

**NCI Protocol #:** N/A

**DF/HCC Protocol #:** 17-080

**TITLE:** A Phase 1/2 Study of alectinib in RET-rearranged non-small cell lung cancer or RET-mutated thyroid cancer

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**NCI-Supplied Agent:** None

**Other Agent:** Alectinib (Alecensa/RO5424802/CH5424802), Genentech/Roche, investigational supply

**IND #:** 132,210

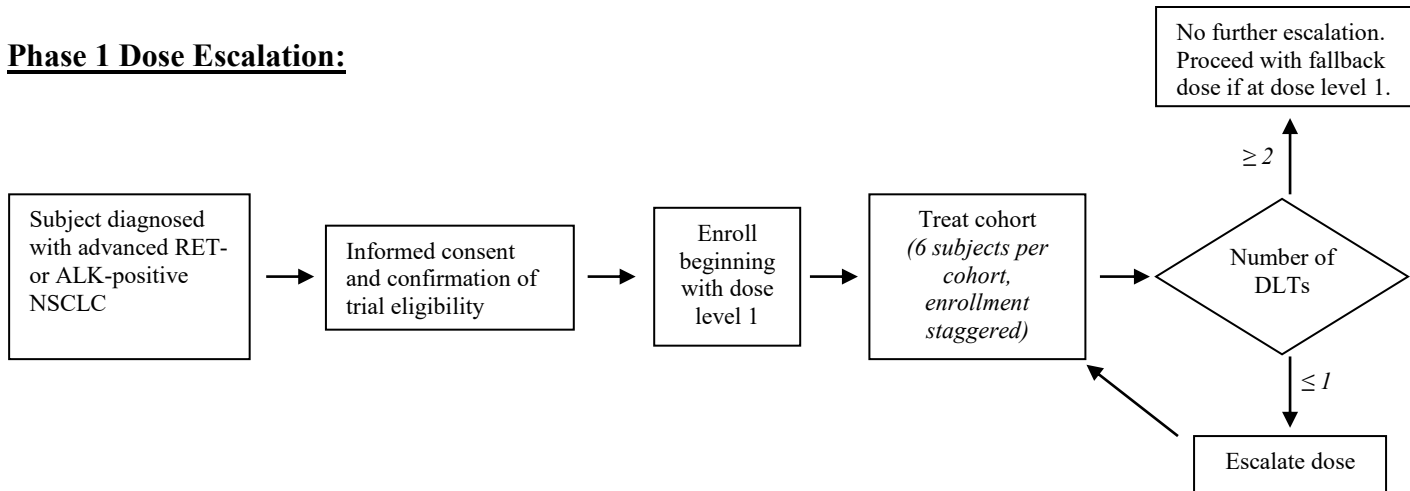
**IND Sponsor:** Investigator-Initiated Study, Mark Awad MD, PhD

**Protocol Type / Version # / Version Date:** Revised/Version #6/January 3, 2018

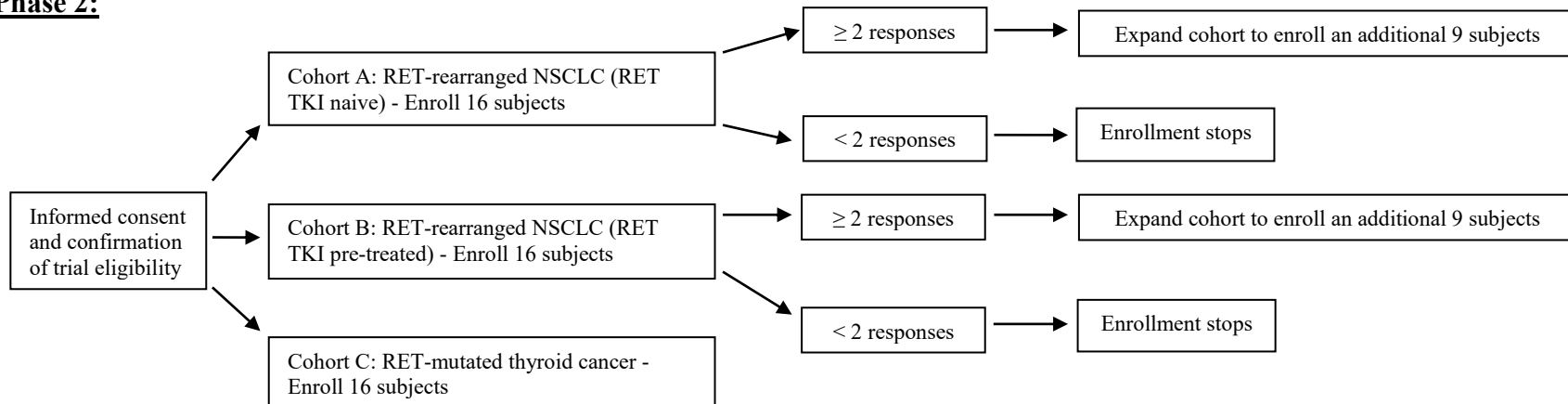


# SCHEMA

## Phase 1 Dose Escalation:



## Phase 2:



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## 1. OBJECTIVES

### 1.1 Study Design

The phase 1 portion of this trial is an open label dose escalation study to determine the recommended phase 2 dose (RP2D) of alectinib in RET- or ALK-positive non-small cell lung cancer (NSCLC). The phase 2 component of the trial will be an open label dose expansion study of alectinib at the determined RP2D in three cohorts:

**Cohort A:** RET-positive NSCLC subjects who are RET tyrosine kinase inhibitor (TKI)-naive

**Cohort B:** RET-positive NSCLC subjects who have received prior RET TKI

**Cohort C:** RET-positive thyroid cancer

### 1.2 Primary Objectives

Phase 1:

- To assess safety and tolerability of alectinib as a single agent at increasing dose levels in subjects with advanced RET- or ALK-positive NSCLC in order to determine the maximal tolerated dose (MTD) and the RP2D.
- To preliminarily evaluate the objective response rate (ORR) of alectinib.

Phase 2:

- To evaluate the ORR of alectinib at the RP2D in subjects with advanced RET-positive NSCLC and advanced RET-positive thyroid cancer.

### 1.3 Secondary Objectives

Phase 1:

- To evaluate the pharmacokinetics (PK) of alectinib.
- To preliminarily assess the progression free survival (PFS), overall survival (OS), and the duration of response (DoR) of alectinib in enrolled subjects.
- Among subjects with central nervous system (CNS) disease at baseline: to preliminarily explore the CNS duration of response, ORR, and progression-free survival rates.

Phase 2:

- To confirm the safety and tolerability of alectinib at the RP2D.
- To confirm the best objective response per RECIST in subjects with advanced RET-positive NSCLC and thyroid cancer.
- To assess progression free survival (PFS), overall survival (OS), and the duration of response (DoR) in subjects with advanced RET-positive NSCLC and thyroid cancer.

Among subjects with central nervous system (CNS) disease at baseline: to preliminarily explore the CNS DoR, ORR, and CNS PFS rates.

#### 1.4 Correlative Objective

- To determine tumor- and blood-based molecular markers of response and resistance to alectinib.

## 2. BACKGROUND

### 2.1 Study Diseases

Lung cancer is the leading cause of cancer-related death worldwide in both men and women, and more people die from lung cancer than from colon, breast, and prostate cancer combined. In the United States, there will be 221,200 new cases of lung cancer in 2015 (115,610 in men and 105,590 in women), and an estimated 158,040 deaths from lung cancer (86,380 in men and 71,660 in women)<sup>1</sup>. NSCLC accounts for 85-90% of lung cancer and is comprised of three main histologic subtypes: adenocarcinoma (accounts for ~40% of lung cancers), squamous cell carcinoma (25-30%), and large cell (undifferentiated) carcinoma (10%).

Over the past 10 years, the successful identification of targetable alterations in NSCLC has revolutionized treatment for subjects whose cancers harbor mutations in genes such as *EGFR*<sup>2-4</sup>, *ALK*<sup>5-7</sup>, and *ROS1*.<sup>8,9</sup> More recently, chromosomal translocations have been discovered in NSCLC that generate fusion transcripts involving the RET tyrosine kinase domain with a variety of upstream binding partners including KIF5B and CCDC6.<sup>10-13</sup> The incidence of RET rearrangements in NSCLC appears to be ~1.4%, is mutually exclusive with other oncogenic driver mutations, and tends to occur in younger subjects, never smokers, and in the setting of adenocarcinoma histology.<sup>11,14</sup>

Preclinical and early clinical data suggests that RET inhibition with small molecule kinase inhibitors represents a promising therapeutic approach for the treatment of NSCLCs harboring this rearrangement. Several multi-kinase inhibitors with RET activity, such as vandetanib, sorafenib, and sunitinib, can effectively inhibit cells expressing KIF5B-RET fusions,<sup>12</sup> and subjects with RET-rearranged NSCLC have responded to cabozantinib, a tyrosine kinase inhibitor (TKI) with activity against RET, MET, VEGFR2, FLT3, and c-KIT.<sup>15</sup> A recent phase II trial of cabozantinib in RET+ lung cancer showed a confirmed response rate of 38% with a median duration of response of 8 months; however, most subjects in this study had to reduce the dose of cabozantinib due to adverse events.<sup>15</sup>

Roughly half of sporadic medullary thyroid cancers harbor activating somatic mutations in *RET*, and certain inherited cancers such as familial medullary carcinoma and multiple endocrine neoplasia type 2 (MEN2) demonstrate germline mutations in *RET*.<sup>16,17</sup> In a randomized, double-blind, placebo-controlled phase III trial of medullary thyroid carcinoma, treatment with the RET inhibitor vandetanib resulting in improved progression-free survival, objective response rate, and disease control rate.<sup>18</sup> A separate randomized, double-blind, placebo-controlled phase III trial in iodine-131-refractory thyroid cancer with lenvatinib, an inhibitor of RET, c-KIT, VEGFR1, 2,



and 3, and FGFR1-4 also showed significant improvements in progression free survival and response rate compared to placebo.<sup>19</sup>

## 2.2 Alectinib

Alectinib (also referred to as Alecensa, RO5424802 or CH5424802) is an oral, small molecule, next-generation, highly selective RET and ALK inhibitor with central nervous system penetration. *In vitro* kinase assays demonstrate that the IC<sub>50</sub> of alectinib is 4.8 nM for RET and 1.9 nM for ALK. Preclinical studies show that alectinib 1) inhibits RET phosphorylation, 2) inhibits growth of the LC-2/ad NSCLC cell line which harbors a CCDC6-RET gene fusion and growth Ba/F3 cells driven by KIF5B-RET, and 3) has antitumor activity in mouse LC-2/ad xenografts.<sup>20</sup>

To date, alectinib has been used primarily in NSCLCs with rearrangements in anaplastic lymphoma kinase (ALK) in a number of studies, including Study AF-0001JP in Japan, Study NP28761/AF-002JG in the U.S and Canada, and the global Study NP28673. In addition, a global phase III study (BO28984) and a Japanese phase III study (JO28929) comparing alectinib to crizotinib in treatment-naive ALK-positive NSCLC are underway.

### 2.2.1 Non-Clinical Pharmacokinetics and Metabolism

Single intravenous (IV) dose pharmacokinetic (PK) studies of alectinib in rats and cynomolgus monkeys showed low total plasma clearance (CL<sub>tot</sub>), a large volume of distribution at steady-state (V<sub>ss</sub>), and moderately long terminal half-life (t<sub>1/2</sub>) of 17.8-24.4 hours in rats and 10.4 hours in monkeys. After single oral administration of alectinib to rats or monkeys, moderate to high oral bioavailability (F) was observed in rats (65.2%-88.6%) and in monkeys (50.4%).

Alectinib PK was also evaluated following repeated oral daily doses in 4-week and 13-week toxicology studies in rats and monkeys. In the 4-week studies, alectinib was administered at 6–60 mg/kg to rats and at 1.7–15 mg/kg to monkeys. In the 13-week studies, alectinib was administered at 3 to 27 mg/kg to rats and 1.3 to 12 mg/kg to monkeys. In all studies, exposures increased with increasing doses. Up to approximately 2-fold accumulations in the area under plasma concentration curve from 0 – 24 hours (AUC<sub>0-24h</sub>) in rats and no marked accumulation in monkeys were observed on Day 91 after daily oral administration.

*In vitro* plasma protein binding of alectinib was high (> 99%) for mice, rats, monkeys and humans. Alectinib was highly bound to human serum albumin (HsA) (97%), but much less bound to alpha-1-acid glycoprotein (AAG) (< 5%). Three tissue distribution studies were performed using quantitative whole-body autoradiography (QWBA) after a single oral administration of [<sup>14</sup>C]-alectinib to albino rats at 1 mg/kg or pregnant rats at 1 mg/kg, or pigmented rats at 10 mg/kg. The results showed:

1. Good distribution of radioactivity to the various tissues. The radioactivity concentration of almost all of the tissues were similar or higher than that of plasma with concentrations in the CNS (cerebrum, cerebellum, and spinal cord) similar to plasma up to 24 hour post-dose suggesting alectinib penetration into the CNS
2. Drug-related material penetrated the fetus with a similar tissue distribution pattern to that

in maternal rats

3. Tissue radioactivity disappeared over time, following a time course comparable to that of plasma radioactivity, except for melanin-containing tissues, such as uveal tract of eyes, which had much higher and more sustained exposure in pigmented rats.

This is consistent with what is commonly observed for lipophilic basic drugs. After a single oral administration of [<sup>14</sup>C]-alectinib to rats, alectinib and its metabolites were excreted mainly in feces, and at 168 hours post-dose, 95.7% and 0.5% of the administered radioactivity had been recovered in feces and urine, respectively. After a single IV dose of [<sup>14</sup>C]-alectinib to bile-duct cannulated rats, 42.5% of total radioactivity was excreted into bile within 48 hours, of which alectinib accounted for 1.3% within 24 hours, suggesting that biliary excretion of parent drug is a minor pathway in rats.

The *in vitro* metabolic profiles of alectinib determined using cryopreserved hepatocytes from mice, rats, monkeys, dogs, and humans were similar in all of the species, and the major metabolite (> 10% of total radioactivity in hepatocytes, except for mice) was RO5468924 (M4), which was formed by morpholine ring opening followed by alkylation. Other minor oxidative metabolites, such as M1 mixture (the major component was M1b, RO7061947) and RO5507197 (M6), were also identified. CYP3A was shown to contribute 40% to 50% metabolism in human hepatocytes. Using recombinantly expressed human CYP isozymes, CYP3A4 was shown to be the major isozyme that mediated alectinib metabolism (estimated at least 80% by CYP3A in human liver microsomes); minor contributions were seen from multiple other CYP isoforms, namely, the CYP1A1, CYP2C8/9, CYP2B6, CYP2D6, CYP3A5, and CYP4A11. Likewise, CYP3A4 was shown to be the main enzyme mediating metabolism of M4. In addition, non-CYP enzymes are likely involved in metabolism of alectinib to produce M1b in hepatocytes.

An *in vivo* metabolism study in rats, following a single oral dose of [<sup>14</sup>C]-alectinib at 1 mg/kg, showed that the major drug-related material in plasma was alectinib (72.6% to 92.1%) in samples collected by 24 hours while eight minor metabolites were detected on the radiochromatograms.

The major human metabolite M4 was measured from single- and repeat-dose PK and toxicokinetic (TK) studies following oral administration of alectinib. The M4-to-parent (M/P) AUC ratios was found to be 3% to 5% in rats and approximately 24% in monkeys. Thus, in monkeys M4 is considered a major metabolite as well. The maximum exposure of M4 (AUC<sub>0-24</sub>) achieved in rats and monkeys was approximately 30% of that observed in humans at 600 mg BID (geometric mean area under plasma concentration–time curve over 24 hours at steady state [AUC<sub>ss,24h</sub>] = 5620 ng•h/mL).

Alectinib and M4 did not show reversible inhibition for CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 (all IC<sub>50</sub> values were > 10 μM), but showed a weak time-dependent inhibition against CYP3A4. Alectinib, but not M4, competitively inhibited CYP2C8 with an inhibition constant (K<sub>i</sub>) of 1.98 μM. In a cryopreserved human hepatocyte study, approximately up to 2-fold induction was observed at 1 μM of alectinib for CYP3A4, CYP1A2, and CYP2B6 (to a similar extent in enzyme activities and mRNA levels).

Alectinib is not a substrate of P-gp or BCRP, whereas M4 is a substrate of P-gp but not of

BCRP. Alectinib and M4 are inhibitors of P-gp ( $IC_{50} = 1.13$  and  $4.68 \mu\text{M}$ , respectively) and BCRP ( $IC_{50} = 0.103$  and  $2.64 \mu\text{M}$ , respectively). Alectinib does not inhibit OATP 1B1, OATP 1B3, OAT 1, OAT3, OCT 2, or MRP2 at clinical concentrations ( $IC_{50} > 3 \mu\text{M}$ ) but inhibits BSEP transporter ( $IC_{50} = 0.912 \mu\text{M}$ ). M4 did not show potent inhibition against MRP2 or BSEP ( $IC_{50} = 22$  and  $70 \mu\text{M}$ , respectively). Alectinib and M4 are not substrates of human hepatic uptake transporters OATP1B1 and OATP1B3 *in vitro*. Furthermore, the uptake of alectinib and M4 in human hepatocytes was not affected by the presence of broad transporter inhibitors *in vitro*.

### 2.2.2 Clinical Safety Summary of Alectinib

Alectinib has been well tolerated in clinical studies to date following multi-dose administration at doses of up to 760 mg BID in subjects with locally advanced or metastatic ALK-positive NSCLC.

The Phase I/II dose-escalation study of alectinib conducted only in Japan (Study AF001-JP), with a dose schedule of 20, 40, 80, 160, 240, and 300 mg orally twice daily (BID) showed that alectinib was generally well tolerated. No dose limiting toxicities (DLTs) were observed for any cohort in Part 1 of the AF-001JP study. Study NP28761/AF-002JG, ongoing in the U.S. and Canada, evaluated the pharmacokinetics, safety, and efficacy of alectinib in subjects with ALK-positive NSCLC who have progressed on previous treatment with crizotinib, with or without at least one line of chemotherapy. The starting dose in Study NP28761 was the highest dosage evaluated in Study AF-001JP, 300 mg BID.

Forty-seven subjects have been included in the phase 1 portion evaluating alectinib doses of 300, 460, 600, 760, and 900 mg BID. In Study NP28761/AF-002JG, no DLTs were observed in the dose-escalation cohorts, up to a dose of 900 mg BID. However, 2 subjects in the subsequent 900 mg BID bridging cohort experienced a DLT, one each of Grade 3 headache and Grade 3 neutrophil count decreased, and both subjects continued study treatment at reduced dose of 600 mg BID. On the basis of efficacy, safety, and PK data, the recommended Phase II dose (RP2D) is 600 mg BID. The phase 2 portion of study NP28761 and the global study, NP28673, established the benefit/risk of alectinib 600 mg BID in ALK-positive NSCLC subjects who have progressed on or are intolerant to crizotinib supporting an accelerated approval by the FDA on December 11, 2015.

### 2.2.3 Adverse Events

In pooled safety data from studies NP28761 and NP28673, almost all subjects (98.4%) reported at least one adverse event (AE). The majority of AEs were of Grade 1 or 2 in severity. Data is depicted in Table 1 below:

<b>Table 1: Summary of Adverse Events with Incidence of <math>\geq 10\%</math> Occurring in Alectinib Studies NP28761 and NP28673</b>	
<b>Adverse Event</b>	<b>N = 253 (%)</b>
Constipation	85 (33.6)
Fatigue	76 (30)
Peripheral Edema	66 (26.1)

<b>Table 1: Summary of Adverse Events with Incidence of <math>\geq 10\%</math> Occurring in Alectinib Studies NP28761 and NP28673</b>	
Myalgia	61 (24.1)
Cough	48 (19)
Nausea	46 (18.2)
Headache	42 (16.6)
Diarrhea	41 (16.2)
AST Increased	40 (15.8)
Dyspnea	40 (15.8)
Anemia	36 (14.2)
ALT Increased	35 (13.8)
Asthenia	32 (12.6)
Back Pain	31 (12.3)
Blood creatinine phosphokinase increased	31 (12.3)
Vomiting	31 (12.3)
Rash*	30 (11.9)
Weight Increased	27 (10.7)
<i>Data Cut-off: 27 April 2015</i>	

\*: Includes rash, maculopapular rash, acneiform dermatitis, erythema, generalized rash, papular rash, pruritic rash, and macular rash.

