# A Phase I/II Trial to Evaluate the Safety and Tolerability of Alectinib and Bevacizumab in Patients with Advanced, ALK-Positive, Non-Small Cell Lung Cancer

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**Agent(s):**
Alectinib (IND pending), Supplier – Genentech, a member of the Roche Group
Bevacizumab (IND pending), Supplier – Genentech, a member of the Roche Group

**IND #:** 125774
Sponsor: Dr. Justin Gainor

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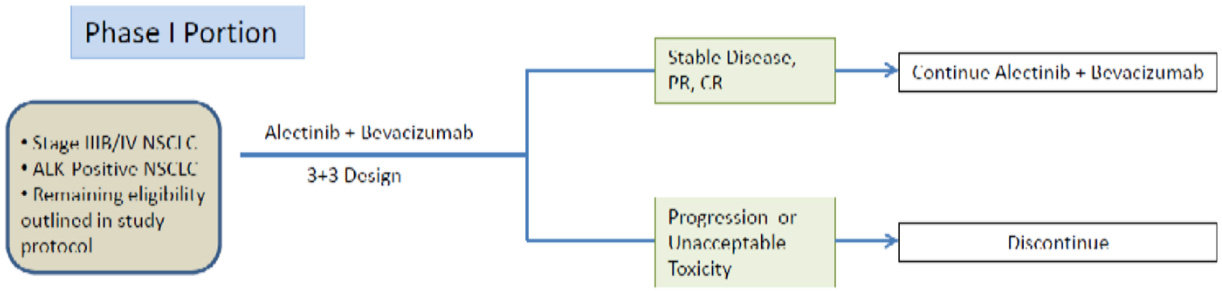
Schema


Phase I Portion
• Stage IIIB/IV NSCLC
• ALK Positive NSCLC
• Remaining eligibility outlined in study protocol
Alectinib + Bevacizumab
3+3 Design
Stable Disease, PR, CR
Continue Alectinib + Bevacizumab
Progression or Unacceptable Toxicity
Discontinue

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# 1. OBJECTIVES

Anaplastic lymphoma kinase (ALK) gene rearrangements define a distinct molecular subset of non-small cell lung cancer that is associated with marked sensitivity to the ALK tyrosine kinase inhibitor (TKI) crizotinib.[1] Despite the efficacy of crizotinib, however, the majority of ALK-positive patients relapse within one to two years. Therapeutic strategies to overcome crizotinib resistance have centered upon using structurally-distinct and more potent, second-generation ALK inhibitors, such as alectinib. Alectinib is a novel, orally-available next-generation ALK TKI that has shown promising anti-tumor activity in preclinical models.[2] In a preliminary report of an ongoing phase I/II study in patients who had previously failed crizotinib alectinib also appeared effective, with responses seen in ~55% of patients.[3] Importantly, responses were also seen in the central nervous system (CNS), which has emerged as a frequent site of relapse for ALK-positive patients treated with crizotinib.

Bevacizumab is a recombinant, humanized monocolonal antibody directed against vascular endothelial growth factor (VEGF). Although initial clinical trials of bevacizumab excluded patients with known brain metastases, more recent data has emerged demonstrating the safety of bevacizumab in NSCLC patients with both treated and untreated brain metastases. Moreover, data has emerged combining bevacizumab with TKIs in molecularly-defined patient populations with encouraging preliminary results.[4] We therefore hypothesize that the combination of alectinib and bevacizumab will be safe and tolerable in ALK-positive patients. Furthermore, we hypothesize that bevacizumab may normalize tumor vasculature, leading to improved drug delivery and increased efficacy of alectinib in the CNS.

## 1.1 Study Design

This is a phase I/II trial evaluating the safety and tolerability of alectinib and bevacizumab in patients with advanced NSCLC harboring ALK rearrangements. In part I of this study, eligible participants with ALK-positive NSCLC will be treated with the combination of alectinib and bevacizumab in order to identify the recommended phase II doses of this combination. Participants will be treated using a 3+3 design. As we expect minimal overlapping toxicities between bevacizumab and alectinib, dose level 1 will consist of the individual recommended phase II doses of alectinib and bevacizumab. The recommended phase II doses for the combination of alectinib and bevacizumab will be defined as either a) the highest dosage cohort in which less than 1/3 of patients experience a DLT or b) alectinib at the previously defined recommended phase II dose (600 mg twice daily PO) as a single agent plus bevacizumab at the highest tolerated dose (15 mg/kg IV every 21 days) investigated in this indication – whichever is the lower dose.

