that are known or suspected to cause QT prolongation.

If no contributing reason is identified and the reason for QTcB prolongation is believed to be due to study medication, dose interruption and reduction guidelines for general non-hematologic toxicities in Table 7.1 for ponatinib should be followed. Additionally, weekly ECG monitoring is recommended for 4 weeks upon resumption of study drug, then monthly for 6 months, and then per the routine ECG schedule.

8 Study Calendar

Table 8-1 lists all of the assessments and indicates with an "X" the visit when they are performed. All data obtained from these assessments must be supported in the participant's source documentation and recorded on the corresponding eCRF pages.

Table 8-1 Schedule of Events

Assessment[1,11]	Baseline[10]	Cycle 1		Cycle 2 Day 1	Every 4 weeks (Cycle 3-10)	Every 8 weeks (Cycle 3-10)	Every 6 weeks (Cycle 11 +)[9]	End of Treatment	30 Days After End of Treatment	Follow-up
		Day 1	Day 15							
Informed consent	X									
Demographics	X									
Inclusion / Exclusion Criteria	X									
Medical & Surgical History	X									
Diagnosis & Extent of Tumor	X									
Prior Cancer Therapy	X									
Tumor Mutational Status[2]	X									
Smoking Status	X									
Vital Signs	X	X	X	X	X		X	X	X	
ECOG Performance Status	X	X	X	X	X		X	X	X	
Physical Exam	X	X		X	X		X	X	X	
Electrocardiogram (ECG)[3]	X				(X)[3]		(X)[3]	X		
Cardiac Imaging (ECHO)	X				(X)[4]					
Hematology	X	X	X	X	X		X	X	X	
Serum Chemistry	X[5]	X	X	X[6]	X		X	X	X	
Pregnancy Test	X							X		
PK Sample		X[7]		X[7]						
Concomitant Medications	X	X	X	X	X	X	X	X	X	
Disease Assessment[8]	X					X	X[8]	X		X[9]
Survival										X

Footnotes for Schedule of Events:

1 This schedule of events table is meant to provide a convenient display of the timing and scope of required assessments expected at each visit. It is not a comprehensive description of each assessment. A complete list of all study related assessments as well as a detailed description of which is expected can be found in Section 5.

2 Tumor mutational status: Any previously identified RET translocation, method of identification, and the dates of identification must be recorded. If available, the presence of additional mutations such as KRAS, EGFR, ALK or ROS should be recorded.

3 All ECGs should be 12-lead ECGs. ECGs are to be performed at screening, Cycle 4 Day 1, Cycle 7 Day 1, and Cycle 13 Day 1. Please see Table 7.1 and Section 7.5 for a description of ECG monitoring requirements if a prolonged QTcB develops in the course of the study period.

4 An additional echocardiogram may be performed on Cycle 4 Day 1 at the discretion of the Investigator based upon participant symptoms.

5 Triglycerides will be collected during the baseline assessment only.

6 Chemistries, including serum lipase, should also be drawn on Cycle 2 Day 15.

7 PK samples will be collected pre-dose on Cycle 1 Day 1 and Cycle 2 Day 1. Additional PK samples will be collected on Cycle 1 Day 1 only at the following time-points: 1, 2, and 4 hours (±10 minutes), and 6 and 8 hrs (±20 minutes) post dose. Whole blood will be collected in EDTA-K2 tubes (lavender top). Refer to site-specific laboratory manual for further details.

8 Disease assessments will initially be performed at 8 week intervals (after cycle 2 [at the beginning of cycle 3 in the table above], after cycle 4 [at the beginning of cycle 5], and so on until cycle 11). From cycle 11 forward, disease assessments will be performed at 12 week intervals (after cycle 13 [at the beginning of cycle 14] and so on). Disease assessments may be limited to the sites of disease. RECIST-defined responses will be confirmed with a repeat assessment in ≥4 weeks (See Section 9). Disease assessments will also be performed at the End of Treatment.

9 Any participant who discontinued study treatment for any reason other than disease progression, death or withdrawal of consent will continue to have disease assessments every 12 weeks (±14 days) until the participant starts another anti-cancer therapy.

10 From cycle 11 forward, study visits will be every 6 weeks but disease assessments will be every 12 weeks (after cycle 13, 16, etc).

11 Baseline procedures are to be obtained within 14 days of the start of study treatment with the exception of obtaining informed consent and baseline disease assessments, which should be obtained within 28 days prior to the start of study treatment.

12 All assessments and procedures (with the exception of baseline) have a +/- 3 day window.

9 Measurement of Effect

Participants will be assessed by RECIST version 1.1 criteria. For the purposes of this study, participants should be reevaluated every 8 weeks. In addition to a baseline scan, confirmatory scans should also be obtained ≥4 weeks following initial documentation of an objective response. If a confirmation scan is performed within 2 weeks of a regularly scheduled scan, then the regularly scheduled scan can be delayed until the next required time point. In practice, the confirmation scan will likely be obtained 8 weeks after the original responsive scan, concurrent with the next scheduled radiographic assessment.

9.1 Antitumor Effect– Solid Tumors

Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) (Eisenhauer et al, 2009) guideline. Changes in the diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria.

9.1.1 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 cycle of therapy, 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.)

9.1.2 Disease Parameters

Measurable disease. Measurable disease is the presence of at least one (1) lesion that can be accurately measured in at least one dimension with longest diameter ≥20 millimeters (mm) using conventional techniques (x-ray) or ≥10 mm with spiral CT scan. Measurable lesions must be at least 2 times the slice thickness in mm. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: A lesion in a previously irradiated area is not eligible for measurable disease unless there is objective evidence of progression of the lesion prior to study enrollment. Lesions in previously irradiated areas must be clearly identified as such.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice

thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses identified by physical exam that are not measurable by reproducible imaging techniques, and cystic lesions are all considered non-measurable.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Lesions must be accurately measured in 1 dimension with a minimum size of 10 mm by CT or MRI (slice thickness no greater than 5 mm), 20 mm by *chest* x-ray. Nodes must have a short axis ≥ 15 mm. The short axis should be included in the sum of the lesions in the calculation of response. Nodes that shrink to < 10 mm are considered normal. Target lesions should be selected on the basis of their size, be representative of all the involved organs, and should be lesions that can be followed with reproducible repeated measurements.