Grade  $\geq 3$  AEs were reported in 86 subjects (34%) among this same group, with the most commonly reported being increased blood creatinine phosphokinase (CPK) (3.6%), dyspnea (3.6%), increased alanine transaminase (ALT) (3.2%), and increased aspartate transaminase (AST) (2.8%).

AEs leading to discontinuation of treatment were reported in 15 subjects (5.9%). The most common AEs leading to treatment discontinuation were ALT increased (4 subjects [1.6%]) and AST increased (3 subjects [1.2%]). AEs requiring treatment interruption were reported in 68 subjects (26.9%). The most common AEs leading to treatment interruption were ALT increased (8 subjects [3.2%]) and blood bilirubin increased (7 subjects [2.8%]).

AEs leading to dose reduction were reported in 29 subjects (11.5%). The most common AEs leading to dose reduction were blood bilirubin increased (5 subjects [2.0%]), blood CPK increased (5 subjects [2.0%]), AST increased (4 subjects [1.6%]), and peripheral edema (3 subjects [1.2%]).

At least one AE related to treatment was reported for the majority of subjects (77.9%). Events reported in  $\geq 10\%$  of subjects were fatigue (17.8%), constipation (17.0%), myalgia (16.2%), AST increased (13.8%), ALT increased (13.0%), edema peripheral (12.6%), and blood CPK increased (11.1%).

#### 2.2.3.1 Serious Adverse Events and Deaths

Among studies NP28761 and NP28673, a total of 68 serious adverse events (SAEs) were reported in 49 of 253 subjects (19.4%). The only SAEs occurring in more than 1 subject were

dyspnea, pulmonary embolism, and hyperbilirubinemia (3 subjects [1.2%]) and influenza, hemoptysis, ALT increased, AST increased, and hemorrhage (2 subjects [0.8%]). Low rates were observed for SAEs leading to study drug withdrawal (3.6%) or study drug interruption or dose reduction (9.9%). Fourteen subjects (5.5%) experienced SAEs that were considered by the investigator to be related to study drug.

A total of 74 subjects had died as of the cut-off date (29%; 28% in NP28761 and 32% in NP28673). Of these, the majority (89.2%) died due to disease progression. Safety-related deaths occurred at a low incidence, with 2.8% (7 of 253) of subjects experiencing an AE with fatal outcome: hemorrhage (2 subjects) and dyspnea, pulmonary embolism, intestinal perforation, endocarditis and death of unknown cause (1 subject each). Two of these seven Grade 5 AEs (one of the two events of hemorrhage and the event of intestinal perforation) were considered by the investigator to be related to study drug.

There were no deaths during the AF-001JP study within 28 days of treatment discontinuation. In Study AF-001JP, 13/70 subjects experienced 15 SAEs: Grade 3 brain edema, Grade 3 radius fracture, Grade 3 tumor hemorrhage, Grade 2 cholangitis sclerosing, Grade 1 alveolitis allergic, Grade 3 maculopathy, Grade 2 metastases to meninges, lung infection (one Grade 2 and two Grade 3), Grade 3 neutrophil count decreased, Grade 1 electrocardiographic T-wave inversion, Grade 2 convulsion, Grade 3 pneumonia, and Grade 3 bacterial prostatitis. Eleven of 58 subjects (19.0%) who received treatment with 300 mg BID in Study AF-001JP experienced at least one SAE.

Overall, alectinib 600 mg BID was well-tolerated and had a manageable safety profile. An ongoing Phase III ALEX study is evaluating alectinib 600 mg BID against crizotinib in the first line setting.

#### 2.2.3.2 Hepatotoxicity

Hepatobiliary findings were observed in both the rat and monkey 4- and 13-week toxicity studies with alectinib, and findings in the 13-week studies were similar to those of the 4-week studies. The findings were at or close to clinically relevant exposures. Hepatobiliary effects included increased hepatic ALP, direct bilirubin, GGT and liver weight, vacuolation/degeneration/necrosis of bile duct epithelium, inflammatory cell infiltration in Glisson's sheath, enlargement/focal necrosis of hepatocytes, and enlargement of Kupffer cells. Abnormal hepatobiliary laboratory test values, such as increased ALT, AST, or bilirubin levels, have been observed after alectinib administration. AST, ALT, and total bilirubin levels temporarily increased in the initial stages of treatment and then improved. In subjects with Grade 3–4 AST/ALT elevations, documented drug-induced liver injury by liver biopsy was reported with uncommon frequency in alectinib pivotal clinical trials. Concurrent elevations in ALT or AST greater than or equal to three times the ULN and total bilirubin greater than or equal to two times the ULN, with normal alkaline phosphatase, occurred with uncommon frequency in subjects treated in alectinib clinical trials. In subjects treated with other tyrosine kinase ALK inhibitor drugs, abnormal liver function tests and drug-induced hepatotoxicity, including cases with fatal outcome, have been reported.

See **Section 6.2** for management and follow-up.

#### 2.2.3.3 Interstitial Lung Disease/Pneumonitis

TKIs, including ALK inhibitor crizotinib, have been associated with the occurrence of treatment-related ILD (including fatalities). Cases of ILD/pneumonitis have been reported in clinical trials with alectinib. See **Section 6.2** for management and follow-up.

#### 2.2.3.4 Severe Myalgia and CPK Elevations

Postmarketing experience with some TKIs includes reports of myopathy and rhabdomyolysis. Blood CPK increases, generally Grades 1 and 2, and muscular AEs have been reported with alectinib treatment. Grade 3 myalgia and CPK elevations have been reported with alectinib treatment and were reversible upon dose reduction and interruption. See **Section 6.2** for management and follow-up.

#### 2.2.3.5 Bradycardia

In the monkey telemetry study, there were no effects on the ECG, any of the other cardiovascular parameters or body temperature at doses up to 15 mg/kg (mean maximum concentration [ $C_{max}$ ]: 279 ng/mL). In a preliminary non-Good Laboratory Practice telemetry study in conscious cynomolgus monkeys, a slight hypotensive effect (approximately 10 mmHg) was seen when alectinib was administered at 20 and 60 mg/kg orally with no effects on ECG or heart rate. The hypotensive effect of alectinib observed in monkeys was considered to likely be caused by vasodilatation induced by L-type  $Ca^{2+}$  channel inhibition. Events of bradycardia have been reported with alectinib. Preliminary heart rate data (based on ECG and pulse measurements) from ongoing alectinib clinical trials show a decrease in heart rate during alectinib treatment, which is mainly asymptomatic. In subjects treated with other ALK inhibitors (crizotinib and ceritinib), bradycardia adverse events, as well as decreases in heart rate based on ECG and pulse measurements, have been reported (XALKORI® U.S. Package Insert; ZYKADIA™ U.S. Package Insert).

In case of bradycardia, concomitant medications must be evaluated to identify those that are known to cause bradycardia, as well as anti-hypertensive medications; and discontinuation or dose reduction of these concomitant medications must be considered. See **Section 6.2** for management and follow-up.

#### 2.2.3.6 Vision Disorders

In a rat quantitative whole body autoradiography study, tissue radioactivity disappeared over time, following a time course comparable to that of plasma radioactivity, with the exception of melanin-containing tissues such as the uveal tract of the eyes, which had a much higher and more sustained exposure in pigmented rats. This is consistent with what is commonly observed for lipophilic basic drugs.

Vision disorders, including diplopia, photopsia, blurred vision, visual impairment, and vitreous

floaters have been reported with several TKIs, including ALK inhibitors (crizotinib and ceritinib). Vision disorders, such as dry eye, blepharitis, conjunctivitis, blurred vision, and impaired vision have been reported with alectinib and were generally of Grades 1 and 2. See **Section 6.2** for management and follow-up.

#### 2.2.3.7 Anemia

Hematologic findings were observed in both the rat and monkey 4- and 13-week toxicity studies with alectinib, and findings in the 13-week studies were similar to those of the 4-week studies. Findings were at or close to clinically relevant exposures. Hematologic adverse effects such as anemia, thrombocytopenia, bleeding, and neutropenia have been observed with most TKIs, including ALK inhibitor crizotinib. Cases of anemia have been reported in subjects treated with alectinib; the majority of the events were Grade 1 or 2. See **Section 6.2** for management and follow-up.

#### 2.2.3.8 Gastrointestinal disorders

GI disorders such as nausea, vomiting, constipation, and diarrhea have been reported with alectinib. Similar GI disorders have been observed with other TKIs, including ALK inhibitor crizotinib. SLS (sodium lauryl sulfate, syn. sodium dodecyl sulfate) is a surfactant excipient in the clinical formulation at a concentration of 50% (w/w SLS to active pharmaceutical ingredient). This excipient is a known GI irritant and may be associated with GI AEs including nausea, vomiting, diarrhea, and abdominal pain. Of note, GI tract toxicity as the safety determinant of SLS is not because of systemic toxicity, but a consequence of local irritation to the GI tract. In general, when mixed with diet, higher levels of SLS, a known GI tract mucosal irritant, are tolerated versus gavage administrations. See **Section 6.2** for management and follow-up.

#### 2.2.3.9 Skin disorders

Results of an in vitro phototoxicity study indicated that alectinib may have phototoxic potential. Skin rash has been reported with majority of TKIs including those targeting the ALK receptor. Cases of skin rash and photosensitivity have been reported with alectinib and were generally Grade 1 or 2. See **Section 6.2** for management and follow-up.

#### 2.2.3.10 Edema

Most TKIs, including ALK inhibitor crizotinib, have been associated with edema. Events of edema have been reported with alectinib, mostly Grade 1 or 2. See **Section 6.2** for management and follow-up.

#### 2.2.3.11 Abnormal renal function

In the 2-week non-human primate study at 60 mg/kg, an increase in creatinine was observed but no changes were observed in histopathology. In all other non-human primate studies, no changes in creatinine were observed. Serum creatinine increases have been reported with alectinib

treatment and were generally Grades 1 and 2. See **Section 6.2** for management and follow-up.

#### 2.2.4 Clinical Efficacy Summary of Alectinib

Clinical data from the Phase 2 portion of the ongoing Study AF-001JP (crizotinib-naïve ALK-positive NSCLC subjects) demonstrated an overall response rate (ORR) of 93.5% (95% CI: 82.1–98.6), and 9 subjects had a complete response (CR) based on independent radiological review (data cut-off for response data 31 January 2014). The median duration of treatment (DOT) in the study has not been achieved, as 86% of subjects are still active on the study, but the projected median DOT is estimated to be at least 14 months as data mature.

Study NP28671 has met its primary objective of demonstrating a clinically meaningful and statistically significant ORR based on independent review committee (IRC) assessments (52.2%; 95% CI: 39.7%, 64.6%) in subjects with ALK-positive advanced NSCLC whose disease had progressed on crizotinib treatment. The result of the secondary endpoint, investigator-assessed ORR (50.6%; 95% CI: 39.6%, 61.5%), was consistent with the primary endpoint. The key CNS secondary endpoint of CORR showed clinically meaningful activity in subjects with measurable CNS lesions at baseline according to RECIST v1.1 criteria (75.0%; 95% CI: 47.6%, 92.7%).

Study NP28673 also met its main objective of demonstrating a clinically meaningful and statistically significant ORR based on IRC assessments (50.8%; 95% CI: 41.6%, 60.0%) in subjects with ALK-positive advanced NSCLC whose disease had progressed on crizotinib treatment. The co-primary objective of IRC-assessed ORR in the subgroup of chemotherapy pretreated subjects, although not statistically significant, was clinically meaningful (44.8%; 95% CI: 34.6%, 55.3%). Due to the hierarchical order of testing, the overall study is considered positive since the first co-primary endpoint met statistical significance. The result of the secondary endpoint, investigator-assessed ORR (50.7%; 95% CI: 42.1%, 59.3%), was supportive of the primary endpoints. The CNS endpoint, CORR, showed clinically meaningful activity in subjects with measurable CNS lesions at baseline according to RECIST v1.1 (58.8%; 95% CI: 40.7%, 75.4%).

**Table 2: Overview of Efficacy Results from Studies NP28761 and NP28673  
 (as of 27 April 2015)**

	<b>Alectinib 600 mg BID</b>	
	<b>NP28761 Phase II</b>	<b>NP28673 Phase II</b>
<b>Primary Efficacy Parameters</b>		
ORR (IRC) in RE population	n=67 <sup>a</sup>	N=122 <sup>a</sup>
Responders, n (%)	35 (52.2)	62 (50.8)
[95% CI <sup>b</sup> ]	[39.7, 64.6]	[41.6, 60.0]
ORR (IRC) in subjects pre-treated with chemotherapy <sup>c</sup>	N=52	N=96
Responders, n (%)	30 (57.7)	43 (44.8)
[95% CI <sup>b</sup> ]	[43.2, 71.3]	[34.6, 55.3]



	<b>Alectinib 600 mg BID</b>	
	<b>NP28761 Phase II</b>	<b>NP28673 Phase II</b>
<b>Secondary Efficacy Parameters</b>		
ORR (investigator) in RE population	N=87	N=138
Responders, n (%)	44 (50.6)	70 (50.7)
[95% CI <sup>b</sup> ]	[39.6, 61.5]	[42.1, 59.3]
ORR (investigator) in subjects pre-treated with chemotherapy	N=64	N=110
Responders, n (%)	33 (51.6)	54 (49.1)
[95% CI <sup>b</sup> ]	[38.7, 64.3]	[39.4, 58.8]
<b>Exploratory Efficacy Parameters</b>		
DCR (IRC) in RE population	N=67 <sup>a</sup>	N=122 <sup>a</sup>
CR + PR + SD, n (%)	43 (64.2) <sup>d</sup>	78 (63.9) <sup>e</sup>
[95% CI <sup>b</sup> ]	[51.5, 75.5]	[54.8, 72.4]
DCR (investigator) in RE population	N=87	N=138
CR + PR + SD, n (%)	41 (61.2) <sup>d</sup>	95 (68.8) <sup>e</sup>
[95% CI <sup>b</sup> ]	[48.5, 72.9]	[60.4, 76.5]
DOR (IRC) in RE population	N=67	N=122
Median time to event, months	13.5	14.1
[95% CI <sup>f</sup> ]	[6.7, NE]	[10.9, NE]
DOR (investigator) in RE population	N=87	N=138
Median time to event, months	11.1	11.2
[95% CI <sup>f</sup> ]	[8.8, NE]	[9.6, NE]
PFS (IRC) in safety population	N=87	N=138
Median time to event, months	8.1	8.9
[95% CI <sup>f</sup> ]	[6.2, 12.6]	[5.6, 12.8]
PFS (investigator) in safety population	N=87	N=138
Median time to event, months	8.4	9.3
[95% CI <sup>f</sup> ]	[5.5, 12.3]	[7.4, 12.8]

BID = twice daily; CI = confidence interval; CR = complete response; DCR = disease control rate; DOR = duration of response; IRC = independent review committee; NE = not estimated; ORR = objective response rate; PFS = progression-free survival; PR = partial response; RE = response-evaluable; SD = stable disease.

- a. There were 20 subjects (NP28761) and 16 subjects (NP28673) who did not have measurable disease at baseline according to the IRC and therefore were not included in the IRC RE population.
- b. 95% CI for rates were constructed using Clopper-Pearson method.
- c. Primary efficacy parameter only in Study NP28673.
- d. DCR is defined as the percentage of subjects with a BOR of CR, PR, or SD lasting for at least 12 weeks after the first dose of alectinib.
- e. DCR is defined as the percentage of subjects with a BOR of CR, PR, or SD lasting for at least 16 weeks.
- f. 95% CI for median was computed using the method of Brookmeyer and Crowley.

### 2.2.5 Clinical Pharmacokinetics

The pharmacokinetics of alectinib and its major active metabolite M4 have been characterized in

subjects with ALK-positive NSCLC and healthy subjects. In subjects with ALK-positive NSCLC, the geometric mean (coefficient of variation %) steady-state maximal concentration ( $C_{\max,ss}$ ) for alectinib was 665 ng/mL (44%) and for M4 was 246 ng/mL (45%) with peak to trough concentration ratio of 1.2. The geometric mean steady-state area under the curve from 0 to 12 hours ( $AUC_{0-12h,ss}$ ) for alectinib was 7,430 ng•h/mL (46%) and for M4 was 2,810 ng•h/mL (46%). Alectinib exposure is dose proportional across the dose range of 300 mg to 900 mg under fed conditions. Alectinib and M4 reached steady-state concentrations by day 7. The geometric mean accumulation was approximately 6-fold for both alectinib and M4.

### 2.2.6 Rationale for Proposed Dose Levels

Given the *in vitro* kinase activity for alectinib against RET appears to be less potent than that reported against ALK, higher doses of alectinib will be evaluated to maximize potential for alectinib efficacy in RET mutated tumors. To accomplish this and to characterize whether higher doses of alectinib are both safe and able to achieve higher plasma concentrations, plasma PK samples will be collected during the dose escalation phase 1 portion of this study for assessment of alectinib pharmacokinetics.

### 2.2.7 Clinical Absorption

Alectinib reached maximal concentrations at approximately 4-6 hours following the administration of 600 mg twice daily under fed conditions in subjects with ALK-positive NSCLC.

The absolute bioavailability of alectinib was 37% (90% CI: 34%, 40%) under fed conditions.

A high-fat, high-calorie meal increased the combined exposure ( $AUC_{0-inf}$ ) of alectinib plus its major active metabolite M4 by 3.1-fold (90% CI: 2.7, 3.6) after oral administration of a single 600 mg dose.

### 2.2.8 Clinical Distribution

The apparent volume of distribution is 4,016 L for alectinib and 10,093 L for M4. Greater than 99% of alectinib and M4 are bound to human plasma proteins, independent of drug concentration.

Alectinib concentrations in the cerebrospinal fluid in subjects with ALK-positive NSCLC approximate estimated alectinib free concentrations in the plasma.

### 2.2.9 Clinical Elimination

Alectinib is metabolized by CYP3A4 to its major active metabolite M4. The geometric mean metabolite/parent exposure ratio at steady-state is 0.4. M4 is subsequently metabolized by CYP3A4. Alectinib and M4 were the main circulating moieties in plasma, constituting 76% of the total radioactivity.

The apparent clearance (CL/F) is 81.9 L/hour for alectinib and 217 L/hour for M4. The

geometric mean elimination half-life is 33 hours for alectinib and 31 hours for M4 in subjects with ALK-positive NSCLC.

Following oral administration under fed conditions of a single radiolabeled dose of alectinib, 98% percent of the radioactivity was excreted in feces. The majority (84%) of the dose was excreted in the feces as unchanged alectinib and 6% of the dose was excreted as M4. Excretion of radioactivity in urine was less than 0.5% of administered radiolabeled dose of alectinib.

#### 2.2.10 Drug-Drug Interaction Studies

Based on *in vitro* data, CYP3A4 is the primary enzyme mediating the metabolism of both alectinib and its major active metabolite M4, and CYP3A contributes to 40% to 50% of total hepatic metabolism. M4 has shown similar *in vitro* potency and activity to alectinib against ALK.