In the phase II portion of this study, we will further evaluate the combination of alectinib plus bevacizumab in a cohort (N=20) of ALK-positive patients. Eligible participants will receive alectinib plus bevacizumab at the recommended phase II doses determined in the phase I portion of the study. Our primary objective will be to evaluate the safety and tolerability of alectinib and bevacizumab in this patient population. Secondary objectives will be to assess the systemic efficacy of this combination, with particular focus on control of brain metastases. Secondary endpoints will include CNS objective response rate (ORR), CNS disease control rate (DCR), CNS progression-free survival, overall ORR, overall DCR, and progression-free survival. Exploratory endpoints will include molecular profiling of pre- and post-alectinib/bevacizumab biopsy tissues to evaluate for potential mechanisms of resistance to therapy. Post-treatment biopsies will be optional. Efficacy assessments (CT chest/abdomen and brain MRI) will be performed every 2 cycles for the first 10 cycles, after which assessments will be performed every 3 cycles. For patients with baseline brain metastases, CNS efficacy will be measured using a modified RECIST criteria.[5] Treatment will continue until disease progression, unacceptable toxicity, patient withdrawal, death or discontinuation from the study for any other reason. Of note, participants who are clinically benefitting may continue on treatment post-progression.

## 1.2 Primary Objectives

Phase I:

- To determine the recommended phase II doses (RP2Ds) of the combination of alectinib and bevacizumab

Phase II:

- To evaluate the safety and tolerability of alectinib and bevacizumab at the RP2Ds as assessed by Common Terminology Criteria for Adverse Events (CTCAE) version 4.0

## 1.3 Secondary Endpoints

Phase I:

- Safety, tolerability and dose-limited toxicities

Phase II:

- CNS Objective Response Rate
- CNS Disease Control Rate
- Time to CNS progression
- Overall (Intra- and Extra-CNS) Objective Response Rate
- Overall (Intra- and Extra-CNS) Disease Control Rate
- Progression-free survival (PFS)
- Patient Reported Functioning and Impact on Disease/Treatment-Related Symptoms of Brain Metastases and Global QOL
- Select tumor genotyping of pre- and post-alectinib/bevacizumab biopsies (optional)

# 2. BACKGROUND

## 2.1 ALK-Positive Lung Cancer

Lung cancer is the leading cause of cancer-related mortality in the United States. The disease is traditionally divided into non-small-cell and small-cell variants, with non-small-cell lung cancer (NSCLC) accounting for approximately 85% of cases.[6] Despite improved therapies, patients with NSCLC often present with an advanced stage, portending a poor long term prognosis.

Recently, it has been recognized that NSCLC can be further divided into molecularly-defined subsets. This, in turn, has translated into effective new targeted therapies. In 2007, Soda et al. identified the echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase (EML4-ALK) fusion

oncogene in NSCLC.[7] This novel oncogene is formed by an inversion in the short arm of chromosome 2, which results in the fusion of the EML4 gene and exons 20-29 of ALK. Multiple variants of EML4-ALK have since been reported. Although the variants preserve the same cytoplasmic portion of ALK, they possess different truncations of EML4.[8] Subsequent work has demonstrated that EML4 is not the sole fusion partner for ALK, though it is the most common in NSCLC.[9] These fusion partners facilitate ligand-independent dimerization of ALK leading to constitutive kinase activation.[10] ALK rearrangements have since been recognized to possess potent transforming activity in cell lines and transgenic mouse models.[11]