Lytic bone lesions or mixed lytic-blastic lesions, *with identifiable soft tissue components*, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered target lesions if the *soft tissue component* meets the definition of measurability as defined above. Cystic lesions thought to represent cystic metastases can be considered as target lesions. However, if non-cystic lesions are present, these are preferred for selection as target lesions. Lesions in previously irradiated areas or areas subject to other loco-regional therapy are usually not considered measurable unless there has been demonstrated progression of that lesion.

Non-target lesions. All other lesions, including small lesions < 10 mm or pathological lymph nodes measuring ≥ 10 mm to < 15 mm in short axis, as well as truly non-measurable lesions, which include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses identified by physical exam that are not measurable by reproducible imaging techniques.

Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation, using a ruler, calipers, or digital measurement tool. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 14 days before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based

evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the anti-tumor effect of a treatment.

Clinical lesions. Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Conventional CT and MRI. These techniques should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen, and pelvis. Head and neck tumors and those of extremities usually require specific protocols.

FDG PET and PET/CT. The acquisition of FDG PET and FDG PET/CT scans should follow the NCI Guidelines for using FDG PET as an indicator of therapeutic response (L.K. Shankar, J.M. Hoffman, S. Bacharach, M.M. Graham, J. Karp, A.A. Lammertsma, S. Larson, D.A. Mankoff, B.A. Siegel, A. Van den Abbeele, J. Yap, D. Sullivan. Consensus recommendations for the use of 18F-FDG PET as an indicator of therapeutic response in patients in National Cancer Institute Trials. J Nucl Med, 47(6):901-903, 2006). Participants should avoid strenuous exercise and be on a low carbohydrate diet for 24 hours prior to the scan. Participants should fast for 4 hours or longer prior to the FDG injection and should have a serum glucose of less than 200 mg/dL at the time of FDG injection. A 10-20 mCi dose of FDG should be injected for typical adult patients. For longitudinal studies with multiple scans, particular attention should be paid to ensure consistent patient preparation and acquisition parameters between the follow-up scan and the baseline scan. When designing a study where PET scans are going to be utilized as one of the modalities to evaluate efficacy, it is important to consult with physicians in nuclear medicine in designing the appropriate criteria to be utilized.

9.1.3 Response Criteria

Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph node must have reduction in short axis to < 10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study with at least a 5 mm absolute increase in the sum of all lesions. The appearance of one or more new lesions* denotes disease progression.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Unknown (UN): Assessment of target lesions cannot be made due to insufficient or unevaluable data. In this case, a concise explanation must be given.

Note: If tumor response data is missing for target lesions, the overall assessment must be UN unless there is new disease that would result in an overall assessment of PD. However, if there is missing or unevaluable data for non-target lesions, but data is available for all target lesions, the overall response for that time point will be assigned based on the sum LD of all target lesions. Additionally, the assessment of CR cannot be made if there is missing or unevaluable data for non-target lesions. In this case, the overall assessment would be PR.

***Definition of New Lesion**: The finding of a new lesion should be unequivocal (i.e. not due to difference in scanning technique, imaging modality, or findings thought to represent something other than tumor (ex: new bone lesions may be healing or flare of pre-existing lesions)). However, a lesion identified on a follow-up scan in an anatomical location that was not scanned at baseline is considered new and will indicate PD. If a new lesion is equivocal (because of small size, etc.), follow-up evaluation will clarify if it truly represents new disease and if PD is confirmed, progression should be declared using the date of the initial scan on which the lesion was discovered.

Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).

Incomplete Response/Stable Disease (SD): Persistence of one or more non-target lesions and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions* (new lesions must be > slice thickness) and/or unequivocal progression of existing non-target lesions.

Overall level of substantial worsening that merits discontinuation of therapy. A useful test that can be applied when assessing non-targets for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease.

Unknown (UN): Assessment of non-target lesions cannot be made due to insufficient or unevaluable data. In this case, a concise explanation must be given.

***Definition of New Lesion**: The finding of a new lesion should be unequivocal (i.e. not due to difference in scanning technique, imaging modality, or findings thought to represent something other than tumor (ex: new bone lesions may be healing or flare of pre-existing lesions). However, a lesion identified on a follow-up scan in an anatomical location that was not scanned at baseline is considered new and will indicate PD. If a new lesion is equivocal (because of small size, etc.), follow-up evaluation will clarify if it truly represents new disease and if PD is confirmed, progression should be declared using the date of the initial scan on which the lesion was discovered.

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 participant's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Participants with Measurable Disease (i.e., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response for when Confirmation is Required:
CR	CR	No	CR	≥4 wks confirmation
CR	Non-CR/Non-PD	No	PR	≥4 wks confirmation
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/Not evaluated	No	PR	
SD	Non-CR/Non-PD/Not evaluated	No	SD	Documented at least once ≥4 wks from baseline
PD	Any	Yes or No	PD	No prior SD, PR or CR
Any	PD*	Yes or No	PD	
Any	Any	Yes	PD	

* In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Participants with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as *"symptomatic deterioration"*. Every effort should be made to document the objective progression even after discontinuation of treatment.

9.1.4 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrence or PD is objectively documented, taking as reference for PD the smallest measurements recorded since the treatment started.

Duration of overall complete response: The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

9.1.5 Progression-Free Survival

Progression-Free Survival (PFS) is defined as the duration of time from study entry to time of objective disease progression.

9.1.6 Response Review

Tumor assessment for RECIST criteria will be performed by independent central review through the DF/HCC Tumor Imaging Metrics Core (TIMC). These reviews will be used only for determining response by RECIST criteria, and do not need to be used for clinical decision making in real time.

For sites outside of DF/HCC, real time clinical decision making will be based upon investigator review of scans. However, copies of required scans (reports plus electronic images on CD) should be sent to the Coordinating Center within 1 week of completion, at which time they will undergo central review through the DF/HCC TIMC. The results of the central review will not be routinely made available to the sites.

10 Adverse Event Reporting Requirements

10.1 Definitions

10.1.1 Adverse Event (AE)

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.

10.1.2 Serious adverse event (SAE)

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 sever 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.