Co-administration of multiple oral doses of 600 mg rifampicin once daily, a strong CYP3A inducer, with a single oral dose of 600 mg alectinib exhibited a minor effect on combined exposure of alectinib and M4 (GMR with/without rifampicin [90% CI]:  $C_{max}$ : 0.96 [0.88 – 1.05],  $AUC_{inf}$ : 0.82 [0.74 – 0.90]). Co-administration of multiple oral doses of 400 mg posaconazole BID, a strong CYP3A inhibitor, with a single oral dose of 300 mg alectinib had a minor effect on combined exposure of alectinib and M4 (GMR with/without posaconazole [90% CI]:  $C_{max}$ : 0.93 [0.81 – 1.08],  $AUC_{inf}$ : 1.36 [1.24 – 1.49]). However, given an objective of this study is to characterize the PK of alectinib, use of CYP3A inhibitors and inducers will be prohibited during the phase 1 portion of the trial due to the potential for confounding effects.

Although the aqueous solubility of alectinib *in vitro* is pH-dependent, a dedicated clinical drug-drug interaction (DDI) study with 40 mg esomeprazole once daily, a proton-pump inhibitor (PPI), demonstrated no clinically relevant effect on the combined exposure of alectinib and M4. Therefore, no dose adjustments are required when alectinib is co-administered with PPIs or other drugs which raise gastric pH (e.g., H<sub>2</sub> receptor antagonists or antacids).

Based on *in vitro* data, alectinib is not a substrate of P-glycoprotein (P-gp). Alectinib and M4 are not substrates of breast cancer resistance protein (BCRP) or organic anion-transporting polypeptide (OATP) 1B1/B3. In contrast, M4 is a substrate of P-gp. Alectinib inhibits P-gp, and therefore, it is not expected that co-medication with P-gp inhibitors will have a relevant effect on M4 exposure.

#### 2.2.11 Post-Marketing Use

Alecensa (alectinib, 300 mg BID in Japan and 600 mg BID in the United States) is approved in Japan and the United States for ALK-fusion gene-positive, unresectable, recurrent/advanced NSCLC. As of 3 January 2015, no regulatory actions were undertaken for safety reasons by the regulatory authorities or the Marketing Authorization Holder in Japan (Chugai Pharmaceuticals Co Ltd for alectinib 300 mg BID). A review of the available post-marketing data did not reveal any new, pertinent safety information for alectinib.

## 2.3 Rationale

In preclinical models of RET-rearranged NSCLC, alectinib has recently been shown to be a potent RET inhibitor. In a kinase inhibitory assay, alectinib inhibited RET kinase activity with an  $IC_{50}$  of 4.8 nM, and in an ATP-competitive binding assay, alectinib bound to RET at a dissociation constant ( $K_D$ ) value of 7.6 nM. Alectinib inhibited growth of the LC-2/ad NSCLC cell line which harbors a *CCDC6-RET* rearrangement, and also inhibited growth of Ba/F3 cells expressing KIF5B-RET. *In vivo*, alectinib also showed potent antitumor activity in a mouse xenograft model of LC-2/ad cells as well as in a mouse KIF5B-RET Ba/F3 model. Furthermore, alectinib maintained potent activity against the RET gatekeeper mutations V804L and V804M.<sup>20</sup>

## 2.4 Correlative Studies Background

### 2.4.1 Plasma genotyping

Genomic analysis of nucleic acid extracted from tumor tissue biopsies has been the main method for determining oncogenic mutations in NSCLC as well as for identifying mechanisms of resistance to kinase inhibitors. More recently, however, improved techniques for isolating cell-free DNA (cfDNA) from plasma have been successfully developed for identifying both fusion transcripts and resistance mutations in NSCLC subjects.<sup>22,23</sup>

In this study baseline, on-treatment, and off study plasma will be collected from each subject and cfDNA sequencing will be performed by the Translational Research Laboratory at the Belfer Center for Applied Cancer Science at the Dana-Farber Cancer Institute (DFCI).

A baseline plasma sample will also be collected from all subjects for RET assay development. The sample will be analyzed at a partner laboratory to detect known as well as currently unknown RET fusions. This assay will use cfRNA isolated from the plasma sample.

### 2.4.2 Next Generation Sequencing

NSCLCs harboring somatic mutations in kinases are often sensitive to small molecule kinase inhibitors. For example, crizotinib, an ALK/ROS1/MET inhibitor is approved for use in NSCLC and has antitumor activity in NSCLCs with genomic alterations in ALK, ROS1, and MET. Unfortunately, the efficacy of these kinase inhibitors has been limited by the invariable development of acquired drug resistance. The identification of resistance mechanisms has been instrumental in the development of strategies aimed at preventing or overcoming resistance<sup>25</sup>. In the case of ALK-rearranged NSCLC, a greater understanding of the various mechanisms of resistance to crizotinib has led to the approval of several next generation ALK inhibitors that are able to overcome resistance<sup>26</sup>.

For subjects who have been treated with a previous RET TKI, a mandatory baseline biopsy will be obtained in order to determine mechanisms of resistance to these agents, including the development of alternate kinase domain mutations or bypass signaling tract activation. These results will be correlated to clinical outcome to investigate whether alectinib is able to overcome certain resistance mechanisms. Similarly, an optional biopsy will be offered to all subjects at the

time of disease progression to further explore mechanisms of resistance. These samples will be submitted for targeted next generation sequencing (NGS) to determine resistance mechanisms.<sup>24</sup> The NGS will be performed at the Brigham and Women's Hospital Center for Advanced Molecular Diagnostics.

Archival tissue will be collected from all subjects enrolling to the trial as described in **Section 9**. The archival tissue will be used to retrospectively verify baseline mutational status.

### 3. SUBJECT SELECTION

Baseline evaluations are to be conducted within two weeks prior to start of protocol therapy, with the exception of the informed consent, baseline tumor imaging, and brain MRI which may be obtained up to 28 days prior to the start of protocol therapy.

#### 3.1 Eligibility Criteria

##### 3.1.1 Tumor Types:

**Phase 1:** Subjects must have a histologically or cytologically confirmed diagnosis of locally advanced (AJCC Stage IIIB) not amenable to curative therapy or metastatic (AJCC Stage IV) NSCLC that carries a RET rearrangement, as determined by fluorescence in situ hybridization (FISH), reverse transcription polymerase chain reaction (RT-PCR), or next generation sequencing (NGS) via a CLIA-certified local diagnostic test (LDT).

**-OR-**

**Phase 1:** Subjects must have a histologically or cytologically confirmed diagnosis of metastatic (AJCC Stage IV) NSCLC that carries an ALK rearrangement with CNS metastases, as determined by FISH, RT-PCR, immunohistochemistry (IHC), or NGS via a CLIA-certified LDT.

**Phase 2 Cohorts A&B:** Subjects must have a histologically or cytologically confirmed diagnosis of locally advanced (AJCC Stage IIIB) not amenable to curative therapy or metastatic (AJCC Stage IV) NSCLC that carries a RET rearrangement, as determined by FISH, RT-PCR, or NGS via a CLIA-certified LDT.

**Phase 2 Cohort C (thyroid cancer):** Subjects must have a histologically or cytologically confirmed diagnosis of metastatic thyroid cancer (Stage IV) that carries either a RET rearrangement or activating RET mutation, as determined by FISH, RT-PCR, or NGS via a CLIA-certified LDT.

3.1.2 Disease Status Requirements:

**Phase 1:** Subjects with a RET rearrangement must have had disease progression after at least one prior line of systemic therapy. Subjects with an ALK rearrangement may be either treatment naïve or may have received prior treatment, and must have CNS disease present at baseline. Subjects cannot have received more than one prior RET TKI (such as, but not limited to, vandetanib, sorafenib, sunitinib, ponatinib, or cabozantinib). Subjects enrolling to the Phase 1 portion of the trial must not have received prior alectinib therapy.

**Phase 2:**

- **Cohort A:** RET-positive NSCLC subjects must have received at least one prior line of therapy, but must be RET TKI-naïve.
- **Cohort B:** RET-positive NSCLC that has previously been treated with one RET TKI. Subjects cannot have received more than one prior RET TKI and must not have received prior alectinib.
- **Cohort C:** RET-positive thyroid cancer, must be radioactive iodine refractory.

3.1.3 Subjects must have at least one measurable target lesion according to RECIST v1.1. See **Section 11** for the evaluation of measurable disease.

3.1.4 Subjects enrolling to the phase 1 portion of the trial who have received a prior RET TKI must be able and willing to undergo a pre-treatment fresh tumor biopsy.

3.1.5 Subjects enrolling to Cohort B or C of the phase 2 portion of the trial who have received a prior RET TKI must be able and willing to undergo a pre-treatment fresh tumor biopsy.

3.1.6 All subjects must have archival tissue confirmed as available for enrollment. Subjects who are TKI naïve who do not have archival tissue may undergo a fresh tumor biopsy in lieu of the archival tissue requirement. The archival tissue requirement may be waived for subjects after discussion with the principal investigator.

3.1.7 Age  $\geq$  18 years.

3.1.8 ECOG performance status  $\leq$  2 (See **APPENDIX A**)

3.1.9 Subjects must have normal organ and marrow function as defined below:

Adequate hematologic function

- Absolute neutrophil count  $\geq$  1,500/mcL
- Platelets  $\geq$  100,000/mcL
- Hemoglobin  $\geq$  9.0 g/dL

Adequate renal function

- Serum creatinine  $\leq$  1.5 x institutional ULN

**-OR-**

- Estimated glomerular filtration rate (eGFR)  $\geq$  45 mL/min/1.73 m<sup>2</sup> as calculated using the Modification of Diet Renal Disease Equation (See

## APPENDIX B)

- 3.1.10 Subjects must have recovered from treatment toxicities to  $\leq$  Grade 1 or to their pretreatment levels. Subjects who have developed interstitial lung disease (ILD) must have fully recovered.
- 3.1.11 For all females of childbearing potential, a negative serum pregnancy test must be obtained within 3 days prior to starting study treatment.
- 3.1.12 For women who are not postmenopausal ( $\geq 12$  months of non-therapy-induced amenorrhea) or surgically sterile (absence of ovaries and/or uterus): agreement to remain abstinent or use single or combined contraceptive methods that result in a failure rate of  $< 1\%$  per year during the treatment period and for at least 3 months after the last dose of study drug. Abstinence is only acceptable if it is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal or postovulation methods) and withdrawal are not acceptable methods of contraception. Examples of contraceptive methods with a failure rate of  $< 1\%$  per year include tubal ligation, male sterilization, hormonal implants, established, proper use of combined oral or injected hormonal contraceptives, and certain intrauterine devices.
- 3.1.13 For men: agreement to remain abstinent or use a contraceptive method that results in a failure rate of  $< 1\%$  per year during the treatment period and for at least 3 months after the last dose of study drug. Abstinence is only acceptable if it is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal or postovulation methods) and withdrawal are not acceptable methods of contraception.

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

### 3.2 Exclusion Criteria

- 3.2.1 Cytotoxic chemotherapy or immunotherapy within 3 weeks of study entry.
- 3.2.2 Oral targeted therapy within 5 half-lives (if known) or 3 weeks (if half-life is unknown) of study entry.
- 3.2.3 **Phase 1:** Subjects who have received prior alectinib therapy.
- 3.2.4 For enrollment to the phase 1 portion of the trial: Administration of any cytochrome P450 (CYP)3A inhibitors or inducers within 14 days prior to the first dose of alectinib and from Cycle 1 Day 1 – Cycle 2 Day 8 of the phase 1 portion of the trial. Following completion of this period, strong/potent cytochrome P450 (CYP)3A inhibitors or inducers are prohibited while on study. Please see **APPENDIX C**.

- 3.2.5 Radiation therapy (except palliative to relieve bone pain) within 2 weeks of study entry. Palliative radiation ( $\leq 10$  fractions) must have been completed at least 48 hours prior to study entry. Stereotactic or small field brain irradiation must have completed at least 2 weeks prior to study entry. Whole brain radiation must have completed at least 4 weeks prior to study entry.
- 3.2.6 Major surgery within 4 weeks of study entry. Minor surgical procedures (e.g., port insertion) are not excluded, but sufficient time should have passed for wound healing (as determined by the treating investigator).
- 3.2.7 Subjects who are receiving any other investigational agents.
- 3.2.8 Liver disease characterized by:
- ALT or AST  $> 3 \times$  institutional ULN ( $\geq 5 \times$  ULN for subjects with concurrent liver metastasis) confirmed on two consecutive measurements
  - OR-
  - Absolute impaired excretory function (e.g., hyperbilirubinemia) or synthetic function or other conditions of decompensated liver disease such as coagulopathy, hepatic encephalopathy, hypoalbuminemia, ascites, and bleeding from esophageal varices
  - OR-
  - Impaired excretory function (e.g., hyperbilirubinemia) or synthetic function or other conditions of decompensated liver disease such as coagulopathy, hepatic encephalopathy, hypoalbuminemia, ascites, and bleeding from esophageal varices
  - OR-
  - Acute viral or active autoimmune, alcoholic, or other types of acute hepatitis
- 3.2.9 Subjects with symptomatic CNS metastases who are neurologically unstable and/or require an increased dose of steroid to manage CNS symptoms within 1 week prior to the first day of treatment are excluded.
- Subjects with brain or leptomeningeal metastases that do not meet the above criteria are allowed.
  - Symptomatic disease is allowed as long as symptoms are controlled and stable.
- 3.2.10 History of hypersensitivity to any of the additives in the alectinib drug formulation.
- 3.2.11 Subjects with symptomatic bradycardia.
- 3.2.12 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.



- 3.2.13 Pregnant or breastfeeding women.
- 3.2.14 Any GI disorder that may affect absorption of oral medications in the opinion of the treating investigator, such as malabsorption syndrome or major bowel or stomach resection.
- 3.2.15 Subjects who are unable to swallow pills.
- 3.2.16 Subjects with a history of a second primary malignancy. Exceptions include: subjects with a history of malignancies that were treated curatively and have not recurred within 3 years prior to study entry; resected basal and squamous cell carcinomas of the skin, and completely resected carcinoma *in situ* of any type.
- 3.2.17 NCI-CTCAE v4.03 Grade 3 or higher toxicities due to any prior therapy (excluding alopecia), which have not shown improvement and are strictly considered to interfere with current study medication.
- 3.2.18 Known HIV positivity or AIDS-related illness.

### **3.3 Inclusion of Women and Minorities**

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

## **4. REGISTRATION PROCEDURES**

### **4.1 General Guidelines for DF/HCC Institutions**

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

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

Following registration, subjects may begin protocol therapy. Issues that would cause treatment delays should be discussed with the Overall Principal Investigator (PI). If a subject does not receive protocol therapy following registration, the subject's registration on the study must be canceled. Registration cancellations must be made in OnCore as soon as possible.

### **4.2 Registration Process for DF/HCC Institutions**

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

### 4.3 General Guidelines for Other Investigative Sites

Eligible subjects will be entered on study centrally at the Dana-Farber Cancer Institute by the Study Coordinator. All sites should call the Study Coordinator to verify dose level availabilities.

Following registration, subjects should begin protocol therapy within 5 days. Issues that would cause treatment delays should be discussed with the Overall PI. If a subject does not receive protocol therapy following registration, the subject's registration on the study must be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

### 4.4 Registration Process for Other Investigative Sites

To register a subject, the following documents should be completed by the research nurse or data manager and faxed or e-mailed to the Study Coordinator:

- Copy of the clinic visit note documenting the subject's history and physical exam
- Copies of the required clinical laboratory tests including: CBC with differential, serum chemistries, CPK, liver function tests, urinalysis, and if applicable serum  $\beta$ -hCG
- Copies of the pathology report(s) and documentation of RET or ALK mutational status
- Baseline tumor imaging assessment reports
- Screening ECG report
- Signed subject consent form
- HIPAA authorization form
- Completed ODQ eligibility checklist

The research nurse or data manager at the participating site will then call or e-mail the Study Coordinator to verify eligibility. To complete the registration process, the Coordinator will follow DF/HCC Standard Operating Procedure for Human Subject Research Titled *Subject Protocol Registration* (SOP #: REGIST-101) and register the subject on the protocol. The coordinator will fax or e-mail the subject study number, and if applicable the dose treatment level, to the participating site. The coordinator will also call the research nurse or data manager at the participating site and verbally confirm registration.

**NOTE:** Registration can only be conducted during regular business hours (between 8 am and 5 pm Eastern Standard Time Monday through Friday, holidays excluded). Same day treatment registrations will only be accepted with prior notice and discussion with the DF/HCC Study Coordinator.

## 5. TREATMENT PLAN

### 5.1 Treatment Regimen

Treatment will be administered on an outpatient basis. Collection and reporting of adverse events and potential risks are described in **Section 7**. Appropriate dose modifications are described in **Section 6**. No investigational or commercial agents or therapies other than those

described below may be administered with the intent to treat the subject's malignancy. Bisphosphonate use is permitted. Palliative radiation to non-target lesions may be allowed on a case-by-case basis following discussion with the principal investigator. Radiation treatment may begin 24 hours after the last dose of alectinib. Subjects should hold alectinib dosing for the duration of the radiation treatment, and may resume alectinib dosing when radiation toxicity has returned to  $\leq$  Grade 1 or baseline.

**Phase 1:** A 7-day lead-in dosing period will be administered at the start of each dose level as depicted in **Table 3**. Each treatment cycle will be defined as 28 consecutive days.

**Phase 2:** Each treatment cycle will be defined as 28 consecutive days.

<b>Table 3: Dose Escalation Schedule</b>	
<b>Dose Level</b>	<b>Dose of Alectinib</b>
Level -1	Lead-in dose of 600 mg PO BID for 7 days at the start of Cycle 1, then escalate to 750 mg PO BID for all subsequent days and cycles
Level 1: Starting Dose	Lead-in dose of 600 mg PO BID for 7 days at the start of Cycle 1, then escalate to 900 mg PO BID for all subsequent days and cycles
Level 2	Lead-in dose of 900 mg PO BID for 7 days at the start of Cycle 1, then escalate to 1200 mg PO BID for all subsequent days and cycles

Six subjects will be enrolled to dose level 1. For safety reasons, enrollment to the dose level will be staggered. A maximum of two participants will be allowed to enroll simultaneously. Upon successful completion of the dose-limiting toxicity (DLT) assessment period, two additional participants will be allowed to enroll. Cohort enrollment will continue in this fashion until all six participants are enrolled. At no point in time will more than two participants in a cohort be in the DLT assessment window. If at any point two or more DLTs are observed, dose escalation will be stopped. Please see description in **Table 4** below.

Subjects enrolled to the dose escalation will be observed from Cycle 1 Day 8 – Cycle 2 Day 8 for toxicity consistent with a DLT definition, located in **Section 5.4**. This DLT window allows for a full 28 day safety assessment period for participants at the escalated alectinib dose.

Dose escalation will proceed as described in **Table 4** below:

<b>Table 4: Dose Escalation Scheme</b>	
<b>Number of Subjects with DLT at a Given Dose Level</b>	<b>Escalation Decision Rule</b>
$\leq 1$ out of 6	Enter 6 subjects at the next dose level.
$\geq 2$ out of 6	Dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered).
$\leq 1$ out of 6 at highest dose level below the maximally administered dose	This is the recommended phase 2 dose.

The maximally administered dose (MAD) of the study medication will be defined as the dose level where at least two subjects develop toxicities consistent with a DLT definition. In this situation, the dose level immediately below the MAD will be defined as the MTD. In the event that dose level 1 is found to be intolerable (with  $\geq 2$  subjects experiencing a DLT), the fallback dose level -1 will be explored. If the fallback dose level is also found to be intolerable, the phase 1 trial will be discontinued and the phase 2 trial will commence at the FDA approved dose level of 600 mg by mouth twice daily. In the situation where none of the dose levels have  $\geq 2$  DLTs, the MTD will be the highest dose administered (i.e. dose level 2). The MTD will be defined in a minimum of six subjects.

Upon determination of the MTD, the Overall Principal Investigator in conjunction with the Site Investigators and in communication with Genentech/Roche will declare the RP2D. The RP2D will be decided based on the MTD, supportive PK data, and taking into consideration cumulative safety data that includes not only observed DLTs but also DLT-equivalent toxicity occurring beyond the DLT assessment window. Therefore, the RP2D may or may not be equivalent to the MTD determined in the dose escalation, but will not be higher than the MTD.