Rearrangements in ALK are identified in approximately 3-5% of patients with NSCLC.[10] Patients harboring ALK rearrangements typically possess unique clinicopathologic features, including younger age, never- or light-smoking history, and adenocarcinoma histology.[12] Consistent with preclinical studies, this subset of patients is uniquely sensitive to targeted tyrosine kinase inhibition. In a phase I trial of the ALK tyrosine kinase inhibitor (TKI) crizotinib, patients with ALK-rearranged, metastatic NSCLC experienced an overall response rate of approximately 60% and a median progression free survival of 10 months.[1,13] Based upon impressive disease activity from this and another early phase clinical trial, crizotinib was granted accelerated approval by the US Food and Drug Administration in August, 2011, followed by full regulatory approval in November 2013. In more recent phase III trials, crizotinib has been shown to produce significant improvements in response rate and PFS compared to first- and second-line cytotoxic chemotherapy.[14,15] In retrospective analyses, crizotinib has also been associated with improved overall survival compared to ALK-positive, crizotinib-naïve controls.[16]

Despite the efficacy of crizotinib in ALK-positive NSCLC, patients invariably relapse - typically within 1-2 years. To date, several different mechanisms of acquired resistance have been identified among ALK-positive patients.[17] Secondary mutations in the *ALK* tyrosine kinase domain have been found in approximately 30% of patients.[17-19] These resistance mutations are distributed throughout the *ALK* tyrosine kinase domain and confer differential sensitivities to next-generation ALK inhibitors *in vitro*. The most common *ALK* secondary mutations are G1269A and the gatekeeper mutation L1196M.[20] In addition to these *ALK* resistance mutations, *ALK* gene amplification has been identified in approximately 10% of crizotinib-resistant patients.[17] It is now appreciated that acquired resistance to crizotinib can also occur as a result of up-regulation of bypass signaling tracts. Specifically, in crizotinib-resistant biopsy specimens, ligand-dependent EGFR activation (~40%) and *c-KIT* gene amplification (15%) have been observed.[17] Still, approximately one-third of crizotinib-resistant patients have no known mechanisms of resistance identified to date. To date, therapeutic strategies to overcome crizotinib resistance have centered on using more potent and structurally-distinct, second-generation ALK inhibitors.

## 2.2 Overview of Alectinib

Alectinib (also RO5424802 or CH5424802) is a newly developed small molecule, highly selective, and potent oral next-generation ALK inhibitor with a benzo[b]carbazole scaffold. In enzyme inhibition assays performed *in vitro*, this compound has been shown to selectively inhibit ALK. The compound also shows high antitumor activity both *in vitro* and *in vivo* against tumor cell lines with ALK gene alterations, including NSCLC and anaplastic large cell lymphoma lines harboring ALK rearrangements and a neuroblastoma line harboring ALK amplification.

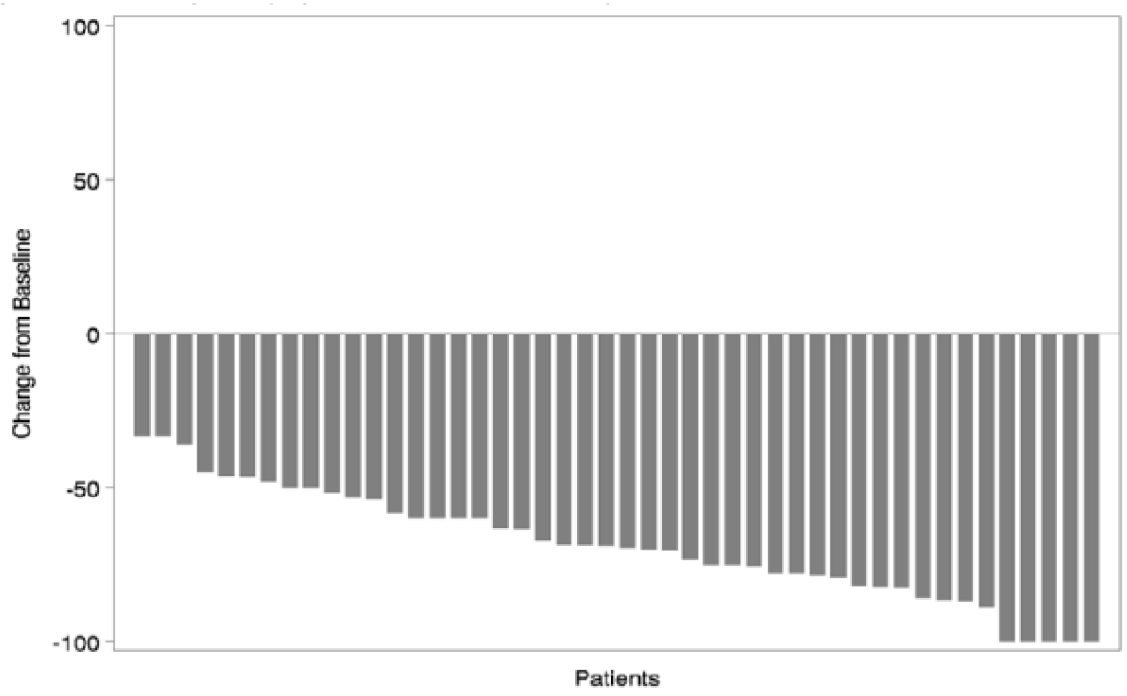
Nonclinical pharmacology studies have demonstrated that alectinib is efficacious in a model of tumors expressing an ALK fusion bearing the L1196M mutation, which is associated with resistance to crizotinib. Alectinib is also effective in mouse NCI H2228 NSCLC xenografts that are already maximally suppressed by crizotinib. Alectinib also prolongs survival in an intracerebral NCI H2228 implantation model, and it reduces tumor growth in an intracranial model monitored using bioluminescence.