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

- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, or for elective procedures
- 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
- respite care

10.1.3 Expectedness

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 the purposes of this study, an adverse event is considered

expected when it appears in the current adverse event list, the Investigator's Brochure, the package insert or is included in the informed consent document as a potential risk.

Please refer to the Investigator's Brochure for a listing of expected adverse events associated with the study agent(s).

Unexpected adverse event

For the purposes of this study, an adverse event is considered unexpected when it varies in nature, intensity or frequency from information provided in the current adverse event list, the Investigator's Brochure, the package insert or when it is not included in the informed consent document as a potential risk.
Please refer to the Investigator's Brochure for a listing of expected adverse events associated with the study agent(s).

10.1.4 Attribution

Attribution is the relationship between an adverse event or serious adverse event and the study treatment. Attribution will be assigned as follows:

- 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.

10.2 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.

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 website at:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

10.3 Reporting Requirements

For multi-site trials where a DF/HCC investigator is serving as the principal investigator/sponsor, each participating investigator is required to abide by the reporting requirements set by the DF/HCC. The study must be conducted in compliance with FDA regulations, local safety reporting requirements, and reporting requirements of the principal investigator.

Each investigative site will be responsible to report SAEs that occur at that institution to their respective IRB. It is the responsibility of each participating investigator to report serious adverse events to the study sponsor and/or others (Coordinating Center) as described below.

10.4 Reporting to the Study Sponsor

10.4.1 DF/HCC Reportable Adverse Event Reporting

In addition to SAEs that meet criteria from Section 10.1.2, the Sponsor requires additional events to be reported to the Coordinating Center. All DF/HCC reportable adverse events that occur after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment must be reported to the Coordinating Center on the local institutional SAE form. This includes the following:

- Grade 2 (moderate) and Grade 3 (severe) Events – Only events that are unexpected and possibly, probably or definitely related/associated with the intervention.

  Note: Grade 2 and Grade 3 lab abnormalities that are considered by the investigator to be clinically insignificant and do not require therapy, or adjustment in prior therapy, do not need to be reported.

- All Grade 4 (life-threatening or disabling) Events – Unless expected AND specifically listed in the protocol as not requiring reporting

- All Grade 5 (fatal) Events – When the participant is enrolled and actively participating in the trial OR when the event occurs within 30 days of the last study intervention.

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

Due to the additional expedited reporting criteria, the table below is a tool to summarize the reporting requirements and timelines for SAEs and DF/HCC reportable adverse events to the Coordinating Center.

Attribution	SAEs	DF/HCC Reportable AEs				
	All SAEs (section 10.1.2)	Gr. 2 & 3 AE Expected#	Gr. 2 & 3 AE Unexpected#	Gr. 4 AE Expected#	Gr. 4 AE Unexpected#	Gr. 5 AE Expected or Unexpected
Unrelated Unlikely	24 hours	Not required	Not required	5 calendar days*	5 calendar days	24 hours
Possible Probable Definite	24 hours	Not required	5 calendar days	5 calendar days*	5 calendar days	24 hours

If event meets SAE criteria listed in section 10.1.2 in addition to grade, attribution and expectedness, event must be reported within 24 hours.
* If listed in protocol as expected and not requiring reporting, event does not need to be reported.

Participating investigators must report each serious adverse event to the Coordinating Center in accordance with the table above. In the event that the participating investigator does not become aware of the serious adverse event immediately (e.g., participant sought treatment elsewhere) or within the timeframes listed in the table above, 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. Report serious adverse events by telephone, email or facsimile to:

[redacted]

Within the following 24-48 hours, the participating investigator must provide follow-up information on the serious adverse event. 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.

10.4.2 Reporting SAE to ARIAD Pharmaceuticals

The study sponsor/Coordinating Center will report all SAEs to ARIAD Drug Safety via fax [redacted] within 72 hours of learning of the event.

10.4.3 Non-Serious Adverse Event Reporting

Non-serious adverse events will be reported to the DF/HCC Overall Principal Investigator on the toxicity Case Report Forms.

10.5 Reporting to the Institutional Review Board (IRB)

Investigative sites within DF/HCC will report all serious adverse events directly to the DFCI Office for Human Research Studies (OHRS).

External investigative sites should report serious adverse events to their respective IRB according to the local IRB's policies and procedures in reporting adverse events. A copy of the submitted institutional SAE form should be forwarded to:

The Coordinating Center will submit SAE reports from outside institutions to the DFCI Office for Human Research Studies (OHRS) according to DFCI IRB policies and procedures in reporting adverse events.

10.6 Reporting to the Food and Drug Administration

The Overall PI, as study sponsor, will be responsible for all communications with the FDA. The Coordinating Center will report to the FDA, regardless of the site of occurrence, any serious adverse event that meets the FDA's criteria for expedited reporting following the reporting requirements and timelines set by the FDA.

Unexpected fatal or life-threatening experiences associated with the use of the study treatment will be reported to FDA as soon as possible but in no event later than 7 calendar days after initial receipt of the information.

All other serious unexpected experiences associated with the use of the study treatment will be reported to FDA as soon as possible but in no event later than 15 calendar days after initial receipt of the information.

Events will be reported to the FDA by telephone (1-800-FDA-1088) or by fax (1-800-FDA-0178) using Form FDA 3500A (Mandatory Reporting Form for investigational agents) or FDA Form 3500 (Voluntary Reporting Form for commercial agents). Forms are available at http://www.fda.gov/medwatch/getforms.htm.

10.7 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.

10.8 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 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 Principal Investigator/Sponsor, Coordinating Center 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.

11 Data and Safety Monitoring

11.1 Data Reporting

11.1.1 Method

The QACT and Coordinating Center will collect, manage, and monitor data for this study.

11.1.2 Data Submission

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

11.2 Safety Meetings

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this trial. 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 Principal Investigator/Sponsor and study team.

The DSMC will meet quarterly and/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 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.

11.3 Monitoring

Involvement in this study as a participating investigator implies acceptance of potential audits or inspections, including source data verification, by representatives designated by the Principal Investigator/Sponsor or Coordinating Center. The purpose of these audits or inspections 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, and any applicable regulatory requirements.

All 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. Refer to Appendix D for details.

12 Regulatory Considerations

12.1 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 participants) 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 Coordinating Center will disseminate protocol amendment information to all participating investigators.