Once the RP2D has been defined, the phase 2 portion of the trial will begin. Subjects enrolling into the phase 2 portion of the trial will be treated at the RP2D identified during the phase 1 portion of the study. The safety of the RP2D will continue to be evaluated during the phase 2 portion of the trial and adverse event data will continue to be collected.

Subjects enrolled to the phase 1 dose escalation portion of the trial will be required to have received at least 75 percent of their doses of alectinib during the DLT assessment window to be considered evaluable for DLT purposes. Subjects who do not meet these parameters for reasons other than toxicity (for example, withdrawal of consent for participation on the trial, or rapid disease progression and subsequent removal from the trial) will be replaced.

All subjects will be requested to maintain a study medication diary that will indicate each dose of oral medication taken to illustrate treatment compliance. The medication diary should be returned to appropriate research staff for review at the end of each treatment cycle.

## 5.2 Pre-Treatment Criteria

### 5.2.1 Cycle 1, Day 1

If screening laboratory values were completed  $\leq 72$  hours before Cycle 1 Day 1, laboratory tests do not need to be repeated on Cycle 1 Day 1 and the screening laboratory values may be used as the Cycle 1 Day 1 values.

If screening laboratory values were completed  $> 72$  hours prior to Cycle 1 Day 1, laboratory tests must be repeated on Cycle 1 Day 1. Laboratory values on Cycle 1 Day 1 must re-meet eligibility criteria, exceptions to this are possible following discussion with the Site Investigator.

### 5.2.2 Subsequent Cycles

For subsequent cycles, management of specific toxicities considered at least possibly related to the study regimen is outlined in **Section 6**.

## 5.3 Agent Administration

### 5.3.1 Alectinib

**Administration:** Alectinib is administered orally twice daily, approximately every 12 hours. A missed dose may be taken up to 6 hours after the scheduled dosing time. Doses that would be outside of this window should be considered missed and should not be taken. Subjects should be instructed not to double dose. A vomited dose should not be retaken; instead subjects should be advised to continue with the next regularly scheduled dose as clinically appropriate.

Alectinib should be taken with food. Alectinib capsules should be swallowed whole; they should not be opened, chewed, or crushed. Subjects should be instructed to wash their hands after handling the capsules and to keep their study medication supply out of the reach of children and animals. The alectinib supply should not be stored above 77° F.

## 5.4 Definition of Dose-Limiting Toxicity (DLT)

Severity of all adverse events will be graded according to NCI CTCAE version 4.03. For the purpose of dose escalation, any of the following adverse events occurring between Cycle 1 Day 8 – Cycle 2 Day 8 that are at least possibly attributable to alectinib as judged by the principal investigator will be considered DLTs.

### **Hematologic:**

- Grade 4 neutropenia lasting  $>7$  days, or necessitating the use of Granulocyte Colony Stimulating Factors (G-CSF) during cycle 1
- Febrile neutropenia, defined as ANC  $<1000/\text{mm}^3$  with a single temperature of  $\geq 38.3^\circ\text{C}$  ( $\geq 101^\circ\text{F}$ ) or a sustained temperature of  $\geq 38^\circ\text{C}$  ( $\geq 100.4^\circ\text{F}$ ) for  $>1$  hour.

- Grade  $\geq 3$  neutropenic infection.
- Grade  $\geq 3$  thrombocytopenia with clinically significant bleeding.
- Grade 4 thrombocytopenia.

**Non-Hematologic:**

- Symptomatic Grade  $\geq 3$  QTcB prolongation (QTc  $\geq 501$  msec on at least two separate ECGs), or asymptomatic Grade  $\geq 3$  QTcB prolongation that has been confirmed by repeat testing and re-evaluation by a qualified person, and persists after correction of reversible causes such as electrolyte abnormalities or hypoxia.
- Other non-hematologic  $\geq$  Grade 3 toxicity. Exceptions will be made for:
  - Grade  $\geq 3$  nausea, vomiting, diarrhea, or constipation that recovers to  $\leq$  Grade 2 following appropriate medical management (e.g. anti-emetics, antidiarrheals, laxatives).
  - Transient (lasting  $\leq 2$  days) Grade  $\geq 3$  electrolyte abnormalities without clinical sequelae and that resolve with repletion, or that are deemed by the treating investigator as not clinically significant.
  - Grade 3 AST/ALT increases that persist for  $\leq 7$  days and are not accompanied by other signs of hepatic injury.
  - Asymptomatic Grade 3 AST/ALT increases in subjects with Grade 2 elevations at baseline.

**Other:**

- Failure to deliver at least 21 out of the 28 prescribed daily total doses (approximately 75% of the planned doses for the 28 day period) due to toxicities at least possibly attributable to the study drug.
- Failure to restart dosing within 7 days after the completion of the DLT assessment window due to toxicities at least possibly attributable to the study drug.

Management and dose modifications are outlined in **Section 6**.

## **5.5 General Concomitant Medication and Supportive Care Guidelines**

Investigators should use appropriate supportive medications to address toxicities that arise during the study, including but not limited to antiemetics, antidiarrheals, and blood product transfusion. Use of G-CSF is not permitted during the DLT assessment window except in cases of medical emergency as judged by the treating investigator. Use of all concomitant medications should be recorded in the Concomitant Medications CRF and reported to the treating investigator.

Alectinib is metabolized by CYP3A4 to its major active metabolite M4. While according to the FDA label for Alecensa® (alectinib), no pharmacokinetic interactions with alectinib requiring dosage adjustment have been identified, potent CYP3A inhibitors or inducers may alter the PK of alectinib and its major active metabolite, M4. Given an objective of the phase 1 portion of the study is to characterize the PK of alectinib, the following therapies (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) are prohibited

during the phase 1 portion of the study and for at least 14 days prior to initiation of alectinib, unless otherwise specified below (see also **APPENDIX C**):

- For Cycle 1 Day 1 – Cycle 2 Day 8 of Phase 1 portion: Use of any inducers of CYP3A within 2 weeks or 5 half-lives (whichever is longer) before the first dose of study drug treatment and while on treatment with the study drug.
- Beyond Cycle 2 Day 8 of Phase 1 portion: any potent inducers of CYP3A (e.g., rifampin, rifabutin, phenobarbital, phenytoin, carbamazepine, and St. John's wort [*Hypericum perforatum*])
- For Cycle 1 Day 1 – Cycle 2 Day 8 of Phase 1 portion: Use of any inhibitors of CYP3A within 2 weeks or 5 half-lives (whichever is longer) before the first dose of study drug treatment and while on treatment with the study drug.
- Beyond Cycle 2 Day 8 of Phase 1 portion: any potent inhibitors of CYP3A (e.g., ketoconazole)
- Systemic immunosuppressive drugs, cytotoxic or chemotherapeutic agents (other than study drug treatment), ergot derivatives, probenecid, and bile acid-binding resins while on study treatment
- Systemic chemotherapy
- Radiotherapy/radionuclide therapy except for palliative radiotherapy to bone lesions for pain control. If palliative radiation is indicated for bone metastases, palliative radiation may start within 24 hours of the last dose of alectinib, unless, in the judgment of the investigator, subject safety will require a longer washout period prior to palliative therapy. Dosing of alectinib may resume with the resolution of any radiation toxicity to  $\leq$  Grade 1
- Additional investigational drug (except for during the follow-up period)

The above lists of medications are not necessarily comprehensive. Thus, the investigator should consult the prescribing information for any concomitant medication as well as the Internet references provided below when determining whether a certain medication strongly inhibits or induces CYP3A. In addition, the investigator should contact the Medical Monitor if questions arise regarding medications not listed above.

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf>

<http://medicine.iupui.edu/clinpharm/ddis/table.aspx>

Please see **APPENDIX C** for more information on concomitant medication restrictions.

Caution should be exercised when the following are co-administered with alectinib:

- For medications that are substrates of P-gp transporter or BCRP transporter, the investigator should use caution and monitoring when considering concomitant use of alectinib. Acetaminophen up to 2 g/day is permitted therapy but should be used with

caution. Alectinib has been shown to have potential for inhibition of these transporters. Substrates with a narrow therapeutic index (e.g., methotrexate, dabagitrin, digoxin) should be avoided. If in the opinion of the treating investigator, co-administration cannot be avoided, it is recommended that signs for toxicity are carefully monitored (see **APPENDIX C**).

### **Sun Exposure:**

Subjects should be advised to avoid prolonged sun exposure while taking alectinib and for at least 7 days after study drug discontinuation. Subjects should also be advised to use a broad-spectrum sun screen and lip balm of SPF  $\geq 50$  to help protect against potential sunburn.

### **5.6 Criteria for Taking a Subject Off Protocol Therapy**

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

- Disease progression. Treatment beyond objective progression may be permitted in cases of perceived clinical benefit, as determined by the site investigator.
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Subject demonstrates an inability or unwillingness to comply with the oral medication regimen and/or documentation requirements
- Subject decides to withdraw from the protocol therapy
- General or specific changes in the subject's condition render the subject unacceptable for further treatment in the judgment of the treating investigator

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

For Centralized Subject Registrations, the research team submits a completed Off Treatment to ODQ when a subject comes off study. This form can be found on the ODQ website or obtained from the ODQ registration staff.

For Decentralized Subject Registrations, the research team updates the relevant Off Treatment information in OnCore.

In the event of unusual or life-threatening complications, treating investigators must immediately notify the Overall PI, Dr. Mark M. Awad at telephone # 617-632-3468.



## 5.7 Duration of Follow Up

Subjects will be followed until death after removal from protocol therapy. This follow up will be performed by review of the medical record, contact with care providers, and/or telephone contact as needed every 3-4 months.

## 5.8 Criteria for Taking a Subject Off Study

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

- Lost to follow-up
- Withdrawal of consent for data submission
- Death

For Centralized Subject Registrations, the research team submits a completed Off Study form to ODQ when a subject comes off study. This form can be found on the ODQ website or obtained from the ODQ registration staff.

For Decentralized Subject Registrations, the research team updates the relevant Off Study information in OnCore.

## 6. DOSING DELAYS/DOSE MODIFICATIONS

Dose delays and modifications will be made as indicated in the following tables during and beyond the DLT period. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 will be utilized for dose delays and dose modifications. A copy of the CTCAE version 4.03 can be downloaded from the CTEP website

[http://ctep.cancer.gov/protocolDevelopment/electronic\\_applications/ctc.htm](http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

### 6.1 Dose Modifications

Dose reductions will be based on the schedule outlined in **Table 5**. Dose reductions below 300 mg PO BID will not be permitted. If a subject requires reduction below 300 mg PO BID, they should be removed from the trial. Unless indicated otherwise in **Table 6**, study medication may be held for a maximum of 21 days to allow for the resolution of toxicity. Subjects requiring a longer hold should be removed from the trial. Exceptions to this requirement are possible should the principal investigator agree that the subject may continue despite the length of time off drug.

Subjects undergoing dose reductions for toxicities may not be re-escalated to a prior dose.

**Table 5: Alectinib Dose Reductions**

<b>Original Alectinib Dose (PO BID)</b>	<b>Alectinib Dose Reduction (PO BID)</b>
600 mg	1 <sup>st</sup> Reduction: 450 mg
	2 <sup>nd</sup> Reduction: 300 mg
750 mg	1 <sup>st</sup> Reduction: 600 mg
	2 <sup>nd</sup> Reduction: 450 mg
900 mg	3 <sup>rd</sup> Reduction: 300 mg
	1 <sup>st</sup> Reduction: 750 mg
	2 <sup>nd</sup> Reduction: 600 mg
1200 mg	3 <sup>rd</sup> Reduction: 450 mg
	4 <sup>th</sup> Reduction: 300 mg
	1 <sup>st</sup> Reduction: 900 mg
	2 <sup>nd</sup> Reduction: 750 mg
	3 <sup>rd</sup> Reduction: 600 mg
	4 <sup>th</sup> Reduction: 450 mg
	5 <sup>th</sup> Reduction: 300 mg

If the study medication is placed on hold for toxicity, the counting of cycle days and pre-planned assessment schedule will continue without interruption. For example, a subject who does not receive their cycle 3 day 16 – cycle 3 day 20 doses of alectinib due to toxicity would restart on cycle 3 day 21 and will proceed with their next regularly scheduled visit (cycle 4 day 1). Additional interim visits can be conducted as clinically necessary to manage toxicity; however once resolved, the cycle will not restart for dosing delays due to toxicity. Exceptions to this are possible after discussion with the site investigator.

Subjects enrolled to the phase 1 portion of the trial may undergo intra-subject dose escalation if subsequent higher dose levels are proven safe per trial guidelines outlined in **Sections 5.1 and 5.4**. Subjects must have completed cycle 4 and must not have experienced any DLTs, DLT-equivalent toxicity, or any other toxicity necessitating a dose reduction at any point during their treatment to be eligible for dose escalation. No subject may be escalated to a dose level above the MTD.

## 6.2 Guidelines for Management of Specific Adverse Events

<b>Table 6: Management of Selected Adverse Events with Alectinib</b>	
<b>Event</b>	<b>Action to Be Taken</b>
Interstitial lung disease (ILD)	<ul style="list-style-type: none"> <li>• Subjects should be monitored for pulmonary symptoms indicative of pneumonitis.</li> <li>• <b>Study drug should be permanently discontinued in subjects diagnosed with ILD.</b></li> </ul>
Hepatotoxicity	<ul style="list-style-type: none"> <li>• If ALT or AST &gt; 3 × baseline, repeat testing of ALT, AST, alkaline phosphatase (alk phos), and total bilirubin within 48–72 hours, with inquiry about symptoms.</li> <li>• If upon repeat testing the transaminases remain &gt; 3 × baseline, but are not &gt; 5 × baseline or not accompanied with bilirubin increases or do not match any other rule for permanent discontinuation, then monitoring can continue as per investigator judgment, and dose modification is not necessary.</li> <li>• At any time during the study treatment, if symptoms compatible with liver injury are observed, liver enzymes (AST, ALT) should be measured as soon as possible.</li> <li>• <b>Study drug treatment has to be permanently discontinued if any of the following occurs:</b> <ul style="list-style-type: none"> <li>○ First observation of ALT or AST &gt; 8 × ULN</li> <li>○ ALT or AST &gt; 5 × ULN for more than 2 weeks</li> <li>○ First observation of ALT or AST &gt; 3 × institutional ULN and total bilirubin &gt; 2 × institutional ULN</li> <li>○ First observation of ALT or AST &gt; 3 × institutional ULN and the appearance of jaundice or signs of hepatic dysfunction (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and eosinophilia [<math>&gt; 5\%</math>]).</li> </ul> </li> <li>• Following study drug discontinuation, weekly monitoring of laboratory values should continue until the abnormal values have normalized to pre-treatment levels and/or an adequate explanation of the abnormal value is found.</li> </ul>

<b>Table 6: Management of Selected Adverse Events with Alectinib</b>	
<b>Event</b>	<b>Action to Be Taken</b>
Gastrointestinal tract AEs (e.g., nausea, vomiting, diarrhea, constipation)	The events are expected to be minimized by taking the study drug with meal. In case GI events occur, appropriate measures should be taken in accordance with local clinical practice guidelines. If GI toxicities are observed and not tolerable, treatment with study drug should be temporarily interrupted until recovery to Grade 1 or lower.
Vision disorders	Investigators should consider referring the subjects for an ophthalmological evaluation according to local clinical practice guidelines, if vision disorders persist or worsen in severity, and to advise subjects to exercise caution when driving or operating machinery due to the risk of developing a vision disorder.
Abnormal kidney function AEs	<ul style="list-style-type: none"> <li>• If eGFR decreases by &gt; 50% of the baseline visit value, the subject has to be carefully monitored. All of the underlying factors that may have acutely impacted serum creatinine levels need to be evaluated and corrected (e.g., dehydration, recent exposure to contrast media, increased amount of cooked meat in diet, concomitant medications affecting renal function as appropriate).</li> <li>• Any eGFR decrease by &gt; 50% of the baseline visit value requires repeat testing.             <ul style="list-style-type: none"> <li>○ If at the repeat test the eGFR decrease is still &gt; 50% of the baseline visit value, the treatment with alectinib should be interrupted.</li> </ul> </li> <li>• Alectinib treatment may be resumed at the same dose level with caution when the eGFR value has increased to approximately the baseline visit value.</li> </ul>
Severe myalgia and CPK elevations	<ul style="list-style-type: none"> <li>• Myopathy should be considered in any subject with diffuse myalgia, muscle tenderness or weakness, and/or marked elevations of CPK levels. Subjects should promptly report unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever. CPK levels should be assessed in subjects reporting these symptoms.             <ul style="list-style-type: none"> <li>○ At the first occurrence of any of asymptomatic CPK values (<math>&gt; 10 \times \text{ULN}</math>, symptomatic CPK <math>&gt; 5 \times \text{ULN}</math>, or in the presence of severe muscular symptoms with CPK <math>&gt; \text{ULN}</math> but <math>\leq 5 \times \text{ULN}</math>) at any time during the study treatment, the subject requires monitoring of the CPK values until they are normalized to pre-treatment levels or a reasonable explanation for the CPK elevation and the symptoms is established.</li> </ul> </li> </ul>

<b>Table 6: Management of Selected Adverse Events with Alectinib</b>	
<b>Event</b>	<b>Action to Be Taken</b>
Skin disorder AEs (e.g., phototoxicity, rash)	Subjects should be advised to avoid prolonged sun exposure while taking alectinib and for at least 5 days after study drug discontinuation. Subjects should also be advised to use a broad-spectrum sun screen and lip balm of at least SPF 50 to help protect against potential sunburn.
Edema	Physical examinations will be performed routinely in clinical trials. In case edema events occur, appropriate measures should be taken in accordance with local clinical practice guidelines
Other AEs (including bradycardia, anemia and CPK elevation) or laboratory abnormalities	<p>Grade 3 or 4:</p> <ul style="list-style-type: none"> <li>• Temporarily interrupt alectinib for a maximum of 3 weeks.</li> <li>• If improvement to Grade <math>\leq</math> 1 or baseline does not occur within 3 weeks, permanently discontinue alectinib.</li> <li>• First episode: If improvement to Grade <math>\leq</math> 1 or baseline within 21 days, decrease the current dose of alectinib by 150 mg (1 capsule) BID.</li> <li>• Second episode: If improvement to Grade <math>\leq</math> 1 or baseline within 21 days, decrease the current dose of alectinib by another 150 mg (1 capsule) BID.</li> <li>• Third episode: Permanently discontinue alectinib.</li> </ul> <p>Grade 2 (except any symptoms and signs that can be corrected with supportive care):</p> <ul style="list-style-type: none"> <li>• Temporarily interrupt alectinib and resume if recovering to Grade <math>\leq</math> 1 or baseline if clinically indicated.</li> <li>• First episode: If improvement to Grade <math>\leq</math> 1 or baseline within 10 days, continue same dose of alectinib. If improvement occurs after 10 days, decrease the current dose of alectinib by 150 mg (1 capsule) BID when resuming treatment.</li> <li>• Second episode: If improvement to Grade <math>\leq</math> 1 or baseline within 10 days, decrease the current dose of alectinib by 150 mg (1 capsule) BID. If improvement occurs after 10 days, decrease the current dose of alectinib by 300 mg when resuming treatment.</li> <li>• Third episode: Permanently discontinue alectinib.</li> </ul> <p>Grade 1: no action required</p>

### 6.3 Overdose

No experience with over-dosage is available for alectinib. Subjects who experience overdose should be closely supervised and supportive care instituted. There is no specific antidote for overdose with alectinib.

## 7. SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording AEs, including SAEs and non-SAEs of special interest, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study. Certain types of events require immediate reporting to the Sponsor, as outlined in the sections below.