The clinical development program for alectinib, to date, comprises three ongoing Phase I/II studies in patients with ALK-positive NSCLC. The ongoing Phase I/II studies are as follows: Study AF-001JP, which is being conducted in Japan; Study NP28761/AF-002JG, which is being conducted in North America; and Study NP28673, which is being conducted globally.

The first-in-human study AF-001JP is an open-label Phase I/II study being conducted in Japan. This study is assessing the pharmacokinetics, safety, and efficacy of alectinib in patients with ALK-positive NSCLC who are crizotinib-naïve and have disease progression after at least one line of chemotherapy. This study has completed enrollment, but it is still ongoing. A total of 70 patients were included (24 patients in the Phase I portion and 46 patients in the Phase II portion of the study). In the Phase I portion of the study, at the data cutoff date of 31 July 2012, 24 patients were treated at doses of 20−300 mg twice daily (BID). No dose-limiting toxicities (DLTs) or adverse events of Grade 4 were noted up to the highest dose; thus, 300 mg BID was evaluated in the Phase II portion of the study without further escalating the dose. In the Phase II portion of the study, 46 patients were treated with the highest evaluated dose of 300 mg BID, of whom 43 achieved an objective response (93.5%; 95% CI: 82.1%, 98.6%) and 7 patients had a complete response (CR) on the basis of an independent radiological review in the 12-month follow-up analysis (data cutoff for response data: 18 April 2013). The median duration of treatment (DOT) in the study has not been achieved at that date because 86% of patients were still on treatment in the study, but the projected median DOT is more than 14 months as data mature.

Figure 2.1 shows the waterfall plot of the best change from baseline in the size of target lesions by an independent radiological review. The majority (86%) of patients had a time to response of within 6 weeks after administration of the first dose.

**FIGURE 2.1: Change in Size of Target Lesions by the Independent Review Committee in Part 2 of Study AF-001JP (Data Cutoff Date: 18 April 2013)**