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

12.2 Informed Consent

All participants must be provided a consent form describing this study and providing sufficient information for participants 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.

12.3 Ethics

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.

12.4 Study Documentation

The investigator 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.

12.5 Records Retention

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

12.6 Multi-center Guidelines

This protocol will adhere to the policies and requirements of the Dana-Farber/Harvard Cancer Center. The specific responsibilities of the DF/HCC Overall Principal Investigator (or Protocol Chair), Coordinating Center, and Participating Institutions are presented in the Dana-Farber/Harvard Cancer Center Multi-Center Data and Safety Monitoring Plan.

- The DF/HCC Overall Principal Investigator/Coordinating Center is responsible for distributing all IND Action Letters or Safety Reports to all participating institutions for submission to their individual IRBs for action as required.
- Mechanisms will be in place to ensure quality assurance, protocol compliance, and adverse event reporting at each site.
- Except in very unusual circumstances, each participating institution will order the agent(s) directly from the supplier. A participating site may order the agent(s) only after the initial IRB approval for the site has been forwarded to the Coordinating Center.

13 Statistical Considerations

13.1 Study Design/Endpoints

This study will enroll patients with advanced (stage IIIB or IV) NSCLC harboring RET translocations. Participants will receive oral ponatinib on an open-label basis, undergoing radiographic assessments of response every 2 cycles. After a participant has completed 10 cycles, disease assessments will be performed at three cycle intervals. Response will be scored by RECIST criteria and consist of partial responses and complete responses. Treatment with

ponatinib will continue until disease progression, unacceptable toxicity, participant withdrawal, death or discontinuation from the study for any other reason. Participants will be allowed to continue receiving ponatinib despite progressive disease if they are deriving clinical benefit.

In order to investigate the preliminary efficacy of ponatinib, the primary endpoint for this cohort is the overall response rate using RECIST criteria. If at least 4 of 20 participants were to achieve a complete or partial response, ponatinib will be considered to have promising clinical activity in this molecularly defined population. The decision rule is associated with 89% power if 30% of patients in the targeted population truly were to have tumors responsive to ponatinib. In contrast, the probability of type 1 error is only 13% if the underlying rate of overall response were 10%, indicating a minimal level of anti-tumor activity. A relatively high rate of overall response is assumed under the alternative hypothesis, as ponatinib is an inhibitor against a molecular target.

13.2 Sample Size/Accrual rate

RET translocations are present in approximately 1-2% of patients with NSCLC. We expect to enroll approximately 1 participant per month between Massachusetts General Hospital, Yale New Haven Hospital and UC Irvine Douglas Hospital. This estimate is in keeping with accrual rates for other trials involving NSCLC patients with mutations (e.g. ROS1) present at a rate of 1%. Thus, we would complete enrollment of 20 patients in approximately 2 years.

13.3 Analysis of Secondary Endpoints

Secondary endpoints will be analyzed for exploratory purposes only.

13.3.1 Disease Control Rates

Disease control rates (DCR) will be scored according to RECIST criteria and consist of complete response, partial response, and stable disease.

13.3.2 Progression-free survival and 1- year overall survival rate

Progression free survival (PFS) rates will be calculated from the endpoints described in Section 9. All time-to-event variables will be recorded from the day of study enrollment. For 1-year overall survival (OS) rate, death events will be recorded. One-year OS rate will be defined by the number of participants alive 1 year from the time of study entry.

13.3.3 Safety

Toxicity will be assessed using CTC v4.0 criteria. All participants who receive any amount of study drug will be evaluable for toxicity.

14 Publication Plan

Upon study completion and finalization of the study report, the results of this study will either be submitted for publication and/or posted in a publically accessible database of clinical study results.

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Appendix A: Performance Status Criteria

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Description	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	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.
2	In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

Appendix B: Prohibited Drugs Affecting the QT interval

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

Generic Name	Clinical Use
Amiodarone	Anti-arrhythmic
Arsenic trioxide	Anti-cancer
Astemizole	Anti-histamine
Bepridil	Anti-anginal
Chloroquine	Anti-malarial
Chlorpromazine	Anti-psychotic / Anti-emetic / Schizophrenia
Cisapride	GI stimulant / heartburn
Clarithromycin	Antibiotic
Disopyramide	Anti-arrhythmic
Dofetilide	Anti-arrhythmic
Domperidone	Anti-nausea
Droperidol	Sedative / Anti-nausea
Erythromycin	Antibiotic / GI stimulant
Halofantrine	Anti-malarial
Haloperidol	Anti-psychotic / schizophrenia
Ibutilide	Anti-arrhythmic
Levomethadyl	Opiate agonist / pain control
Mesoridazine	Anti-psychotic
Methadone	Opiate agonist / pain control
Pentamidine	Anti-infective
Pimozide	Anti-psychotic
Probucol	Anti-lipemic
Procainamide	Anti-arrhythmic
Quinidine	Anti-arrhythmic
Sotalol	Anti-arrhythmic
Sparfloxacin	Antibiotic
Terfenadine	Anti-histamine
Thioridazine	Anti-psychotic

Appendix C: List of co-medications with known CYP3A4 interaction

The following medications should be used with caution. This is not a comprehensive list of medications. Please contact the medical monitor with any questions.

Drug Name	Class
Afentanil	Analgesic
Alprazolam	Benzodiazepine
Budesonide	Corticosteroid
Buspirone	Anxiolytic
Carbamazepine	Anti-epileptic
Chlorpheniramine	Anti-histamine
Clarithromycin	Antibiotic
Diazepam	Benzodiazepine
Ebastine	Anti-histamine
Efavirenz	Anti-viral
Eletriptan	5-HT agnoist
Everolimus	Immune modulator
Felodipine	Calcium channel blocker
Imatinib	Anti-leukemia
Itraconazole	Anti-fungal
Lovastatin	HMG CoA reductase inhibitor
Midazolam	Benzodiazepine
Nisoldipine	Calcium channel blocker
Phenobarbital	Barbiturate
Phenytoin	Anti-epileptic
Rifampin	Antibiotic
Ritonavir	Anti-viral
Sildenafil	PDE-5 agonist
Simvastatin	HMG CoA reductase inhibitor
Triazolam	Benzodiazepine
Voriconazole	Anti-fungal

Source:
FDA guidance drug interaction studies: study design, data analysis, and implications for dosing and labeling, 2006.