### 7.1 Adverse Event Characteristics

An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational medicinal product (IMP) or other protocol-imposed intervention, regardless of attribution.

This includes the following:

- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with the underlying disease that were not present prior to the AE reporting period.
- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as cardiac catheterizations).
- If applicable, AEs that occur prior to assignment of study treatment associated with medication washout, no treatment run-in, or other protocol-mandated intervention.
- Pre-existing medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.

Investigators should use correct medical terminology/concepts when reporting AEs or serious adverse events (SAEs). Avoid colloquialisms and abbreviations.

**Pre-existing Medical Conditions:** A pre-existing medical condition is one that is present at the start of the study. Such conditions should be reported as medical and surgical history. A pre-existing medical condition should be re-assessed throughout the trial and reported as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When reporting such events, it is important to convey the concept that the pre-existing condition has changed by including applicable descriptors (e.g., “more frequent headaches”).

**CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the

CTCAE version 4.03. A copy of the CTCAE version 4.03 can be downloaded from the CTEP web site: [http://ctep.cancer.gov/protocolDevelopment/electronic\\_applications/ctc.htm](http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

**Methods and timing for capturing and assessing safety parameters:** The investigator is responsible for ensuring that all AEs are recorded on the Adverse Event eCRF and reported to Genentech in accordance with instructions provided in this section. For each AE recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness, severity, and causality.

**Adverse Event Reporting Period:**

Investigator will seek information on AEs at each subject contact. All AEs, whether reported by the subject or noted by study personnel, will be recorded in the subject's medical record and on the Adverse Event eCRF.

After informed consent has been obtained but prior to initiation of study drug, only SAEs caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported.

After initiation of study drug, all AEs will be reported until 4 weeks after the last dose of study drug. After this period, the investigator should report any SAEs that are believed to be related to study drug treatment.

**Deaths:**

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol-specified AE reporting period that are attributed by the investigator solely to progression of underlying disease should be recorded only on the Study Completion/Early Discontinuation eCRF. All other on-study deaths, regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor and Genentech.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. The term "sudden death" should be used only for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a subject with or without preexisting heart disease, within 1 hour after the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the subject was last seen alive and stable. If the cause of death is unknown and cannot be ascertained at the time of reporting, "unexplained death" should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death.

During survival follow-up, deaths attributed to progression of underlying disease should be recorded only on the Survival eCRF.

## 7.2 Serious Adverse Events

An AE should be classified as a SAE if the following criteria are met:

- It results in death (i.e., the AE actually causes or leads to death).

- It is life threatening (i.e., the AE, in the view of the investigator, places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death).
- It requires or prolongs inpatient hospitalization.
- It results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the subject's ability to conduct normal life functions).
- It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the IMP.
- It is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the subject or may require medical/surgical intervention to prevent one of the outcomes listed above).

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE. If a subject is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be reported as the SAE. For example, if a subject is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass as the SAE.

Hospitalizations for the following reasons do not require reporting:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for pre-existing conditions
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study or
- Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study.

**Pregnancy:** If a female subject becomes pregnant while receiving the study drug or within 90 days after the last dose of study drug, a report should be completed and expeditiously submitted to both the Overall PI and Genentech, Inc. Follow-up to obtain the outcome of the pregnancy should also occur. Abortion, whether accidental, therapeutic, or spontaneous, should always be classified as serious, and expeditiously reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a female subject exposed to alectinib should be reported as an SAE.

**Post-Study Adverse Events:** The investigator should expeditiously report any SAE occurring after a subject has completed or discontinued study participation if attributed to prior alectinib exposure. If the investigator should become aware of the development of cancer or a congenital anomaly in a subsequently conceived offspring of a female subject who participated in the study, this should be reported as an SAE.

**Diagnosis vs. Signs and Symptoms:** If known at the time of reporting, a diagnosis should be reported rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, it is acceptable to report the information that is currently available. If a diagnosis is subsequently established, it should be reported as follow-up information.



**Lack of Efficacy or Worsening of Non-Small Cell Lung Cancer:** Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as AEs. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on RECIST criteria v1.1. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression using objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an AE.

### 7.3 Non-Serious Adverse Events of Special Interest

Non-SAEs of Special Interest (AESIs) are required to be reported by the investigator to the Overall PI and Genentech immediately.

AEs of special interest for this study are the following:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law (see below)
- The finding of an elevated ALT or AST ( $> 3 \times$  baseline value) in combination with either an elevated total bilirubin ( $> 2 \times$  institutional ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury.

Therefore, investigators must report as an AE the occurrence of either of the following:

- Treatment-emergent ALT or AST  $> 3 \times$  baseline value in combination with total bilirubin  $> 2 \times$  institutional ULN (of which  $\geq 35\%$  is direct bilirubin)
- Treatment-emergent ALT or AST  $> 3 \times$  baseline value in combination with clinical jaundice
- The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded and reported to the Overall PI and Genentech immediately (i.e., no more than 24 hours after learning of the event), either as an SAE or an AESI.
- Suspected transmission of an infectious agent by the study drug, as defined below: Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a subject exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.

### 7.4 Procedures for Eliciting, Recording, and Reporting Adverse Events

A consistent methodology for eliciting AEs at all subject evaluation time points should be adopted. Examples of non-directive questions include:

- "How have you felt since your last clinical visit?"
- "Have you had any new or changed health problems since you were last here?"

## **7.5 Assessment of Adverse Events for Reporting to Genentech/Roche**

All AEs and SAEs whether volunteered by the subject, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means will be reported appropriately. Each reported AE or SAE will be described by its duration (i.e., start and end dates), regulatory seriousness criteria if applicable, suspected relationship to alectinib, and actions taken.

To ensure consistency of AE and SAE causality assessments, investigators should apply the following general guideline:

### **Yes**

There is a plausible temporal relationship between the onset of the AE and administration of alectinib, and the AE cannot be readily explained by the subject's clinical state, intercurrent illness, or concomitant therapies; and/or the AE follows a known pattern of response to alectinib; and/or the AE abates or resolves upon discontinuation of alectinib or dose reduction and, if applicable, reappears upon re-challenge.

### **No**

Evidence exists that the AE has an etiology other than alectinib (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to alectinib administration (e.g., cancer diagnosed 2 days after first dose of study drug).

Expected adverse events are those adverse events that are listed or characterized in the Package Insert (P.I) or current Investigator Brochure (I.B).

Unexpected adverse events are those not listed in the P.I or current I.B or not identified. This includes adverse events for which the specificity or severity is not consistent with the description in the P.I. or I.B. For example, under this definition, hepatic necrosis would be unexpected if the P.I. or I.B. only referred to elevated hepatic enzymes or hepatitis.

## **7.6 Adverse Event Reporting to Genentech/Roche**

### **7.6.1 Required SAE/AE Reporting:**

The investigator is responsible for ensuring that all AEs, pregnancies and SAEs that are observed or reported during the study are collected and reported to the Overall PI, appropriate IRB(s), and Genentech/Roche, Inc. in accordance with CFR 312.32 (IND Safety Reports).

Investigators must report all SAEs and Non-Serious Adverse Events of Special Interest to Genentech/Roche within the timelines described. The completed MedWatch/case report should be faxed immediately upon completion to Genentech Drug Safety at:

**(650) 225-4682**  
**OR**  
**(650) 225-4630**

SAEs, pregnancy reports, and AESIs where the subject has been exposed to alectinib, will also be sent on a MedWatch or CIOMS I form to Genentech/Roche. Transmission of these reports (initial and follow-up) will be either electronically or by fax and within the timelines specified below:

SAEs, pregnancy and AESI reports shall be transmitted to Roche on an SAE form within one (1) business day of the awareness date, regardless of causality relationship to study drug.

In addition to all SAEs, pregnancy reports, and AESIs, the following Special Situations Reports should be collected and transmitted to Genentech/Roche even in the absence of an AE within thirty (30) calendar days:

- Data related to alectinib usage during pregnancy or breastfeeding
- Data related to overdose, abuse, off-label use, misuse, inadvertent/erroneous administration, medication error or occupational exposure, with or without association with an AE/SAE unless otherwise specified in the protocol
- Data related to a suspected transmission of an infectious agent via a medicinal product (STIAMP)

### **Aggregate Reports**

The investigator will forward a copy of the Final Study Report to Genentech/Roche upon completion of the Study.

For questions related to safety reporting, please contact Genentech/Roche Drug Safety:

- Tel: (888) 835-2555
- Fax: (650) 225-4682 or (650) 225-4630

### **MedWatch 3500A Reporting Guidelines**

In addition to completing appropriate subject demographic and suspect medication information, the report should include the following information within the Event Description (section 5) of the MedWatch 3500A form:

- Protocol description (and number, if assigned)
- Description of event, severity, treatment, and outcome if known
- Supportive laboratory results and diagnostics
- Investigator's assessment of the relationship of the adverse event to each investigational and product and suspect medication

### **Follow-up Information**

Additional information may be added to a previously submitted report by any of the following methods:

- Adding to the original MedWatch 3500A report and submitting it as follow-up
- Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500A form
- Summarizing new information and faxing it with a cover letter including subject identifiers (i.e. D.O.B. initial, subject number), protocol description and number, if assigned, brief adverse event description, and notation that additional or follow-up information is being submitted (the subject identifiers are important so that the new information is added to the correct initial report)

Occasionally Genentech may contact the reporter for additional information, clarification, or current status of the subject for whom an adverse event was reported. For questions regarding SAE reporting, you may contact the Genentech Drug Safety representative noted above or the MSL assigned to the study. Relevant follow-up information should be submitted to Genentech Drug Safety as soon as it becomes available and/or upon request.

The MedWatch 3500A (Mandatory Reporting) form is available at:  
<http://www.fda.gov/medwatch/getforms.html>

## 7.7 Reconciliation

The Overall PI agrees to conduct reconciliation for the product. Genentech/Roche and the Overall PI will agree to the reconciliation periodicity and format, but agree at minimum to exchange quarterly line listings of cases received by the other party.

If discrepancies are identified, the Overall PI and Genentech/Roche will cooperate in resolving the discrepancies. The responsible individuals for each party shall handle the matter on a case-by-case basis until satisfactory resolution. The Overall PI shall receive reconciliation guidance documents within the 'Activation Package'.

## 7.8 Expedited Adverse Event Reporting

- 7.8.1 Investigators **must** report to the Overall PI any serious adverse event (SAE) that occurs after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment on the local institutional SAE form.
- 7.8.2 For multi-institution studies where a DF/HCC investigator is serving as the Overall Principal Investigator, each participating institution **must** abide by the reporting requirements set by the DF/HCC. This applies to any medical event equivalent to an unexpected grade 2 or 3 with a possible, probable or definite attribution, and grade 4 toxicities and grade 5 (death) regardless of study phase, expectedness, or attribution.

### 7.8.3 DF/HCC Expedited Reporting Guidelines

Investigative sites within DF/HCC will report AEs directly to the DFCI Office for Human Research Studies (OHRS) per the DFCI IRB reporting policy.

Other investigative sites will report AEs to their respective IRB according to the local IRB's policies and procedures in reporting adverse events. A copy of the submitted institutional AE form should be forwarded to the Overall PI within the timeframes detailed in the table below.

Attribution	Table 7: DF/HCC Reportable AEs				
	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	Not required	Not required	5 calendar days <sup>#</sup>	5 calendar days	24 hours*
Possible Probable Definite	Not required	5 calendar days	5 calendar days <sup>#</sup>	5 calendar days	24 hours*
# If listed in protocol as expected and not requiring expedited reporting, event does not need to be reported.					
* For subjects enrolled and actively participating in the study <i>or</i> for AEs occurring within 30 days of the last intervention, the AE should be reported within <u>1 business day</u> of learning of the event.					

The Overall PI will submit AE reports from outside institutions to the DFCI OHRS according to DFCI IRB policies and procedures in reporting adverse events.

### 7.9 **Expedited Reporting to the Food and Drug Administration (FDA)**

The Overall PI, as study sponsor, will be responsible for all communications with the FDA. The Overall PI 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.

**All written IND Safety Reports submitted to the FDA by the Investigator must also be faxed to Genentech/Roche Drug Safety:**

Fax: (650) 225-4682 or (650) 225-4630

### 7.10 **Expedited 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.

### 7.11 **Routine Adverse Event Reporting**

All Adverse Events **must** be reported in routine study data submissions to the Overall PI on the toxicity case report forms. **AEs reported through expedited processes (e.g., reported to the**

**IRB, FDA, etc.) must also be reported in routine study data submissions.**

## **8. PHARMACEUTICAL INFORMATION**

A list of the adverse events and potential risks associated with the investigational agent administered in this study can be found in **Section 7.1**.

### **8.1 Alectinib**

#### **8.1.1 Description**

Alectinib is a kinase inhibitor for oral administration. The molecular formula for alectinib is  $C_{30}H_{34}N_4O_2 \cdot HCl$ . The molecular weight is 482.62 g/mol (free base form) and 519.08 g/mol (hydrochloride salt). Alectinib is described chemically as 9-ethyl-6, 6-dimethyl-8-[4-(morpholin-4-yl)piperidin-1-yl]-11-oxo-6, 11-dihydro-5H -benzo[b ]carbazole-3-carbonitrile hydrochloride.

#### **8.1.2 Form**

Alectinib HCl is a white to yellow white powder or powder with lumps with a pKa of 7.05 (base).

Alectinib is supplied as hard capsules containing 150 mg of alectinib (equivalent to 161.33 mg alectinib HCl) and the following inactive ingredients: lactose monohydrate, hydroxypropylcellulose, sodium lauryl sulfate, magnesium stearate, and carboxymethylcellulose calcium. The capsule shell contains hypromellose, carrageenan, potassium chloride, titanium dioxide, corn starch, and carnauba wax. The printing ink contains red iron oxide (E172), yellow iron oxide (E172), FD&C Blue No. 2 aluminum lake (E132), carnauba wax, white shellac, and glyceryl monooleate.

#### **8.1.3 Storage and Stability**

The recommended storage conditions for the alectinib drug product are room temperature, not to exceed 77°F. The product should be stored in original bottles in order to protect from moisture.

#### **8.1.4 Compatibility**

N/A

#### **8.1.5 Handling**

Qualified personnel, familiar with procedures that minimize undue exposure to

themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

#### 8.1.6 **Availability**

Alectinib will be supplied as an investigational agent free of charge by Genentech/Roche.

#### 8.1.7 **Preparation**

N/A

#### 8.1.8 **Administration**

Alectinib is administered orally twice daily. A missed dose may be taken up to 6 hours after the scheduled dosing time. Doses that would be outside of this window should be considered missed and should not be taken. Subjects should be instructed not to double dose. A vomited dose should not be retaken; instead subjects should be advised to continue with the next regularly scheduled dose as clinically appropriate.

Alectinib should be taken with food. Alectinib capsules should be swallowed whole; they should not be opened, chewed, or crushed. Subjects should be instructed to wash their hands after handling the capsules and to keep their study medication supply out of the reach of children and animals.

#### 8.1.9 **Ordering**

Drug supply will be ordered from Genentech/Roche by site pharmacy personnel.

#### 8.1.10 **Accountability**

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

#### 8.1.11 **Destruction and Return**

Returned supplies of alectinib should be destroyed according to institutional policies. Destruction will be documented in the Drug Accountability Record Form. Accurate records of all drug supply received at, dispensed from, returned to, and disposed of by the study site should be recorded on a Drug Inventory Log.

## 9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

### 9.1 Pharmacokinetic (PK) Studies

At each PK assessment time point venous blood samples will be collected to measure plasma concentrations of alectinib and its major metabolite, M4. Intensive and sparse samples for PK assessments will be obtained to characterize the pharmacokinetics of alectinib. Concentrations of alectinib and the M4 metabolite will be determined in plasma using validated liquid chromatography tandem mass spectroscopy methods. The PK parameters for alectinib and M4 will be determined by standard non-compartmental methods as appropriate and if data allow.

The following PK parameters will be determined, as appropriate and if data allow:

- $C_{max}$ : Maximum observed plasma alectinib concentration
- $AUC_{0-last}$ : Area under the plasma alectinib concentration-time curve from time 0 to the last measureable concentration
- $T_{max}$ : Time of  $C_{max}$  for alectinib
- $C_{max}$ ,  $T_{max}$ , and  $AUC_{0-last}$  of M4 metabolite
- $t_{1/2}$ : apparent terminal half-life of alectinib and M4 metabolite, if appropriate
- M4 metabolite/parent exposure ratio for  $AUC_{last}$  and  $C_{max}$ , if appropriate
- Additional PK parameters may be determined as appropriate.

Plasma concentrations and the computed plasma PK parameters will be listed for alectinib and M4. Individual and mean concentration versus time data will be plotted on linear and semi-logarithmic scales. Summary statistics of PK parameters (primary and secondary) will be presented for each treatment period including mean, geometric mean, standard deviation (SD), coefficient of variation (CV), median, and range, as appropriate. Inter-subject, intra-subject and/or total variability in reported PK parameters will be calculated if available and appropriate. Additional analyses or summaries may be considered, as appropriate. Results of any PK analyses may be reported outside the clinical study report.

#### 9.1.1 Collection of Specimens for Pharmacokinetic Analysis

Label the 2 mL EDTA blood collection tube with the appropriate protocol number, subject number, date/time of collection, and sample numbers on the label.

At the nominated time point, draw 2 mL of blood into the pre-labeled collection tube.

#### Phase 1 (Dose escalation)

Blood will be collected at the time points shown in **Table 9** below:

<b>Table 8: PK Collection Schedule (Phase 1)</b>		
<b>Visit Day</b>	<b>Time of Collection</b>	<b>Sample Number</b>
Cycle 1 Day 1	<b>Pre-dose</b> (any time prior to the first alectinib dose – baseline)	1



<b>Table 8: PK Collection Schedule (Phase 1)</b>		
<b>Visit Day</b>	<b>Time of Collection</b>	<b>Sample Number</b>
	sample)	
Cycle 1 Day 8	<b>Pre-dose</b> (any time prior to the first increased alectinib dose)	2
Cycle 1 Day 15	<b>Pre-dose</b> (any time prior to the first alectinib dose of the day)	3
Cycle 2 Day 1	<b>Pre-dose</b> (any time prior to the first alectinib dose of the day)	4
Cycle 2 Day 1	<b>0.5 hours</b> post-alectinib dose ( $\pm$ 5 minute window)	5
Cycle 2 Day 1	<b>1 hour</b> post-alectinib dose ( $\pm$ 10 minute window)	6
Cycle 2 Day 1	<b>2 hours</b> post-alectinib dose ( $\pm$ 15 minute window)	7
Cycle 2 Day 1	<b>4 hours</b> post-alectinib dose ( $\pm$ 30 minute window)	8
Cycle 2 Day 1	<b>6 hours</b> post-alectinib dose ( $\pm$ 30 minute window)	9
Cycle 2 Day 1	<b>8 hours</b> post-alectinib dose ( $\pm$ 30 minute window)	10
Cycle 2 Day 1	<b>10 hours*</b> post-alectinib dose ( $\pm$ 60 minute window)	11
Cycle 3 Day 1	<b>Pre-dose</b> (any time prior to the first alectinib dose of the day)	12
Cycle 4 Day 1	<b>Pre-dose</b> (any time prior to the first alectinib dose of the day)	13

\*Optional if collection is not feasible at site.

### 9.1.2 Handling of Specimens

- Immediately following collection, invert gently several times the tubes backwards and forwards, 8-10 times, (without shaking) to ensure the anticoagulant is mixed well with the blood.
- Note the exact start time of blood draw in the eCRF.
- The blood must be stored on wet ice at 4°C until centrifugation (for no longer than 30 min after blood collection).
- Start centrifuging samples within 30 minutes after blood sampling for 10 minutes at 1500 x g at 4°C.
- Note the exact “time in centrifuge” in the eCRF.
- Once the blood has finished the spin, transfer the plasma (~0.8 mL) from the blood collection tube into 1 (one) 3.5 mL polypropylene screw storage tube.
- Label tube: Alectinib RET PK with protocol number, subject number, sample number, and date/time of collection
- Immediately cap the tube.
- Once the plasma is removed, discard the blood collection tube.
- Place (within 60 minutes after blood collection) the samples temporarily on dry-ice and note the time of placing the sample on dry ice in the eCRF.
- After the complete round place the plasma storage tubes upright in a freezer at or below -20°C or -70°C until shipment. Stability is valid for 396 days -20°C, 721 days -70°C.