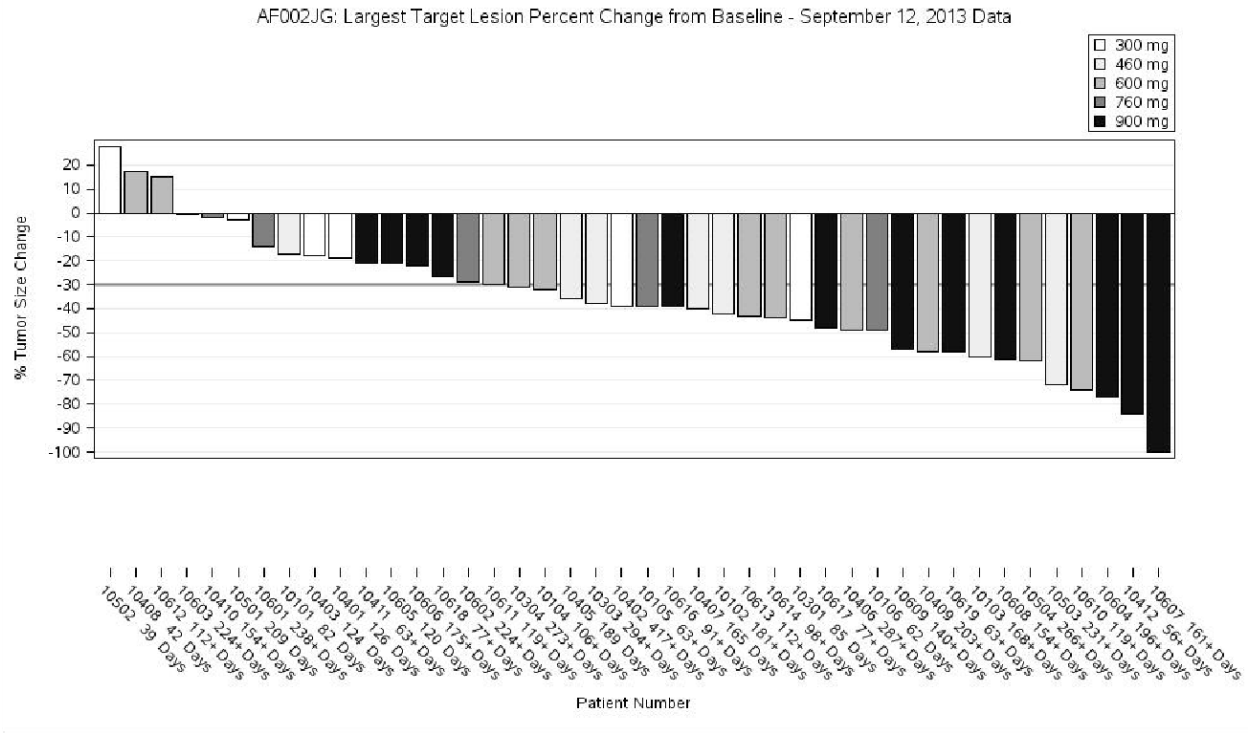
Two of 7 patients who were assessed as having a CR had lymph nodes as the target lesions. Per Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1), the percent change from baseline for patients with CR can be less than 100% when lymph nodes are identified as the target lesions. Therefore, they were assessed as having CR, although their tumor change from baseline was less than 100%.

In Study NP28761/AF-002JG (crizotinib-failed ALK-positive NSCLC patients), the Phase I portion has completed enrollment. Two 'bridging' cohorts of patients receiving alectinib using the 150-mg capsule at 600 and 900 mg BID were included in Study NP28761/AF-002JG to transition/facilitate the planned formulation for the Phase II trials. A total of 47 patients were enrolled in Phase I (Part 1). There does not appear to be any substantial difference in pharmacokinetics between the two formulations (20/40-mg capsule and the 150-mg capsule) at the 600-mg dose on the basis of available data.

The radiological imaging analysis performed in 44 evaluable patients who had a baseline scan and at least one follow-up scan (data cutoff date: 12 September 2013) has shown that 2 of 7 patients in the 300-mg BID dosage cohort, 5 of 7 patients in the 460-mg BID dosage cohort, 4 of 10 patients in the 600-mg BID dosage cohort, and 4 of 13 patients (including 1 patient with CR) in the 900-mg BID dosage cohort have achieved a confirmed partial response (PR), as assessed by the investigator. Three of 10 patients in the 600-mg BID dosage cohort, 2 of 7 patients in the 760-mg BID dosage cohort, and 4 of 13 patients in the 900-mg BID dosage cohort have achieved a PR, as assessed by the investigator, which is still to be confirmed. Three patients (all in the 600-mg BID dosage cohort) were not evaluable. The ORR was 54.5% (i.e., 24 of 44 evaluable patients who had a baseline scan and at least one post-treatment scan available to determine overall response, or who had a best overall response of progressive disease [PD] determined by the investigator, on the basis of symptomatic progression [3 patients]), including unconfirmed responses across all dose cohorts. Thirty-three of the 47 (70%) treated patients were still receiving study treatment.

The waterfall plot for the 42 patients, with a post-baseline radiological tumor assessment, is shown in Figure 2.2. On the basis of the data analyzed at that date, 27 patients experienced tumor shrinkage of > 30%, of whom 23 patients were assessed as experiencing PR (9 of which are still to be confirmed by a second tumor assessment).