Appendix D: Data and Safety Monitoring Plan

DFCI IRB Protocol #: 13-103

APPENDIX D

Dana-Farber/Harvard Cancer Center
Multi-Center Data and Safety Monitoring Plan

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1.0 INTRODUCTION

The Dana-Farber/Harvard Cancer Center Multi-Center Data and Safety Monitoring Plan (DF/HCC DSMP) outlines the procedures for conducting a DF/HCC Multi-Center research protocol. The DF/HCC DSMP should serve as a reference for any sites external to DF/HCC that will be participating in the research protocol.

1.1 Purpose

To establish standards that will ensure that a Dana-Farber/Harvard Cancer Center Multi-Center protocol will comply with Federal Regulations, Health Insurance Portability and Accountability Act (HIPAA) requirements and applicable DF/HCC Standard Operating Procedures.

1.2 Multi-Center Data and Safety Monitoring Plan Definitions

DF/HCC Multi-center Protocol: A research protocol in which one or more outside institutions are collaborating with Dana-Farber/Harvard Cancer Center where a DF/HCC investigator is the sponsor. DF/HCC includes Dana-Farber/Partners Cancer Care (DF/PCC) Network Clinical Trial Affiliates.

Lead Institution: One of the Dana-Farber/Harvard Cancer Center consortium members (Dana-Farber Cancer Institute (DFCI), Massachusetts General Hospital (MGH), Beth Israel Deaconess Medical Center (BIDMC), Children's Hospital Boston (CHB), Brigham and Women's Hospital (BWH)) responsible for the coordination, development, submission, and approval of a protocol as well as its subsequent amendments per the DFCI IRB and applicable regulatory guidelines (CTEP, Food and Drug Administration (FDA), Office of Biotechnology Activities (OBA) etc.). The Lead Institution is typically the home of the DF/HCC Sponsor. The Lead Institution also typically serves as the Coordinating Center for the DF/HCC Multi-Center Protocol.

DF/HCC Sponsor: The person sponsoring the submitted Multi-Center protocol. Within DF/HCC, this person is the Overall Principal Investigator who takes responsibility for initiation, management and conduct of the protocol at all research locations. In applicable protocols, the DF/HCC Sponsor will serve as the single liaison with any regulatory agencies (i.e. CTEP Protocol and Information Office (PIO), FDA, OBA etc.). The DF/HCC Sponsor has ultimate authority over the protocol and is responsible for the conduct of the study at DF/HCC and all Participating Institutions. In most cases the DF/HCC Sponsor is the same person as the DF/HCC Principal Investigator; however, both roles can be filled by two different people.

Participating Institution: An institution that is outside the DF/HCC and DF/PCC consortium that is collaborating with DF/HCC on a protocol where the sponsor is a DF/HCC

Investigator. The Participating Institution acknowledges the DF/HCC Sponsor as having the ultimate authority and responsibility for the overall conduct of the study.

Coordinating Center: The entity (i.e. Lead Institution, Medical Monitor, Contract Research Organization (CRO), etc.) that provides administrative support to the DF/HCC Sponsor in order that he/she may fulfill the responsibilities outlined in the protocol document and DSMP, and as specified in applicable regulatory guidelines (i.e. CTEP Multi-Center Guidelines). In general, the Lead Institution is the Coordinating Center for the DF/HCC Multi-Center Protocol. Should the DF/HCC Sponsor decide to use a CRO, the CRO will be deemed the Coordinating Center.

DF/HCC Quality Assurance Office for Clinical Trials: A unit within DF/HCC developed to computerize and manage data, and to provide a Quality Control and Quality Assurance function for DF/HCC trials.

2.0 GENERAL ROLES AND RESPONSIBILITIES

For DF/HCC Multi-Center Protocols, the DF/HCC Sponsor, the Coordinating Center, and the Participating Institutions are expected to adhere to the following general responsibilities:

2.1 DF/HCC Sponsor

The DF/HCC Sponsor, Alice Shaw, MD will accept responsibility for all aspects of conducting a DF/HCC Multi-Center protocol which includes but is not limited to:

- Oversee the coordination, development, submission, and approval of the protocol as well as subsequent amendments.
- Ensure that the investigators, study team members, and Participating Institutions are qualified and appropriately resourced to conduct the protocol.
- Submit the Multi-Center Data and Safety Monitoring Plan as an appendix to the protocol.
- Ensure all Participating Institutions are using the correct version of the protocol.
- Ensure that each participating investigator and study team receives adequate protocol training and/or a Site Initiation Visit prior to enrolling participants and throughout trial's conduct as needed.
- Ensure the protocol will be provided to each participating site in a language understandable to all site personnel when English is not the primary language.
- Monitor progress and overall conduct of the study at all Participating Institutions.
- Ensure all DFCI Institutional Review Board (IRB), DF/HCC and other applicable (i.e. FDA) reporting requirements are met.
- Review data and maintain timely submission of data for study analysis.
- Act as the single liaison with FDA (investigator-held IND trials), as applicable.
- Ensure compliance with all requirements as set forth in the Code of Federal Regulations, applicable DF/HCC requirements, HIPAA requirements, and the approved protocol.

- Commit to the provision that the protocol will not be rewritten or modified by anyone other than the DF/HCC Sponsor.
- Identify and qualify Participating Institutions and obtain accrual commitments prior to extending the protocol to that site.

2.2 Coordinating Center

The Coordinating Center will assume the following general responsibilities:

- Assist in protocol development
- Maintain copies of Federal Wide Assurance and Institutional Review Board (IRB) approvals from all Participating Institutions.
- Maintain FDA correspondence, as applicable.
- Maintain updated roster of participants.
- Verify eligibility.
- Verify response.
- Oversee the data collection process from Participating Institutions.
- Maintain documentation of Serious Adverse Event (SAE) reports submitted by Participating Institutions and submit to DF/HCC Sponsor for timely review.
- Distribute adverse events reported to the DF/HCC Sponsor that fall under the DFCI IRB Adverse Event Reporting Policy to all participating investigators.
- Provide Participating Institutions with information regarding DF/HCC requirements that they will be expected to comply with.
- Monitor Participating Institutions either by on-site or virtual monitoring.
- Maintain Regulatory documents of all Participating Institutions.
- Conduct regular communications with all Participating Institutions (conference calls, emails, etc).
- Maintain documentation of all communications.
- Ensure that each Participating Institution has the appropriate assurance on file with the Office of Human Research Protection (OHRP).