### 9.1.3 Shipping of Specimens

For sample shipment:

Q Squared Solutions BioSciences LLC  
Laboratory Operations Manager  
Christopher Binns  
19 Brown Road  
Ithaca NY 14850 USA  
phone +1 607-330-9817  
fax +1-607-266-0749  
christopher.binns@q2labsolutions.com

Lab contact:

Christopher Binns  
Project Manager  
Q Squared Solutions BioSciences LLC  
19 Brown Road  
Ithaca, NY 14850 USA  
Office: +1 607-330-9817  
Fax: +1 607-266-0749  
christopher.binns@q2labsolutions.com

### 9.1.4 Sites Performing Correlative Study

All sites will be participating in the collection of blood for pharmacokinetic studies.

## 9.2 Germline and Tumor Genomic Analysis

Genomic analysis of germline DNA and tumor tissue (both fresh and archival) will be performed to investigate factors that confer sensitivity or resistance to alectinib.

### 9.2.1 Tumor Tissue Collection

A baseline fresh tumor biopsy is required for any subject who has received a prior RET TKI. Additionally, archival tissue is required for all subjects enrolling to the trial. For subjects enrolling who are RET TKI naive, a baseline fresh tumor biopsy may be obtained in lieu of archival tumor tissue if archival tumor tissue is not available. The archival tissue requirement may be waived for subjects who do not have sufficient tissue after discussion with the principal investigator.

An optional fresh tumor biopsy at the time of disease progression will also be offered to all subjects if clinically feasible. Whenever possible, the time of progression biopsy should be obtained prior to the initiation of another cancer treatment. In the event this is not possible, the time of progression biopsy can be obtained up to 30 days after the last dose of alectinib.

Collection and processing of fresh tumor tissue by core biopsy, surgical resection,

fine needle aspiration (FNA), or drainage of effusions should be performed according to local standards at each participating site. Biopsies performed for the purposes of obtaining tumor tissue for this study will be paid for by the study budget. Tumor specimens will be evaluated by a pathologist to ensure adequacy for analysis.

Whenever possible, core biopsy samples should be collected for analysis. Three-to-four biopsy passes utilizing a 16-18 gauge needle are preferable, but 20 gauge core needle biopsies are also acceptable at the discretion of the interventionalist performing the biopsy procedure.

If a core biopsy is judged to be too unsafe or difficult for the subject in the opinion of the treating investigator or interventionalist performing the procedure, an FNA or cytology sample can also be collected. The goal for a thoracentesis or paracentesis procedure will be 500 – 1000 mL collected in a standard collection tube. The goal for an FNA will be three distinct passes. Less than the goal amount of tissue is acceptable for any of the biopsy collection methods, and should be based upon the clinical judgment of the treating investigator and the clinician performing the procedure.

Biopsy samples should be formalin-fixed and paraffin embedded (FFPE) per routine local procedures. Cytology samples should be made into blocks per routine local procedures.

#### 9.2.2 Germline Blood Sample Collection

Germline DNA will additionally be extracted from peripheral leukocytes obtained from a peripheral blood sample and studied as a control. The blood for germline DNA testing is to be collected on on Cycle 1 Day 1. Blood may be collected any time prior to the first dose of alectinib.

#### 9.2.3 Handling and Shipping of Specimens

Tumor Tissue: 10 unstained slides or a tumor block of paraffin embedded tissue should be sent at room temperature to:

The Jänne Lab  
Dana-Farber Cancer Institute  
360 Longwood Avenue, LC4118  
Boston, MA 02215

Blood: A blood specimen for germline DNA analysis should be collected in one 10 ml EDTA-containing (“purple top”) tube and shipped at room temperature to:

The Jänne Lab  
Dana-Farber Cancer Institute  
360 Longwood Avenue, LC4118  
Boston, MA 02215

#### 9.2.4 Sites Performing Correlative Study

All sites will be participating in the collection of tumor tissue and blood specimens

for genomic analysis.

### 9.3 Plasma Collection for cfDNA

#### 9.3.1 Collection of Specimens

The baseline plasma genotyping sample should be collected on Cycle 1 Day 1. Blood may be collected any time prior to the first dose of alectinib.

On the first day of each subsequent cycle and at the off study visit, a sample should be collected. The sample can be obtained at any time during the clinic visit.

#### 9.3.2 Handling of Specimens

- NOTE: Time period from draw to freezing of plasma must be less than 3 hours.
- Draw venous blood into one (1) 10 mL EDTA tubes labeled cfDNA and immediately gently invert the tubes 8-10 times. Write the subject and draw date number on the tube.
- Immediately centrifuge for 10 minutes at 1500 (+/- 150) x g. NOTE: Brake switch must be off so the cell/plasma interface is not disturbed.
- Pipette the plasma layer into a 15 mL tube labeled “cfDNA/with subject #”. Do not ship. NOTE: Do not dip the tip of the pipette into the plasma/cell interface. Leave a thin plasma layer intact over the interface.
- Centrifuge the 15 mL tube containing the plasma only for 10 minutes at 3000 (+/- 150) x g.
- Using a fresh pipette, transfer the supernatant into a second 15 mL tube labeled “cfDNA super.do not ship”. NOTE: Leave about 0.3 mL of supernatant in the centrifuged 15 mL tube. This leftover 0.3 mL contains cellular debris.
- Using a fresh pipette, transfer 1 mL of plasma from the “super.do not ship” tube into max four (4) 2 mL cryovials labeled cfDNA.ship.subject#/#
- Freeze immediately upright at -70°C or colder until shipping.

#### 9.3.3 Shipping of Specimens

Specimens should be shipped to:

Alectinib RET study

ATTN: Julianna Supplee

Belfer Center for Applied Cancer Research

360 Longwood Avenue, LC-4302

Boston, MA 02215

215-429-7186

e-mail: julianna\_supplee@DFCI.HARVARD.EDU

#### 9.3.4 Sites Performing Correlative Study

All sites will be participating in the collection of blood specimens for genomic analysis.

## 9.4 Plasma Collection for RET Diagnostic Assay Development

### 9.4.1 Collection of Specimen

The baseline plasma sample should be collected on Cycle 1 Day 1. Blood may be collected any time prior to the first dose of alectinib.

### 9.4.2 Handling of Specimen

- Draw two (2) 10 mL tubes of blood into K2-EDTA blood collection tubes labeled with the subject number, date, protocol number, and “RET.”
- Immediately centrifuge for 10 minutes at 1500 x g. NOTE: Brake switch must be off so the cell/plasma interface is not disturbed.
- Pipette the plasma layer from each collection tube into a single 15 mL fresh tube labeled with the subject number, date, protocol number, and RET. NOTE: Do not dip the tip of the pipette into the plasma/cell interface. Leave a thin plasma layer intact over the interface.
- Centrifuge the 15 mL tube containing the plasma only for 10 minutes at 3000 x g. NOTE: Brake switch must be off so the cell/plasma interface is not disturbed.
- Using a fresh pipette, distribute the plasma into two storage tubes each labeled with the protocol number, subject number, date, and “RET plasma.” NOTE: Do not dip the tip of the pipette into the plasma/cell interface. Leave a thin plasma layer intact over the interface.
- Store upright at -70°C until shipping.

### 9.4.3 Shipping of the Specimen

Laboratory and shipment address are provided in **Appendix H**.

### 9.4.4 Sites Performing Correlative Study

All sites will be participating in the collection of blood specimens for genomic analysis.

## 10. STUDY CALENDAR

Baseline evaluations are to be conducted within two weeks prior to start of protocol therapy, with the exception of the informed consent, baseline tumor imaging, and brain MRI which may be obtained up to 28 days prior to the start of protocol therapy. In the event that the subject's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

**Table 9: Study Calendar**

	Pre-Study <sup>A</sup>	Cycle 1 Day 1	Cycle 1 Day 8	Cycle 1 Day 15 <sup>B</sup>	Cycle 2 Day 1 <sup>C</sup>	Cycle 2 Day 15 <sup>B</sup>	Cycle 3 Day 1 <sup>C</sup>	Cycle 3 Day 15 <sup>B</sup>	Cycle 4 Day 1 <sup>C</sup>	Every 8 Weeks After Cycle 4 Day 1 <sup>C</sup>	Off Treatment <sup>D</sup>	Every 3 Months after Discontinuing Therapy <sup>E</sup>
Informed consent	X											
Demographics	X											
Medical history	X											
Concomitant meds	X	X-----X									X	
Physical exam <sup>F</sup>	X	X			X		X		X	X	X	
Vital signs <sup>G</sup>	X	X			X		X		X	X	X	
Height	X											
Weight	X	X		X			X		X	X	X	
ECOG Performance status	X	X		X	X		X		X	X	X	
CBC w/diff, plts <sup>H</sup>	X	X	X	X	X		X		X	X	X	
Serum chemistry <sup>I</sup>	X	X	X	X	X		X		X	X	X	
CPK <sup>J</sup>	X	X		X	X		X		X	X	X	
Liver Function Tests (LFTs) <sup>K</sup>	X <sup>L</sup>	X	X	X	X	X	X	X	X	X	X	
Urinalysis	X											
ECG <sup>M</sup>	X								X	X	X	
Adverse event evaluation	X	X-----X									X	
Tumor assessments <sup>N</sup>	X						X			X <sup>N</sup>	X	
MRI brain <sup>O</sup>	X						X			X <sup>O</sup>	X	
Serum β-HCG <sup>P</sup>	X	X									X	
Tissue collection <sup>Q</sup>	X										(X)	
Alectinib <sup>R</sup>		<i>As described in Section 5</i>										



**Table 9: Study Calendar**

	Pre-Study <sup>A</sup>	Cycle 1 Day 1	Cycle 1 Day 8	Cycle 1 Day 15 <sup>B</sup>	Cycle 2 Day 1 <sup>C</sup>	Cycle 2 Day 15 <sup>B</sup>	Cycle 3 Day 1 <sup>C</sup>	Cycle 3 Day 15 <sup>B</sup>	Cycle 4 Day 1 <sup>C</sup>	Every 8 Weeks After Cycle 4 Day 1 <sup>C</sup>	Off Treatment <sup>D</sup>	Every 3 Months after Discontinuing Therapy <sup>E</sup>
PK assessment (Phase 1) <sup>S</sup>		X	X	X	X		X		X			
Plasma collection <sup>T</sup>		X			X		X		X	X	X	
Blood for germline DNA collection <sup>U</sup>		X										
Telephone or Care Provider Contact												X

Footnotes:

(X) refers to an optional assessment/measurement/procedure

- A. Baseline evaluations are to be conducted within 14 days prior to start of protocol therapy, with the exception of the informed consent, baseline tumor imaging, and brain MRI which may be obtained up to 28 days prior to the start of protocol therapy.
- B. Day 15 visits have a  $\pm 3$  day scheduling window to accommodate adverse weather, holidays, vacations, etc.
- C. Starting with Cycle 2 Day 1, the start of a cycle may be delayed by up to 7 days for scheduling issues (vacations, holidays, adverse weather, etc.).
- D. Off-study evaluation to be completed within 30 days of the last dose of study medication. Note: follow up visits or other contact is required in order to identify SAEs during the 30 days following the end of study treatment for subjects.
- E. Subjects will be followed until death or withdrawal of consent after removal from protocol therapy. This follow up will be performed by review of the medical record, contact with care providers, and/or telephone contact as needed every 3-4 months.
- F. Routine physical exam.
- G. Vital signs to include heart rate, blood pressure, temperature, respiratory rate, and oxygen saturation (SpO<sub>2</sub>).
- H. Laboratory assessments to be completed locally. Results must be reviewed prior to dosing with the study agent.
- I. Sodium, potassium, chloride, CO<sub>2</sub>, blood urea nitrogen (BUN), creatinine, eGFR, glucose, globulin, calcium, magnesium, and phosphorus. Other tests may be ordered as clinically indicated. Laboratory assessments to be completed locally. Results must be reviewed prior to dosing with the study agent.
- J. Creatinine phosphokinase (CPK), additional testing as clinically indicated. Laboratory assessments to be completed locally.
- K. Liver function tests to include albumin, alkaline phosphatase, total and direct bilirubin, SGOT [AST], SGPT [ALT], total protein, and gamma-glutamyl transferase (GGT). Laboratory assessments to be completed locally. Results must be reviewed prior to dosing with the study agent.
- L. Screening liver function test results to be confirmed on two consecutive measurements obtained within 14 days prior to enrollment.
- M. Single ECG to be performed at each time point. ECGs to be collected at time points specified and as clinically indicated. ECGs collected on days where alectinib will be

**Table 9: Study Calendar**

	Pre-Study <sup>A</sup>	Cycle 1 Day 1	Cycle 1 Day 8	Cycle 1 Day 15 <sup>B</sup>	Cycle 2 Day 1 <sup>C</sup>	Cycle 2 Day 15 <sup>B</sup>	Cycle 3 Day 1 <sup>C</sup>	Cycle 3 Day 15 <sup>B</sup>	Cycle 4 Day 1 <sup>C</sup>	Every 8 Weeks After Cycle 4 Day 1 <sup>C</sup>	Off Treatment <sup>D</sup>	Every 3 Months after Discontinuing Therapy <sup>E</sup>
<p>administered may be performed any time prior to the first dose of alectinib on that day. QTc to be calculated using Bazett's formula.</p> <p>N. CT or MRI imaging of any disease involved site. Radiologic measurements should be performed at the end of cycle 2 (cycle 2 day 28) and at the end of every 2 cycles of treatment thereafter (i.e. cycle 4 day 28, cycle 6 day 28, and so on). There is a <math>\pm 7</math> day window on imaging evaluations.</p> <p>O. Baseline brain MRI required for all subjects enrolling to the phase 1 portion of the trial or enrolling to Cohort A or B of the phase 2 portion of the trial. Baseline brain MRI also required in any subject enrolling to any portion of the trial with a history of CNS disease or with suspected CNS disease. In subjects with brain metastases, subsequent MRIs are required at the end of cycle 2 (cycle 2 day 28) and at the end of every 2 cycles of treatment thereafter (i.e. cycle 4 day 28, cycle 6 day 28, and so on). There is a <math>\pm 7</math> day window on imaging evaluations. In subjects without brain metastases at baseline, subsequent brain MRIs are not required unless clinically indicated.</p> <p>P. Serum pregnancy test only required for women of childbearing potential. Childbearing potential defined as any female who is not post-menopausal (<math>\geq 12</math> months of non-therapy-induced amenorrhea) or surgically sterile (absence of ovaries and/or uterus).</p> <p>Q. A fresh tumor biopsy is required at baseline in subjects who have received prior RET TKIs or in TKI-naïve subjects for whom archival tissue is not available. An optional tumor biopsy can be obtained at the time of disease progression. Please see <b>Section 9.2</b> 9.2 for further detail.</p> <p>R. Adequate alectinib supply should be dispensed to accommodate any planned scheduling delays.</p> <p>S. Pharmacokinetic (PK) assessments should be performed as described in <b>Section 9.1</b>.</p> <p>T. Plasma genotyping baseline samples to be collected on Cycle 1 Day 1. Blood may be collected any time prior to the first dose of alectinib. Additional samples to be collected at any time on the first day of each subsequent cycle (the exact time of the sample should be recorded) and at the off study visit. Please see <b>Section 9.3</b> for more detail.</p> <p>U. Blood for germline DNA testing to be collected on Cycle 1 Day 1. Blood may be collected any time prior to the first dose of alectinib. Please see <b>Section 9.2</b> for further detail.</p>												



## 11. MEASUREMENT OF EFFECT

All subjects will be assessed by standard criteria. Although response is not the primary endpoint of the phase 1 portion of the trial, response will also be assessed during phase 1. For the purposes of this study, subjects should be re-evaluated every 8 weeks. In addition to a baseline scan, confirmatory scans will also be obtained not less than 4 weeks following initial documentation of an objective response.

### 11.1 Antitumor Effect – Solid Tumors

For the purposes of this study, subjects should be re-evaluated for response every 8 weeks. In addition to a baseline scan, confirmatory scans should also be obtained not less than 4 weeks following initial documentation of objective response.

Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

#### 11.1.1 Definitions

Evaluable for Target Disease response. Only those subjects 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 target disease response. These subjects will have their response classified according to the definitions stated below. (Note: Subjects who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response. Subjects who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

#### 11.1.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as  $\geq 20$  mm by chest x-ray or  $\geq 10$  mm with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.



Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be  $\geq 15$  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  $\geq 10$  to  $< 15$  mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all considered non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

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

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. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow up.

### 11.1.3 Methods for Evaluation of Disease

All measurements should be taken and recorded in metric notation using a ruler, calipers, or a digital measurement tool. All baseline evaluations should be performed as closely as

possible to the beginning of treatment and never more than 4 weeks 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 unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions. Clinical lesions will only be considered measurable when they are superficial (*e.g.*, skin nodules and palpable lymph nodes) and  $\geq 10$  mm in diameter as assessed using calipers (*e.g.*, skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray. Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung; however, CT is preferable.

Conventional CT and MRI. This guideline has defined measurability of lesions on CT scan based on the assumption that CT thickness is 5mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size of a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (*e.g.* for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

FDG-PET. While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

- (a) Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
- (b) No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a

pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

(c) FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

PET-CT. At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

MIBG (meta-iodobenzylguanidine). The following is recommended, to assure high quality images are obtained.

Subject preparation: Iodides, usually SSKI (saturated solution of potassium iodide), are administered to reduce thyroidal accumulation of free radioiodine, preferably beginning the day prior to injection and continuing for 3 additional days (4 days total). For infants and children, one drop t.i.d. is sufficient, for adolescents 2 drops t.i.d., and for adults 3 drops t.i.d. Subjects and/or parents are asked about exposure to potential interfering agents. If none is noted, an indwelling intravenous line is established. The dose of MIBG is administered by slow intravenous injection over 90 seconds.

Images from the head to the distal lower extremities should be obtained.

I-123MIBG scintigraphy is performed to obtain both planar and tomographic images.

Planar: Anterior and posterior views from the top of the head to the proximal lower extremities are obtained for 10 minutes at 24 hours and occasionally at 48 hours following injection of 10 mCi/1.7 square meters of body surface area (~150  $\mu$ Ci/kg, maximum 10 mCi). Anterior views of the distal lower extremities are adequate. A large field of view dual head gamma camera with low energy collimators is preferred.

SPECT: Most subjects receiving I-123 MIBG also undergo SPECT at 24 hours, using

a single or multi-headed camera with a low energy collimator. The camera is rotated through 360 degrees, 120 projections at 25 seconds per stop. Data are reconstructed using filtered back projections with a Butterworth filter and a cut off frequency of 0.2-0.5. SPECT/CT may be performed at institutions with this capacity.

Ultrasound. Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure from CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy. The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers. Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a subject to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [*JNCI* 96:487-488, 2004; *J Clin Oncol* 17, 3461-3467, 1999; *J Clin Oncol* 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [*JNCI* 92:1534-1535, 2000].

Cytology, Histology. These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (*e.g.*, residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

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

#### 11.1.4 Response Criteria

##### 11.1.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) 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 (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

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.

#### 11.1.4.2 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).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a subject to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of “non-target” lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

#### 11.1.4.3 Evaluation of New Lesions

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 (for example, some ‘new’ bone lesions may be simply 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.