**Figure 2.2: Best Percent Change in Size of Target Lesions from Baseline as Assessed by the Investigator in Part 1 of Study NP28761/AF-002JG**




Study NP28673 started enrollment on 20 June 2013 and has since completed enrollment. No data are available to report at this time.

The first Phase I 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 BID orally, showed that alectinib was generally well tolerated without major toxicities. Of the 58 patients who received treatment with 300 mg BID alectinib in Study AF-001JP, 27 experienced Grade 3 adverse events and 9 experienced serious adverse events. No deaths were reported during this study and up to 28 days after treatment discontinuation. There were 5 adverse events leading to treatment discontinuation in Part 2 (brain edema, sclerosing cholangitis, interstitial lung disease [ILD], ALT increased, and tumor hemorrhage). Alectinib was well tolerated at all doses investigated in this study. Its adverse event profile was consistent with other ALK TKIs.

In the Phase II Study NP28761/AF-002JG, alectinib was well tolerated, with no DLTs or treatment-related dose modifications up to 600 mg BID. Two DLTs were reported at 900 mg BID. The recommended alectinib Phase II dosage of 600 mg BID was chosen as having the best balance between clinical safety, efficacy, and pharmacokinetic (PK) data as observed in the Phase I/II studies.

More recently, two randomized trials have evaluated the role of alectinib in newly-diagnosed, ALK-positive NSCLC. J-ALEX was a randomized phase III trial exclusively conducted in Japan (Hida T, et al. Lancet 2017). Eligible patients had ALK inhibitor naïve NSCLC and were randomized to receive either crizotinib or alectinib (300 mg twice daily). Among 207 patients, alectinib produced a significant improvement in PFS (median not reached versus 10.2 months, respectively; HR 0.34, $p<0.0001$). In a subsequent global, randomized phase III trial (ALEX), similar findings were observed (Peters S, et al. NEJM 2017). Among 303 previously treated, ALK-positive NSCLC patients, alectinib produced significant improvements in PFS (HR 0.47) compared to crizotinib. Based upon these findings, alectinib has become a new standard of care for newly diagnosed, ALK+ NSCLC patients.

## 2.3 Overview of Bevacizumab

Bevacizumab is a recombinant monoclonal antibody targeting vascular endothelial growth factor (VEGF), a predominant factor in tumour angiogenesis.[21] Bevacizumab has been evaluated in more than 3700 patients over multiple Phase I, II and III studies in various types of tumours (colorectal, breast, lung and kidney cancer) and in >3000 patients during post-marketing studies on metastatic colorectal cancer.

In 1st line treatment of NSCLC, bevacizumab administered in combination with carboplatin and paclitaxel has shown encouraging results in a randomised Phase II study.[22] During this study, 99 patients presenting with NSCLC, relapsed or stage IIIb or IV, were randomised to receive paclitaxel/carboplatin (PC) alone or paclitaxel/carboplatin plus bevacizumab (at 7.5 mg/kg or 15 mg/kg every 21 days). The best confirmed response rate was greater in the arm treated at the higher dose of bevacizumab as compared to that of the control arm (investigator's evaluation: 32% vs. 19%). Furthermore, the time to progression of the disease was greater for the arm at 15 mg/kg (investigator's evaluation: median of 225 days vs. 129 days for the control arm).

Two pivotal phase III studies on bevacizumab combined with chemotherapy have been conducted in NSCLC:

- The phase III study of the Eastern Cooperative Oncology Group (E4599), which evaluated bevacizumab combined with first-line carboplatin/paclitaxel chemotherapy in patients with non-squamous, locally advanced or metastatic NSCLC.[23]
- The AVAIL study (BO17704), an international, phase III, randomised, double-blind, controlled, multicentre study evaluated the efficacy and safety of two doses of bevacizumab (7.5 and 15 mg/kg) in combination with cisplatin/gemcitabin.[24]

In study E4599, the addition of bevacizumab to first-line carboplatin/paclitaxel chemotherapy in patients with non-squamous, locally advanced or metastatic NSCLC demonstrated an improvement in overall survival and progression-free survival (PFS) as compared to chemotherapy alone. Median survival increased from 10.3 months for chemotherapy alone to 12.3 months for carboplatin, paclitaxel and bevacizumab (HR 0.79, p = 0.003). Median progression-free survival went from 4.5 months for chemotherapy to 6.2 months for Bev/CP (HR 0.66, p < 0.001).[23]

In the AVAIL study, both bevacizumab doses significantly improved progression-free survival and the response rate. The results are presented in Table 2.3.