2.3 DF/HCC Quality Assurance Office for Clinical Trials (QACT)

In addition to the Coordinating Center, the DF/HCC QACT provides the following support services to assist the DF/HCC Sponsor:

- Develop protocol specific case report forms (CRF/eCRFS).
- QA/QC data of protocol specific CRFs.
- Provide a central participant registration, which includes review of consent and eligibility.
- Provide auditing services (funding and QACT approval required).

2.4 Participating Institution

Each Participating Institution is expected to comply with all applicable Federal Regulations and DF/HCC requirements, the protocol and HIPAA requirements. All Participating Institutions will provide a list of personnel assigned to the role for oversight of data management at their site to the Coordinating Center.

The general responsibilities for each Participating Institution are as follows:

- Commit to the accrual of participants to the protocol.
- Submit protocol and/or amendments to their local IRB.
- Maintain a regulatory binder in accordance with DF/HCC requirements.
- Provide the Coordinating Center with regulatory documents as requested.
- Participate in protocol training prior to enrolling participants and throughout the trial as needed (i.e. teleconferences).
- Update Coordinating Center with research staff changes on a timely basis.
- Register participants through the Coordinating Center.
- Submit source documents, research records, and CRFs per protocol specific submission guidelines to the Coordinating Center.
- Submit Serious Adverse Event (SAE) reports to local IRB per local requirements and to the Coordinating Center, in accordance with DF/HCC requirements.
- Submit protocol deviations and violations to local IRB per local requirements and to the DF/HCC Sponsor in accordance with DF/HCC requirements.
- Secure and store investigational agents and/or other protocol mandated drugs per federal guidelines and protocol requirements.
- Have office space, office equipment, and internet access that meet HIPAA standards.
- For protocols using investigational agents, the Participating Institution will order their own investigational agents regardless of the supplier (i.e. National Cancer Institute (NCI), pharmaceutical company).

3.0 DF/HCC REQUIREMENTS FOR MULTI-CENTER PROTOCOLS

The following section will clarify DF/HCC Requirements and further detail the expectations for participating in a DF/HCC Multi-Center protocol.

3.1 Protocol Distribution

The Coordinating Center will distribute the final DFCI IRB approved protocol and any subsequent amended protocols to all Participating Institutions.

3.2 Protocol Revisions and Closures

The Participating Institutions will receive notification of protocol revisions and closures from the Coordinating Center. It is the individual Participating Institution's responsibility to notify its IRB of these revisions.

- **Non life-threatening revisions:** Participating Institutions will receive written

notification of protocol revisions regarding non life-threatening events from the Coordinating Center. Non-life-threatening protocol revisions must be IRB approved and implemented within 90 days from receipt of the notification.

- **Revisions for life-threatening causes:** Participating Institutions will receive immediate notification from the Coordinating Center concerning protocol revisions required to protect lives with follow-up by fax, mail, e-mail, etc. Life-threatening protocol revisions will be implemented immediately followed by IRB request for approval.

- **Protocol closures and temporary holds:** Participating Institutions will receive notification of protocol closures and temporary holds from the Coordinating Center. Closures and holds will be effective immediately. In addition, the Coordinating Center, will update the Participating Institutions on an ongoing basis about protocol accrual data so that they will be aware of imminent protocol closures.

3.3 Informed Consent Requirements

The DF/HCC approved informed consent document will serve as a template for the informed consent for Participating Institutions. The Participating Institution consent form must follow the consent template as closely as possible and should adhere to specifications outlined in the DF/HCC Guidance Document on Model Consent Language for PI-Initiated Multi-Center Protocols. This document will be provided separately to each Participating Institution.

Participating Institutions are to send their version of the informed consent document and HIPAA authorization, if a separate document, to the Coordinating Center for review and approval prior to submission to their local IRB. The approved consent form must also be submitted to the Coordinating Center after approval by the local IRB.

The Principal Investigator (PI) at each Participating Institution will identify the physician members of the study team who will be obtaining consent and signing the consent form for therapeutic protocols. Participating Institutions must follow the DF/HCC requirement that only attending physicians obtain informed consent and re-consent.

3.4 IRB Documentation

The following must be on file with the Coordinating Center:

- Approval letter of the Participating Institution's IRB
- Copy of the Informed Consent Form approved by the Participating Institution’s IRB
- Participating Institution’s IRB approval for all amendments

It is the Participating Institution's responsibility to notify its IRB of protocol amendments. Participating Institutions will have 90 days from receipt to provide the Coordinating Center their IRB approval for amendments to a protocol.

3.5 IRB Re-Approval

Verification of IRB re-approval from the Participating Institutions is required in order to continue research activities. There is no grace period for continuing approvals.

The Coordinating Center will not register participants if a re-approval letter is not received from the Participating Institution on or before the anniversary of the previous approval date.

3.6 Participant Confidentiality and Authorization Statement

In 1996, congress passed the first federal law covering the privacy of health information known as the Health Insurance Portability and Accountability Act (HIPAA). Any information, related to the physical or mental health of an individual is called Protected Health Information (PHI). HIPAA outlines how and under what circumstances PHI can be used or disclosed.

In order for covered entities to use or disclose PHI during the course of a study, the study participant must sign an Authorization. This Authorization may or may not be separate from the informed consent document. The Coordinating Center, with the approval from the DFCI IRB and if applicable NCI/CTEP, will provide a consent template, which covered entities (Participating Institutions) must use.

The DF/HCC Sponsor will use all efforts to limit its use of PHI in its trials. However, because of the nature of these trials, certain PHI must be collected per NCI requirements. These are the primary reasons why DF/HCC has chosen to use Authorizations, signed by the participant in the trial, rather than limited data sets with data use agreements.