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

**For Subjects with Measurable Disease (i.e., Target Disease)**

<b>Table 10: Criteria for Subjects with Measurable Disease</b>				
<b>Target Lesions</b>	<b>Non-Target Lesions</b>	<b>New Lesions</b>	<b>Overall Response</b>	<b>Best Overall Response when Confirmation is Required*</b>
CR	CR	No	CR	$\geq 4$ wks Confirmation**
CR	Non-CR/Non-PD	No	PR	$\geq 4$ 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 $\geq 4$ 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	
* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion. ** Only for non-randomized trials with response as primary endpoint. *** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.  <u>Note:</u> Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as “ <i>symptomatic deterioration.</i> ” Every effort should be made to document the objective progression even after discontinuation of treatment.				

**For Subjects with Non-Measurable Disease (i.e., Non-Target Disease)**

<b>Table 11: Criteria for Subjects with Non-Measurable Disease</b>		
<b>Non-Target Lesions</b>	<b>New Lesions</b>	<b>Overall Response</b>
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD
* ‘Non-CR/non-PD’ is preferred over ‘stable disease’ for non-target disease since SD is		

increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

#### 11.1.5 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 recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started, or death due to any cause. Subjects without events reported are censored at the last disease evaluation).

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 progressive disease is objectively documented, or death due to any cause. Subjects without events reported are censored at the last disease evaluation.

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, including the baseline measurements.

#### 11.1.6 Progression-Free Survival

Overall Survival: Overall Survival (OS) is defined as the time from randomization (or registration) to death due to any cause, or censored at date last known alive.

Progression-Free Survival: Progression-Free Survival (PFS) is defined as the time from randomization (or registration) to the earlier of progression or death due to any cause. Subjects alive without disease progression are censored at date of last disease evaluation.

#### 11.1.7 Response Review

The DF/HCC Tumor Imaging Metrics Core (TIMC) will be utilized for central review of imaging measurements.

## 12. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in **Section 7** (Adverse Events: List and Reporting Requirements).

### 12.1 **Data Reporting**

#### 12.1.1 Method

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



### 12.1.2 Responsibility for Data Submission

Investigative sites within DF/HCC or DF/PCC are responsible for submitting data and/or data forms to the ODQ according to the schedule set by the ODQ.

## 12.2 **Data Safety Monitoring**

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

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

## 12.3 **Multicenter Guidelines**

This protocol will adhere to the policies and requirements of the DF/HCC Multi-Center Data and Safety Monitoring Plan. The specific responsibilities of the Overall PI, Coordinating Center, and Participating Institutions and the procedures for auditing are presented in Appendix E.

- The Overall PI/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 study agent directly from the supplier. A participating site may order the agent only after the initial IRB approval for the site has been forwarded to the Coordinating Center.

## 12.4 **Collaborative Agreements Language**

N/A

## 12.5 Genentech/Roche Reporting Requirements

Any study report submitted to the FDA by the Sponsor-Investigator should be copied to Genentech/Roche. This includes all IND annual reports and the Clinical Study Report (final study report). Additionally, any literature articles that are a result of the study should be sent to Genentech/Roche. Copies of such reports should be emailed to the assigned Clinical Operations contact for the study at [alectinib-gsur@gene.com](mailto:alectinib-gsur@gene.com), attention Alectinib IIS Clinical Operations.

Additional Reporting Requirements for IND Holders: For Investigator-Initiated IND Studies, some additional reporting requirements for the FDA apply in accordance with the guidance set forth in 21 CFR § 600.80.

Events meeting the following criteria need to be submitted to the Food and Drug Administration (FDA) as expedited IND Safety Reports according to the following guidance and timelines:

### **7 Calendar Day Telephone or Fax Report:**

The Investigator is required to notify the FDA of any fatal or life-threatening adverse event that is unexpected and assessed by the Investigator to be possibly related to the use of alectinib. An unexpected adverse event is one that is not already described in the alectinib Investigator Brochure. Such reports are to be telephoned or faxed to the FDA and Genentech within 7 calendar days of first learning of the event.

### **15 Calendar Day Written Report:**

The Investigator is also required to notify the FDA and all participating investigators, in a written IND Safety Report, of any serious, unexpected AE that is considered reasonably or possibly related to the use of alectinib. An unexpected adverse event is one that is not already described in the alectinib investigator brochure.

Written IND Safety reports should include an Analysis of Similar Events in accordance with regulation 21 CFR § 312.32. All safety reports previously filed by the investigator with the IND concerning similar events should be analyzed and the significance of the new report in light of the previous, similar reports commented on.

Written IND safety reports with Analysis of Similar Events are to be submitted to the FDA, Genentech, and all participating investigators within 15 calendar days of first learning of the event. The FDA prefers these reports on a MedWatch 3500 form, but alternative formats are acceptable (e.g., summary letter).

### **FDA fax number for IND Safety Reports:**

Fax: 1 (800) FDA 0178

**All IND annual reports submitted to the FDA by the Sponsor-Investigator should be copied to Genentech/Roche.** Copies of such reports should be faxed to Genentech/Roche Drug Safety:

Fax: (650) 225-4682 or (650) 225-4630

## 12.6 Trial Completion

The overall PI will forward a copy of the Publication to Roche/Genentech upon completion of the Study.

## 13. STATISTICAL CONSIDERATIONS

The phase 1 dose escalation portion of this study will evaluate the safety and tolerability of alectinib to establish the MTD and RP2D, and preliminarily explore the antitumor activity of alectinib in subjects with RET- or ALK-positive NSCLC. The phase 2 portion of this study will evaluate the antitumor activity of alectinib in RET-positive NSCLC and thyroid cancer and continue to evaluate the safety of the RP2D.

The phase 1 portion of the trial will require a minimum of twelve and a maximum of 18 subjects to determine the MTD and RP2D. Following identification of the MTD and RP2D, a three-arm phase 2 study will commence.

### 13.1 Study Design/Endpoints

#### 13.1.1 Phase 1 Portion

Primary Endpoint:

The primary endpoint of the phase 1 portion of this study is to assess safety and tolerability of alectinib as a single agent at increasing dose levels in subjects with advanced RET- or ALK-positive NSCLC in order to estimate the MTD and select the RP2D. Toxicity will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. DLTs are defined in **Section 5.4** and the dose escalation schedule and decision rules are located in **Section 5.1**.

Six subjects will be enrolled to each dose level. The MAD of the study medication will be defined as the dose level where at least two subjects develop toxicities consistent with a DLT definition. In this situation, the dose level immediately below the MAD will be defined as the MTD. In the situation where none of the dose levels have  $\geq 2$  DLTs, the MTD will be the highest dose administered (i.e. dose level 2).

The MTD will be defined in a minimum of six subjects. Determination of the RP2D will be based on the MTD, PK data, and cumulative toxicity data that also factors in toxicities observed beyond the DLT assessment window. In the event that dose level 1 is found to be intolerable (with  $\geq 2$  subjects experiencing a DLT), the fallback dose level -1 will be explored. If the fallback dose level is also found to be intolerable, the phase 1 portion of the trial will be discontinued and the phase 2 portion will commence at the FDA approved dose of 600 mg by mouth twice daily.

The probabilities of escalation if the true but unknown DLT rates are 10, 20, 30, 40, and

50% are 89, 66, 42, 23 and 11%, respectively.

#### Secondary Endpoints:

PK analyses will be performed on plasma taken from subjects during the phase 1 portion of this study in collaboration with Genentech/Roche. PK parameters will be estimated using non-compartmental models. Comparisons across dose levels will be made to assess proportionality. ORR, PFS, and DoR will be measured by RECIST 1.1 criteria. Subjects with central nervous system disease will be monitored for the duration of CNS response, CNS ORR, and PFS rates separately from extracranial response.

#### 13.1.2 Phase 2 Portion

##### Primary Endpoint:

The primary objective of the phase 2 portion of this study is to evaluate the objective response rate (ORR) of alectinib at the RP2D utilizing RECIST 1.1 criteria in subjects with advanced RET-positive NSCLC and advanced RET-positive thyroid cancer.

For the dose expansion cohorts A and B, each NSCLC cohort will follow its own Simon two-stage design in which 16 subjects will be enrolled to a first stage of accrual. If a total of 2 or more responses (complete or partial) are observed among those 16 subjects, an additional 9 subjects will be enrolled for a total of 25 subjects in that cohort. If 1 or fewer responses are observed among the first 16 subjects in either cohort, then that cohort will be stopped early. Otherwise, a total of 5 or more responses are needed among the group of 25 subjects in a single cohort to declare study success for that cohort. This design has 90% power to test the alternative hypothesis that the underlying response rate associated with alectinib treatment is 0.30 against the null hypothesis that the response rate is  $< 0.10$  while testing at a one-sided significance level of 0.10. The probability that a cohort will stop early under the null is 0.51.

For dose expansion cohort C, a cohort of 16 subjects with thyroid cancer with RET alterations will be enrolled. Alectinib will be considered promising if it confers a 20% response rate in this subject population. If the true but unknown underlying response is in fact 20%, then there is a 0.86 probability of observing 2 or more responses in this cohort; if, however, the drug is ineffective and the underlying response rate is low (5%) then the probability that we observe at least 2 responses is 0.19.

##### Secondary Endpoints:

Secondary efficacy measures include PFS and OS, as well as the DoR. Subjects with central nervous system disease will be monitored for the duration of CNS response and CNS PFS rates separately from extracranial response.

Progression-free survival (PFS) is defined as the time from registration to documented disease progression or death from any cause, whichever occurs first. Subjects who have

not experienced an event of interest by the time of analysis will be censored at the date of the last disease assessment. For cases that experience death without progression, the death will be counted as an event only if the death occurs within 60 days of the time following the date last known progression-free. Overall survival is defined as the time from registration to death from any cause, and subjects who are thought to be alive at the time of final analysis will be censored at the last date of contact. Duration of response is defined as the time from documented objective response until progression or death, whichever occurs first. Best objective response will be evaluated via RECIST v.1.1 criteria. Patients who are deemed unevaluable for response will be included in the denominator of the response calculations assuming the patients are eligible and received treatment. Patients in the expansion cohorts will not be replaced.

The safety of the RP2D will continue to be followed during phase 2 and toxicities will be reported using CTCAE v.4.03 criteria.

Time-to-event distributions will be estimated using the Kaplan-Meier method. Comparisons of subgroups will be made using the log rank test and Cox modeling. Response and toxicity rates will be compared between subgroups using Fisher's exact tests; multivariable logistic regression modeling will be used to adjust for the effect of any covariates that are associated with these categorical outcomes.

### 13.1.3 Correlative Endpoints (Both Trial Phases)

We plan to analyze the correlatives by cohort rather than combining across all 3 expansion groups.

Tumor DNA levels obtained from the serial collection of cfDNA samples will be examined to explore whether clinical outcome is associated with fluctuations in DNA levels following the administration of alectinib therapy.

For the aims related to plasma genotyping and serial plasma collection, a variety of statistical techniques will be employed for the analyses. The rate of change at a particular time point may be compared to baseline measures of cfDNA and that measure will be analyzed for association with subject demographics and/or disease characteristics using the Kruskal Wallis test. Landmark analyses of PFS and OS in which the landmark time is defined by the cfDNA measurements at a particular time point, may be used as well. Presence or absence of mutations in plasma will be analyzed for association with other variables using Fisher's exact test. To account for the repeated measures of plasma over time, we may potentially use these data as time varying covariates in multivariable Cox models to study their impact on outcomes like PFS and OS. If we are to dichotomize patients according to the median change in plasma levels from baseline to a second timepoint such as cycle 2 day 1, with at least 16 patients in the analysis we would have 80% power to detect a difference in response rates of 20% among those with low plasma response and 80% among those with high plasma response while testing with a one-sided 0.10 level Fisher's exact test.

The results of the NGS obtained on the fresh and archival tumor tissue samples will be compared to the clinical outcomes of the subjects to explore molecular markers of response and resistance. The role of the tumor specimen is identification of mutations present prior to enrollment onto this trial; however, when paired with genomic results obtained from the biopsy at progression, it is of interest to identify new alterations that were not present at baseline. Initial analyses of these data will utilize tests for association comparing the frequency of a particular genomic aberration at baseline and at progression (for example, using McNemar’s test) and association between alterations and baseline characteristics (for example, using Fisher’s exact test). More sophisticated analyses may include multivariable logistic regression modeling and/or competing risks analysis, however it is expected that analyzable results will not be obtained from 100% of subjects (either due to things like assay failure, inability to biopsy at progression due to poor subject health, etc). If 50% of patients developed a genetic abnormality at the time of progression, with at least 16 patients in the analysis we would have 80% power to detect a difference in response rates of 20% and 80% between those with/without the resistance abnormality while testing with a one-sided 0.10 level Fisher’s exact test.

With respect to the biopsies at the time of study entry: for patients who are TKI naïve, we are asking for archival tissue so that we can confirm the RET rearrangement centrally, and if no tissue is available, then a biopsy would be needed to confirm study eligibility. For patients who are TKI pre-treated, we are requesting a biopsy to determine the mechanism of resistance to the prior TKI. The latter samples will be explored for the presence of genetic abnormalities that may explain resistance to prior TKI; with a sample size of 16 patients the maximum width of the 95% exact binomial confidence interval for the frequency of a particular finding is 51%; for a sample size of 20 patients it is 46%.

### 13.2 Sample Size, Accrual Rate and Study Duration

The anticipated accrual rate for the phase 1 portion of the trial across multiple sites is two subjects per month. A minimum of 12 subjects and a maximum of 12 subjects will be required to determine the MTD and RP2D. The planned total sample size for the phase 2 portion of this study is up to 66 subjects. The expected accrual rate for the phase 2 portion of the trial is two subjects per month across multiple sites.

The estimated total duration of trial recruitment is 24 months with a follow-up period of up to 12 months after the last subject is accrued to observe the subject’s response after the 12th cycle of therapy. The total study duration is estimated to be 3 years.

Ethnic Category	Sex/Gender		
	Females	Males	Total
Hispanic or Latino	3	3	6

Not Hispanic or Latino	36	+	36	=	72
<b>Ethnic Category: Total of all subjects</b>	39 (A1)	+	39 (B1)	=	78 (C1)
<b>Racial Category</b>					
American Indian or Alaskan Native	0	+	0	=	0
Asian	2	+	2	=	4
Black or African American	4	+	4	=	8
Native Hawaiian or other Pacific Islander	0	+	0	=	0
White	33	+	33	=	66
<b>Racial Category: Total of all subjects</b>	39 (A2)	+	39 (B2)	=	78 (C2)
	(A1 = A2)		(B1 = B2)		(C1 = C2)

### 13.3 Stratification Factors

N/A

### 13.4 Analysis of Primary and Secondary Endpoints

The primary and secondary analyses will include all eligible subjects who started assigned therapy. The exception to this includes the planned analysis of toxicity data, which will include all subjects who received study drug regardless of eligibility.

In the event that a subject enrolled to the MTD/RP2D dose level of the phase 1 trial met all inclusion criteria for entrance to Cohort A (RET-positive NSCLC, RET TKI naive) or Cohort B (RET-positive NSCLC, RET TKI pre-treated) of the phase 2 trial, that subject will be included in the phase 2 analysis of the trial. This will work such that subjects otherwise qualifying for phase 2 who enroll at the MTD/RP2D of part one will be double counted in both the phase 1 and phase 2 analyses, and the corresponding phase 2 cohort(s) will subsequently enroll fewer new subjects to reach the enrollment target.

In the event that there are missing data points, no imputation of the missing data will be conducted.

### 13.5 Reporting and Exclusions

#### 13.5.1 Evaluation of Toxicity

All subjects will be evaluable for toxicity from the time of their first dose of study medication.

#### 13.5.2 Evaluation of the Primary Efficacy Endpoint

All eligible subjects included in the study who started on assigned therapy will be assessed for response, even if there are major protocol therapy deviations. Each subject

should be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data). By arbitrary convention, category 9 usually designates the "unknown" status of any type of data in a clinical database.

#### **14. PUBLICATION PLAN**

The results should be made public within 24 months of reaching the end of the study. The end of the study is the time point at which the last data items are to be reported, or after the outcome data are sufficiently mature for analysis, as defined in the section on Sample Size, Accrual Rate and Study Duration. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. A full report of the outcomes should be made public no later than three (3) years after the end of the study.



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**APPENDIX A PERFORMANCE STATUS CRITERIA**

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	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 ( <i>e.g.</i> , 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      MODIFICATION OF DIET IN RENAL DISEASE (MDRD) FORMULA**

The estimated glomerular filtration rate (eGFR) will be calculated on the basis of the following formula:

$$\text{eGFR [mL/min/1.73 m}^2\text{]} = 175 \times \text{SCRT}^{-1.154} \times \text{AGE}^{-0.203} [\times 0.742 \text{ if female}] \\ [\times 1.212 \text{ if African American}] \text{ (conventional units)}$$

where SCRT = serum creatinine in conventional units, i.e. mg/dL.

The following conversion factor should be used in case the serum creatinine value is provided by the lab in  $\mu\text{mol/L}$  units:

$$\text{Serum creatinine [mg/dL]} = \text{Serum creatinine [\mu mol/L]} \times 0.0113$$

### **References:**

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## APPENDIX C CONCOMITANT MEDICATION CONSIDERATIONS

### List of Substrates, Inhibitors and Inducers of Drug-Metabolizing Enzymes and Transporters

This representative list is not intended to be an exhaustive list. Each subject’s concomitant medications should be carefully considered by the investigator with regard to the risk-benefit for the particular subject and appropriate monitoring, including any concomitant medication, dose adjustment, or therapeutic alternatives, which should be determined by the investigator caring for the subject.

Any CYP3A Inducers and Inhibitors are prohibited from Cycle 1 Day 1 – Cycle 2 Day 8 of the phase 1 trial and potent CYP3A Inducers and Inhibitors are prohibited beyond Cycle 2 Day 8 of the phase 1 trial and in phase 2 of the trial as described in **Protocol Section 5.5**:

Prohibited Medications	
CYP3A Inducers	CYP3A Potent Inhibitors
avasimibe, aminoglutethimide, barbiturates, carbamazepine, dexamethasone, efavirenz, ethosuximide, garlic supplements, glucocorticoids, glutethimide, griseofulvin, modafinil, nafcillin, nevirapine, oxcarbazepine, phenobarbital, phenytoin, pioglitazone, primidone, rifabutin, rifampin, rifapentine, St. John’s wort, troglitazone	aprepitant, atazanavir, boceprevir, ciprofloxacin, clarithromycin, conivaptan, diltiazem, erythromycin, fluconazole, grapefruit, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, troleandomycin, verapamil, voriconazole

The following medications should be used with caution as described in **Protocol Section 5.5**:

P-gp	
Substrates	Inducers
aliskiren, ambrisentan, colchicine, dabigatran, digoxin, everolimus, fexofenadine, imatinib, lapatinib, maraviroc, nilotinib, posaconazole, pravastatin, ranolazine, saxagliptin, sirolimus, sitagliptin, talinolol, tolvaptan, topotecan	avasimibe, carbamazepine, phenytoin, rifampin, St John’s wort, tipranavir

The information in this appendix is adapted from Levien and Baker 2003<sup>1</sup>, Zhang 2010<sup>2</sup>, and FDA Guidance on Drug-Drug Interactions.

Also see:

- <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm>
- <http://medicine.iupui.edu/clinpharm/ddis/table.aspx>

Potent inhibitors of CYP3A are those considered to be “strong CYP3A inhibitors” previously shown to result in a ≥ 5-fold increase in the AUC of a concomitantly administered CYP3A substrate. These are based on the available

<sup>1</sup> Levien TL, and Baker DE Cytochrome P450 Drug Interactions. Therapeutic Research Center Pharmacist’s Letter/Prescriber’s Letter [resource on the Internet]. 2003. Available from: [www.pharmacistsletter.com](http://www.pharmacistsletter.com) and [www.prescribersletter.com](http://www.prescribersletter.com).