3.6.1 DF/HCC Multi-Center Protocol Confidentiality

All documents, investigative reports, or information relating to the participant are strictly confidential. Whenever reasonably feasible, any participant specific reports (i.e. Pathology Reports, MRI Reports, Operative Reports, etc.) submitted to the Coordinating Center must have the participant's full name & social security number "blacked out" and the assigned DF/HCC QACT case number (as described below) and DF/HCC protocol number written in (with the exception of the signed informed consent document). Participant initials may only be included or retained for cross verification of identification.

3.7 DF/HCC Multi-Center Protocol Registration Policy

3.7.1 Participant Registration and Randomization

To register a participant, the following documents should be completed by the Participating Institution and faxed [redacted] or e-mailed ([redacted] to the Coordinating Center:

- Copy of source documentation for all inclusion/exclusion criteria
- Signed informed consent document
- HIPAA authorization form (if separate from the informed consent document)
- Eligibility Checklist

The Coordinating Center will review the submitted documents in order to verify eligibility and consent. To complete the registration process, the Coordinating Center will:

- Register the participant on the study with the DF/HCC QACT
- Upon receiving confirmation of registration by the QACT, the Coordinating Center will inform the Participating Institution and provide the study specific participant case number, and if applicable the dose treatment level.

Treatment may not begin without confirmation from the Coordinating Center that the participant has been registered.

Randomization can only occur during QACT's normal business hours, Monday through Friday from 8:00 AM to 5:00 PM Eastern Time.

3.7.2 Initiation of Therapy

Participants must be registered with the DF/HCC QACT before receiving treatment. Treatment may not be initiated until the Participating Institution receives a faxed or e-mailed copy of the participant's registration confirmation memo from the Coordinating Center. Therapy must be initiated per protocol guidelines. The DF/HCC Sponsor and DFCI IRB must be notified of any exceptions to this policy.

3.7.3 Eligibility Exceptions

CTEP specifically prohibits registration of a participant on any NCI Sponsored protocol that does not fully and completely meet all eligibility requirements. The DF/HCC QACT will make no exceptions to the eligibility requirements for a protocol without DFCI IRB approval. The DF/HCC QACT requires each institution to fully comply with this requirement.

3.7.4 Verification of Registration, Dose Levels, and Arm Designation

A registration confirmation memo for participants registered to DF/HCC Multi-Center Protocol will be faxed or emailed to the registering institution within one business day of

the registration. Treatment may not be initiated until the site receives a faxed or e-mailed copy of the registration confirmation memo.

3.8 DF/HCC Protocol Case Number

Once eligibility has been established and the participant successfully registered, the participant is assigned a five digit protocol case number. This number is unique to the participant on this trial and must be used for QACT CRF/eCRF completion and correspondence, and correspondence with the Coordinating Center.

3.9 Protocol Deviations, Exceptions and Violations

Federal Regulations require an IRB to review proposed changes in a research activity to ensure that researchers do not initiate changes in approved research without IRB review and approval, except when necessary to eliminate apparent immediate hazards to the participant. DF/HCC requires all departures from the defined procedures set forth in the IRB approved protocol to be reported to the DF/HCC Sponsor, who in turn is responsible for reporting to the DFCI IRB.

For reporting purposes, DF/HCC uses the terms "violation", "deviation" and "exception" to describe derivations from a protocol. All Participating Institutions must adhere to these requirements for reporting to the DF/HCC Sponsor and will follow their institutional policy for reporting to their local IRB.

3.9.1 Definitions

Protocol Deviation: Any departure from the defined procedures set forth in the IRB-approved protocol which is *prospectively approved* prior to its implementation.

Protocol Exception: Any protocol deviation that relates to the eligibility criteria, e.g. enrollment of a participant who does not meet all inclusion/exclusion criteria.

Protocol Violation: Any protocol deviation that was not *prospectively approved* by the IRB prior to its initiation or implementation.

3.9.2 Reporting Procedures

DF/HCC Sponsor: is responsible for ensuring that clear documentation is available in the medical record and/or regulatory documents to describe all protocol exceptions, deviations and violations. The DF/HCC Sponsor will also be responsible for ensuring that all protocol violations/deviations are promptly reported per DFCI IRB guidelines.

Participating Institutions: Protocol deviations require prospective approval from the DFCI IRB. The Participating Institution must submit the deviation request to the Coordinating

Center who will then submit the deviation request to the DFCI IRB. Upon DFCI IRB approval the deviation is submitted to the Participating Institution IRB, per institutional policy. A copy of the Participating Institution's IRB report and determination will be forwarded to the Coordinating Center within 10 business days after the original submission.

All protocol violations must be sent to the Coordinating Center in a timely manner.

Coordinating Center: Upon receipt of the violation/deviation report from the Participating Institution, the Coordinating Center will complete the DFCI Major Deviation/Violation/Exception – Other Event Reporting Form and submit the report to the DF/HCC Sponsor for review. Subsequently, the Coordinating Center will submit the event to the DFCI IRB for review per DFCI IRB reporting guidelines.

3.10 Safety Assessments and Toxicity Monitoring

The study teams at all Participating Institutions are responsible for protecting the safety, rights and well-being of study participants. Recording and reporting of adverse events that occur during the course of a study help ensure the continuing safety of study participants.

All participants receiving investigational agents and/or other protocol mandated treatment will be evaluated for safety. The safety parameters include all laboratory tests and hematological abnormalities, physical examination findings, and spontaneous reports of adverse events reported by participants. All toxicities encountered during the study will be evaluated according to the NCI criteria specified in the protocol. Life-threatening toxicities must be reported immediately to the DF/HCC Sponsor via the Coordinating Center.

Additional safety assessments and toxicity monitoring will be outlined in the protocol.

3.10.1 Guidelines for Reporting Serious Adverse Events

Guidelines for reporting Adverse Events (AEs) and Serious Adverse Events (SAEs) are detailed in protocol Section 10.

Participating Institutions must report the AEs to the DF/HCC Sponsor and the Coordinating Center following the DFCI IRB AE Reporting Requirements.

The Coordinating Center will maintain documentation of all Participating Institution Adverse Event reports and be responsible for communicating to all Participating Investigators, any observations reportable under the DFCI IRB Reporting Requirements. Participating Investigators will review any distributed AE reports, send a copy to their IRB according to their local IRB's policies and procedures, and file a copy with their regulatory documents.

3.10.2 Guidelines for Processing IND Safety Reports

FDA regulations require sponsors of clinical studies to notify the FDA and all Participating Investigators of any adverse experience associated with the use of the investigational agent that is both serious and unexpected. The DF/HCC Sponsor will review all IND Safety Reports and ensure that all IND Safety Reports are distributed to the Participating Institutions. The Participating Investigators are to review, send a copy to their IRB according to their local IRB's policies and procedures, and file a copy with their regulatory documents.

3.11 Data Management

The DF/HCC QACT develops a set of either paper or electronic case report forms (CRF/eCRFs), for use with the protocol. These forms are designed to collect data for each study. The DF/HCC QACT provides a web based training for eCRF users.

3.11.1 Data Forms Review

When data forms arrive at the DF/HCC QACT, they are reviewed for completeness, protocol treatment compliance, adverse events (toxicities) and response. Data submissions are monitored for timeliness and completeness of submission. Participating Institutions are notified of their data submission delinquencies in accordance with the following:

Incomplete or Questionable Data
If study forms are received with missing or questionable data, the submitting institution will receive a written or electronic query from the DF/HCC QACT Data Analyst or study monitor. Responses to all queries should be completed and submitted within 14 calendar days. Responses may be returned on the written query or on an amended paper case report form, or in the case of electronic queries, within the electronic data capture (eDC) system. In the case of a written query for data submitted on a paper case report form, the query must be attached to the specific data being re-submitted in response.

Missing Forms
If study forms are not submitted on schedule, the Participating Institution will receive a Missing Form Report from the Coordinating Center noting the missing forms. These reports are compiled by the DF/HCC QACT and distributed a minimum of four times a year.

4.0 REQUISITIONING INVESTIGATIONAL DRUG

The ordering of investigational agent is specified in section 6.5 of the protocol.

Participating Institutions should order their own agent regardless of the supplier (i.e., NCI or a pharmaceutical company.)

If the agent is investigational, ensure that the pharmacy will be able to receive and store the agent according to state and federal requirements. The local IRB should be kept informed of

who will supply the agent (i.e., NCI or a pharmaceutical company) so that any regulatory responsibilities can be met in a timely fashion.

5.0 MONITORING: QUALITY CONTROL

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.

5.1 Ongoing Monitoring of Protocol Compliance

The Participating Institutions will 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.

The Coordinating Center will implement ongoing monitoring activities to ensure that Participating Institutions are complying with regulatory and protocol requirements, data quality, and participant safety. Monitoring will occur before the clinical phase of the protocol begins, continue during protocol performance and through study completion. Monitoring practices may include, but are not limited to, review of the following; source verification, review and analysis of the following: eligibility requirements of all participants, informed consent procedures, adverse events and all associated documentation, study drug administration/treatment, regulatory files, protocol deviations, pharmacy records, response assessments, and data management.

One on-site monitoring visit will be conducted after the first participant is enrolled at each site. Monitors should be given full access to participants' complete medical record and source documentation. Subsequent monitoring visits will be conducted remotely at least every five months. Participating Institutions will be required to forward copies of participants' de-identified medical records and source documentation to the Coordinating Center.

Participating institutions will be required to participate in monthly Coordinating Center initiated teleconferences while patients are on treatment. Communication via email highlighting overall protocol progress and important announcements will be distributed on an as-needed basis.

All data submitted to the DF/HCC QACT will be monitored for timeliness of submission, completeness, and adherence to protocol requirements. The Coordinating Center and if applicable, QACT Data Analysts assigned to the protocol, will perform the ongoing protocol data compliance monitoring.

5.2 Evaluation of Participating Institution Performance

5.2.1 Monitoring Reports

The DF/HCC Sponsor will review all monitoring reports for on-site and virtual monitoring of Participating Institutions to ensure protocol compliance and ability to fulfill responsibilities of participating in the study. The DF/HCC Sponsor may increase the monitoring activities at Participating Institutions that are unable to comply with the protocol, DF/HCC Sponsor requirements or federal and local regulations. Participating Institutions may also be subject to an audit as determined by the DF/HCC Sponsor.

6.0 AUDITING: QUALITY ASSURANCE

Auditing is a method of Quality Assurance. Its main focus is to measure whether standards and procedures were followed. Auditing is the systematic and independent examination of all trial related activities and documents. Audits determine if evaluated activities were appropriately conducted and whether data was generated, recorded and analyzed, and accurately reported per the protocol, Standard Operating Procedures (SOPs), and the Code of Federal Regulations (CFR).

6.1 DF/HCC Sponsored Trials

One on-site audit will be scheduled by the QACT, assuming at least three participants have been treated on protocol at the site. Approximately 3-4 participants would be audited at the site over a 2 day period. If violations which impact participant safety or the integrity of the study are found, more participant records may be audited.

6.2 Participating Institution

It is the Participating Institution's responsibility to notify the Coordinating Center of all scheduled audit dates (internal or external) and re-audit dates (if applicable), which involve this protocol. All institutions will forward a copy of final audit and/or re-audit reports and corrective action plans (if applicable) to the Coordinating Center, within 12 weeks after the audit date.

6.3 DF/HCC Sponsor and Coordinating Center

The DF/HCC Sponsor will review all final audit reports and corrective action plans if applicable. The Coordinating Center, must forward these reports to the DF/HCC QACT per DF/HCC policy for review by the DF/HCC Audit Committee. Based upon the audit assessments the DF/HCC Audit Committee could accept or conditionally accept the audit rating and final report. Conditional approval could require the DF/HCC Sponsor to implement recommendations or require further follow-up. For unacceptable audits, the

DF/HCC Audit Committee would forward the final audit report and corrective action plan to the DFCI IRB as applicable.

6.4 Sub-Standard Performance

The DF/HCC Sponsor and DFCI IRB, is charged with considering the totality of a Participating Institution's performance in considering institutional participation in the protocol.

6.4.1 Corrective Actions

Participating Institutions that fail to meet the performance goals of accrual, submission of timely accurate data, adherence to protocol requirements, and compliance with state and federal regulations, will be recommended for a six-month probation period. Such institutions must respond with a corrective action plan and must demonstrate during the probation period that deficiencies have been corrected, as evidenced by the improved performance measures. Participating Institutions that fail to demonstrate significant improvement will be considered by the DF/HCC Sponsor for revocation of participation.