<sup>2</sup> Zhang L. Transporter Mediated Drug-Drug Interactions. FDA. Clinical Pharmacology Advisory Committee Meeting Topic 4: Transporter-Mediated Drug-Drug Interactions Atlanta, GA, March 17, 2010.

published literature and, thus, are not considered exhaustive or inclusive. See FDA Guidance on Drug-Drug Interactions for further detail.

**APPENDIX D GENENTECH/ROCHE SAFETY REPORTING FAX COVER SHEET**



**SAFETY REPORTING FAX COVER SHEET  
Genentech Supported Research**

**AE / SAE FAX No: (650) 225-4682**

**Alternate Fax No: (650) 225-4630**

<b>Genentech Study Number</b>	
<b>Principal Investigator</b>	
<b>Site Name</b>	
<b>Reporter name</b>	
<b>Reporter Telephone #</b>	
<b>Reporter Fax #</b>	

<b>Initial Report Date (DD/MON/YY)</b>	/ /
<b>Follow-up Report Date (DD/MON/YY)</b>	/ /

<b>Subject Initials (Enter a dash if subject has no middle name)</b>	[ ]-[ ]-[ ]
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SAE or Safety Reporting questions, contact Genentech Drug Safety: (888) 835-2555

PLEASE PLACE MEDWATCH REPORT or SAFETY REPORT BEHIND THIS COVER SHEET

**APPENDIX E            MULTICENTER GUIDELINES**

*DFCI IRB Protocol #: 17-080*

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





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## 15. 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 serves as a reference for any sites external to DF/HCC that are participating in a DF/HCC clinical trial.

### 15.1 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.

### 15.2 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), Boston Children's Hospital (BCH), 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 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. FDA). 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 Overall 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.

**DF/HCC Office of Data Quality (ODQ):** A group within DF/HCC responsible ensuring high-quality standards are used for data collection and the ongoing management of clinical trials, auditing, and data and safety monitoring. ODQ also coordinates quality assurance efforts related to multi-center clinical research.

**DF/HCC Clinical Trials Research Informatics Office (CTRIO):** A group within DF/HCC responsible for providing a comprehensive data management platform for managing clinical trial data.

## 16. 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:

### 16.1 DF/HCC Sponsor

The DF/HCC Sponsor, Mark Awad MD, PhD 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.
- Include 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 member 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 applicable 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 FDA reporting requirements are met.
- Review data and maintain timely submission of data for study analysis.
- Act as the single liaison with the FDA..
- 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.
- Monitor accrual and address Participating Institutions that are not meeting their accrual requirements.

## **16.2 Coordinating Center**

The general responsibilities of the Coordinating Center may include but are not limited to:

- Assist in protocol development.
- Maintain FDA correspondence, as applicable.
- Review registration materials for eligibility and register participants from Participating Institutions in the DF/HCC clinical trial management system (CTMS).
- Distribute protocol and informed consent document updates to Participating Institutions as needed.
- Oversee the data collection process from Participating Institutions.
- Maintain documentation of Serious Adverse Event (SAE) reports and deviations/violation submitted by Participating Institutions and provide to the DF/HCC Sponsor for timely review and submission to the DFCI IRB, as necessary.
- Distribute serious adverse events reported to the DF/HCC Sponsor that fall under the DFCI IRB Adverse Event Reporting Policy to all Participating Institutions.
- Provide Participating Institutions with information regarding DF/HCC requirements that they will be expected to comply with.
- Carry out plan to monitor Participating Institutions either by on-site or remote monitoring.
- Maintain Regulatory documents of all Participating Institutions which includes but is not limited to the following: local IRB approvals/notifications from all Participating Institutions, confirmation of Federalwide Assurances (FWAs) for all sites, all SAE submissions, Screening Logs for all sites, IRB approved consents for all sites
- Conduct regular communications with all Participating Institutions (conference calls, emails, etc) and maintain documentation all relevant communications.

## **16.3 Participating Institution**

Each Participating Institution is expected to comply with all applicable federal regulations and DF/HCC requirements, the protocol and HIPAA requirements.

The general responsibilities for each Participating Institution may include but are not limited to:

- Document the delegation of research specific activities to study personnel.
- Commit to the accrual of participants to the protocol.
- Submit protocol and/or amendments to their local IRB.
- Maintain regulatory files as per sponsor requirements.

- Provide the Coordinating Center with regulatory documents or source documents as requested.
- Participate in protocol training prior to enrolling participants and throughout the trial as required (i.e. teleconferences).
- Update Coordinating Center with research staff changes on a timely basis.
- Register participants through the Coordinating Center prior to beginning research related activities.
- Submit Serious Adverse Event (SAE) reports to local IRB per institutional requirements and to the Coordinating Center, in accordance with DF/HCC requirements..
- Submit protocol deviations and violations to local IRB per institutional requirements and to the DF/HCC Sponsor in accordance with DF/HCC requirements.
- Order, store and dispense 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.
- Participate in any quality assurance activities and meet with monitors or auditors at the conclusion of a visit to review findings.
- Promptly provide follow-up and/or corrective action plans for any monitoring queries or audit findings.

## **17. 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.

### **17.1 Protocol Distribution**

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

### **17.2 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.

### **17.3 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 upon request.

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 for all consent versions.

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 for all interventional drug, biologic, or device research.

### **17.4 IRB Documentation**

The following must be on file with the Coordinating Center:

- Initial approval letter of the Participating Institution's IRB.
- Copy of the Informed Consent Form(s) approved by the Participating Institution's IRB.
- Participating Institution's IRB approval for all amendments.
- Annual approval letters by the Participating Institution's IRB.

### **17.5 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.

## **17.6 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 protected health information during the course of a study, the study participant must sign an authorization statement. This authorization statement may or may not be separate from the informed consent document. The Coordinating Center, with the approval from the DFCI IRB, will provide a consent template, with information regarding authorization for the disclosure of protected health information.

The DF/HCC Sponsor will use all efforts to limit its use of protected health information in its trials. However, because of the nature of these trials, certain protected health information must be collected. DF/HCC has chosen to use authorizations, signed by the participant in the trial, rather than limited data sets with data use agreements.

### **17.6.1 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 should be de-identified. It is recommended that the assigned protocol case number (as described below) be used for all participant specific documents. Participant initials may be included or retained for cross verification of identification.

## **17.7 DF/HCC Multi-Center Protocol Registration Policy**

### **17.7.1 Participant Registration and Randomization**

To register a subject, the following documents should be completed by the research nurse or data manager and faxed or e-mailed to the Study Coordinator:

- Copy of the clinic visit note documenting the subject's history and physical exam
- Copies of the required clinical laboratory tests including: CBC with differential, serum chemistries, CPK, liver function tests, urinalysis, and if applicable serum  $\beta$ -hCG

- Copies of the pathology report(s) and documentation of RET or ALK mutational status
- Baseline tumor imaging assessment reports
- Screening ECG report
- Signed subject consent form
- HIPAA authorization form
- Completed ODQ 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 Clinical Trial Management System (CTMS).
- Upon receiving confirmation of registration, the Coordinating Center will inform the Participating Institution and provide the study specific participant case number, and, if applicable, assigned treatment and/or dose level.

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

### 17.7.2 Initiation of Therapy

Participants must be registered with the DF/HCC CTMS before the initiation of treatment or other protocol-specific interventions. Treatment and other protocol-specific interventions may not be initiated until the Participating Institution receives confirmation of the participant's registration from the Coordinating Center. The DF/HCC Sponsor and DFCI IRB must be notified of any violations to this policy.

### 17.7.3 Eligibility Exceptions

No exceptions to the eligibility requirements for a protocol without DFCI IRB approval will be permitted. All Participating Institutions are required to fully comply with this requirement. The process for requesting an eligibility exception is defined below.

## 17.8 DF/HCC Protocol Case Number

At the time of registration, the following identifiers are required for all subjects: initials, date of birth, gender, race and ethnicity. Once eligibility has been established and the participant successfully registered, the participant is assigned a unique protocol case number. Participating Institutions should submit all de-identified subsequent



communication and documents to the Coordinating Center, using this case number to identify the subject.

### **17.8.1 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 departures 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.

### **17.8.2 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 departure that was not *prospectively approved* by the IRB prior to its initiation or implementation.

### **17.8.3 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. The deviation may not be implemented without all required approvals.

All protocol violations must be sent to the Coordinating Center in a timely manner. The Coordinating Center will provide training for the requirements for the reporting of violations.

Coordinating Center: Upon receipt of the violation/deviation report from the Participating Institution, the Coordinating Center will submit the report to the DF/HCC Sponsor for review. Subsequently, the Participating Institution's IRB violation/deviation report will be submitted to the DFCI IRB for review per DFCI IRB reporting guidelines. DF/HCC will forward all violation reports to CTEP via an internal DF/HCC process, as applicable.

## **17.9 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 therapy 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.

### **17.9.1 Guidelines for Reporting Serious Adverse Events**

Guidelines for reporting Adverse Events (AEs) and Serious Adverse Events (SAEs) are detailed in **protocol section 7**.

Participating Institutions must report the SAEs to the DF/HCC Sponsor and the Coordinating Center following the [DFCI IRB Adverse Event Reporting Policy](#).

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 Institutions will review and submit to their IRB according to their institutional policies and procedures

### **17.9.2 Guidelines for Processing IND Safety Reports**

The DF/HCC Sponsor will review all IND Safety Reports and ensure that all IND Safety Reports are distributed to the Participating Institutions. Participating Institutions will review/submit to their IRB according to their institutional policies and procedures.

## **17.10 Data Management**

DF/HCC CTRIO develops case report forms (CRF/eCRFs), for use with the protocol. These forms are designed to collect data for each study. DF/HCC CTRIO provides a web based training for all eCRF users.

#### **17.10.1 Data Forms Review**

Data submissions are monitored for timeliness and completeness of submission. If study forms are received with missing or questionable data, the submitting institution will receive a written or electronic query from the DF/HCC Office of Data Quality, Coordinating Center, or designee.

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.

If study forms are not submitted on schedule, the Participating Institution will periodically receive a Missing Form Report from the Coordinating Center noting the missing forms.

### **18. REQUISITIONING INVESTIGATIONAL DRUG**

The ordering of investigational agent is specified in the **protocol section 8**.

Participating Institutions should order their own agent regardless of the supplier. If the agent is commercially available, check with the local Director of Pharmacy and/or the Research Pharmacy to ensure that the agent is in stock. If the agent is not stocked, ensure that the agent can be ordered once the protocol is approved by the local IRB.

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., the pharmaceutical company) so that any regulatory responsibilities can be met in a timely fashion.

### **19. 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 DF/HCC Office of Data Quality, provides quality control oversight for the protocol.

#### **19.1 Ongoing Monitoring of Protocol Compliance**

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

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 practices may include but are not limited to source data verification, and review and analysis of eligibility requirements, informed consent procedures, adverse events and all associated documentation, review of study drug administration/treatment, regulatory files, protocol departures reporting, pharmacy records, response assessments, and data management.

During the Phase 1 Dose Escalation portion of the study, the participating institutions will be required to participate in bi-weekly teleconferences initiated by the Coordinating Center. “Newsletters” highlighting overall protocol progress and important announcements will be distributed regularly.

Remote monitoring will be performed on an as-needed basis by the Clinical Trial Monitor. Sites will be asked to provide source documentation via fax, email, or mail as specified by the Clinical Trial Monitor for virtual monitoring.

On-Site Monitoring will occur on an as needed basis. Additionally, one initial site visit will occur within 6 months of the first participant enrolling, and during years 2, 3, and 4, a minimum of 4 on-site visits will occur per year. Participating Institutions will be required to provide access to participants’ complete medical record and source documents for source documentation verification during the visits. In addition, Participating Institutions should provide access to regulatory documents, pharmacy records, local policies related to the conduct of research, and any other trial-related documentation maintained by the Participating Site. On-site monitoring visits can be substituted with remote (virtual) monitoring visits at the discretion of the Principal Investigator.

## **19.2 Monitoring Reports**

The DF/HCC Sponsor will review all monitoring reports to ensure protocol compliance. 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.

## **19.3 Accrual Monitoring**

Prior to extending a protocol to an external site, the DF/HCC Sponsor will establish accrual requirements for each participating institution. Accrual will be monitored for each participating institution by the DF/HCC Sponsor or designee. Sites that are not meeting their accrual expectations may be subject to termination. Accrual expectations for each site will be 2 patients annually.

## **20. AUDITING: QUALITY ASSURANCE**

Auditing is a method of Quality Assurance and involves 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, applicable Standard Operating Procedures (SOPs), and the Code of Federal Regulations (CFR).

### **20.1 DF/HCC Internal Audits**

All Participating Institutions are subject to audit by the DF/HCC Office of Data Quality (ODQ). Typically, 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.

### **20.2 Audit Notifications**

It is the Participating Institution's responsibility to notify the Coordinating Center of all scheduled audit dates (internal or NCI) 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.

### **20.3 Audit Reports**

The DF/HCC Sponsor will review all final audit reports and corrective action plans, if applicable. The Coordinating Center, must forward any reports to the DF/HCC ODQ per DF/HCC policy for review by the DF/HCC Audit Committee. For unacceptable audits, the DF/HCC Audit Committee would forward the final audit report and corrective action plan to the DFCI IRB as applicable.

### **20.4 Participating Institution Performance**

The DF/HCC Sponsor and DFCI IRB are charged with considering the totality of an institution's performance in considering institutional participation in the protocol.

Participating Institutions that fail to meet the performance goals of accrual, submission of timely and accurate data, adherence to protocol requirements, and compliance with state and federal regulations, may 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. A DF/HCC Sponsor and/or the DFCI IRB may terminate a site's participation if it is determined that a site is not fulfilling its responsibilities as described above.

**APPENDIX F TUMOR TISSUE AND GERMLINE BLOOD SAMPLE REQUISITION FORM**

**17-080 - TUMOR TISSUE AND GERMLINE BLOOD SAMPLE REQUISITION FORM  
A Phase 1/2 Study of alectinib in RET-rearranged non-small cell lung cancer or RET-mutated thyroid cancer**

Complete this form and include with the specimen shipment. Label ALL materials with subject initials, DFCI subject study ID, and the date the specimen was obtained. Include a pathology report with any archival tissue specimens being submitted.

Ship specimen(s) to: The Jänne Laboratory, Dana-Farber Cancer Institute, 360 Longwood Avenue, LC4118, Boston MA 02215

**Specimen Information**

Subject Initials (FML): \_\_\_\_\_ DFCI Subject Study ID Number: \_\_\_\_\_ Date specimen(s) shipped: \_\_\_\_\_

Specimen Type <i>(indicate inclusion in shipment by checking box)</i>	Pathology Number(s) or Serial Coding	Quantity submitted	Date specimen obtained	Time specimen obtained
<input type="checkbox"/> Archival Tissue Block				
<input type="checkbox"/> Archival Tissue Slides				
<input type="checkbox"/> Biopsy core(s) - FFPE				
<input type="checkbox"/> Germline blood sample				
<input type="checkbox"/> Other, specify: _____				
<input type="checkbox"/> Other, specify: _____				

Responsible contact: \_\_\_\_\_

Email: \_\_\_\_\_

Phone number: \_\_\_\_\_

Site: \_\_\_\_\_

Mailing address (to \_\_\_\_\_

return slides): \_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_



**APPENDIX G PLASMA GENOTYPING SAMPLE REQUISITION FORM**

**17-080 - PLASMA GENOTYPING SAMPLE REQUISITION FORM  
A Phase 1/2 Study of alectinib in RET-rearranged non-small cell lung cancer or RET-mutated thyroid cancer**

Complete this form and include with the specimen shipment. Label ALL materials with subject initials, DFCI subject study ID, and the date the specimen was obtained.

Ship specimen(s) to: Alectinib RET study ATTN: Julianna Supplee, Belfer Center for Applied Cancer Research, 360 Longwood Avenue LC-4302, Boston, MA 02215

**Specimen Information**

Subject Initials (FML): \_\_\_\_\_ DFCI Subject Study ID Number: \_\_\_\_\_ Date specimen(s) shipped: \_\_\_\_\_

<b>Specimen Type and Time Point (e.g. "Cycle 2 Day 1")</b> <i>(indicate inclusion in shipment by checking box)</i>	<b>Pathology Number(s) or Serial Coding</b>	<b>Quantity submitted</b>	<b>Date specimen obtained</b>	<b>Time specimen obtained</b>
<input type="checkbox"/> Plasma Genotyping Sample: _____				
<input type="checkbox"/> Plasma Genotyping Sample: _____				
<input type="checkbox"/> Plasma Genotyping Sample: _____				
<input type="checkbox"/> Plasma Genotyping Sample: _____				
<input type="checkbox"/> Plasma Genotyping Sample: _____				
<input type="checkbox"/> Plasma Genotyping Sample: _____				
<input type="checkbox"/> Plasma Genotyping Sample: _____				

**Responsible contact:** \_\_\_\_\_

**Email:** \_\_\_\_\_

**Phone number:** \_\_\_\_\_

**Site:** \_\_\_\_\_

**Mailing address:** \_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_



## APPENDIX H RET FUSION ASSAY SAMPLE REQUISITION FORM

### 17-080 - PLASMA RET FUSION ASSAY SAMPLE REQUISITION FORM A Phase 1/2 Study of alectinib in RET-rearranged non-small cell lung cancer or RET-mutated thyroid cancer

Complete this form and include with the specimen shipment. Label ALL materials with the DFCI subject study ID number and the date the specimen was obtained. Notify Ellen Ordinario before initiating any shipment.

Ship specimen(s) to:  
Ellen Ordinario  
Roche Molecular Diagnostics  
4300 Hacienda Dr  
Pleasanton, CA 94588.  
ellen.ordinario@roche.com

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#### Specimen Information

DFCI Subject Study ID Number: \_\_\_\_\_ Date specimen(s) shipped: \_\_\_\_\_

Specimen Type <i>(indicate inclusion in shipment by checking box)</i>	Pathology Number(s) or Serial Coding	Local RET testing methodology used (FISH/RT-PCR/NGS)	Specify RET alterations detected by local testing	Quantity submitted	Date specimen obtained	Time specimen obtained
<input type="checkbox"/> RET Fusion Assay Plasma Sample						

Responsible contact: \_\_\_\_\_

Email: \_\_\_\_\_

Phone number: \_\_\_\_\_

Site: \_\_\_\_\_

Mailing address: \_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_





**APPENDIX I PK ASSAY SAMPLE REQUISITION FORM**

**17-080- PHARMACOKINETIC (PK) ASSAY SAMPLE REQUISITION FORM  
A Phase 1/2 Study of alectinib in RET-rearranged non-small cell lung cancer or RET-mutated thyroid cancer**

Complete this form and include with the specimen shipment. Label ALL materials with the DFCI subject study ID number, the date, and the time the specimen was obtained.

Ship specimen(s) to: Q Squared Solutions BioSciences LLC, Laboratory Operations Manager Christopher Binns, 19 Brown Road, Ithaca NY 14850 USA

**Specimen Information**

DFCI Subject Study ID Number: \_\_\_\_\_ Date specimen(s) shipped: \_\_\_\_\_

<b>Specimen Type and Sample Number</b> <i>(indicate inclusion in shipment by checking box)</i>	<b>Pathology Number(s) or Serial Coding</b>	<b>Quantity submitted</b>	<b>Date specimen obtained</b>	<b>Time specimen obtained</b>
<input type="checkbox"/> PK Blood Sample: _____				
<input type="checkbox"/> PK Blood Sample: _____				
<input type="checkbox"/> PK Blood Sample: _____				
<input type="checkbox"/> PK Blood Sample: _____				
<input type="checkbox"/> PK Blood Sample: _____				
<input type="checkbox"/> PK Blood Sample: _____				
<input type="checkbox"/> PK Blood Sample: _____				

**Responsible contact:** \_\_\_\_\_

**Email:** \_\_\_\_\_

**Phone number:** \_\_\_\_\_

**Site:** \_\_\_\_\_

**Mailing address:** \_\_\_\_\_

\_\_\_\_\_

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