**Table 2.3: Efficacy results – Studies E4599 and AVAIL (BO17704)**

| | **Overall survival (months)** | **Progression-free survival (months)** | **Overall response rate** |
|---|---|---|---|
| **Study E4599** | | | |
| Carboplatin/paclitaxel (n = 444) | 10.3 | 4.8 | 12.9% |
| Carboplatin/paclitaxel + bevacizumab 15 mg/kg/every 3 weeks (n = 434) | 12.3<br>HR = 0.80 (p = 0.003)<br>95% CI (0.69 – 0.93) | 6.4<br>HR = 0.65 (p < 0.0001)<br>95% CI (0.56 – 0.76) | 29.0%<br>(p < 0.0001) |

| AVAIL Study | | | |
|---|---|---|---|
| Cisplatin/gemcitabin/ placebo (n = 347) | - | 6.1 | 20.1%* |
| Cisplatin/gemcitabin/ bevacizumab 7.5 mg/kg/ every 3 weeks (n = 345) | - | 6.7 HR = 0.75 (p = 0.0026) 95% CI (0.62 – 0.91) | 34.1%* (p< 0.0001) |
| Cisplatin/gemcitabin/ bevacizumab 15 mg/kg/ every 3 weeks (n = 351) | - | 6.5 HR = 0.82 (p = 0.0301) 95% CI (0.68 – 0.98) | 30.4%* (p = 0.0023) |

*Patients for whom the disease was measurable upon entry into the study

Marketing authorisation of bevacizumab in combination with carboplatin and paclitaxel, in first-line treatment of non-squamous, non-resectable, locally advanced, relapsed or metastatic NSCLC, was granted in the United States by the FDA in October 2006 and in Europe in August 2007 following the results of these trials.

In the initial Phase I and II clinical trials, four potential bevacizumab-associated safety signals were identified: hypertension, proteinuria, thromboembolic events, and hemorrhage. Additional completed Phase II and Phase III studies of bevacizumab as well as spontaneous reports have further defined the safety profile of this agent. Bevacizumab-associated adverse events identified in Phase III trials include congestive heart failure (CHF) (primarily in metastatic breast cancer), gastrointestinal perforations, wound healing complications, and arterial thromboembolic events (ATE). These and other safety signals are described in further detail in Section 7 and in the bevacizumab Investigator Brochure.

## 2.4 Rationale

Despite the significant activity of ALK inhibitors, such as crizotinib and alectinib, in ALK-positive NSCLC, patients invariably develop resistance to therapy. Thus, additional strategies are needed to further improve outcomes. Beyond strategies aimed at developing increasingly potent and select ALK inhibitors, an alternative therapeutic approach is to explore combination therapy. To date, combination partners have included PD-1 inhibitors, MEK inhibitors and heat-shock protein 90 inhibitors, but few outcomes have been reported.

In this study, we aim to explore the combination of alectinib and bevacizumab. This has been, in part, informed by the experience of a similar combination in EGFR-mutant NSCLC. At the 2014 ASCO Annual Meeting.[4] Kato and colleagues presented data from an open-label, randomized study comparing the combination of erlotinib and bevacizumab versus erlotinib alone in EGFR-mutant NSCLC without CNS metastases. A total of 154 patients were enrolled. Median PFS was 16.0 months for the combination arm and only 9.7 months for the erlotinib alone arm (HR 0.54, 95% CI, 0.36-0.79; log rank p = 0.0015), suggesting that the addition of bevacizumab to EGFR TKIs results in improved systemic efficacy in a molecularly-defined population. As bevacizumab has also been shown to improve overall survival when combined with platinum-based chemotherapy in a general NSCLC patient population (ECOG 4599), we hypothesize that the combination of alectinib and bevacizumab will improve outcomes in ALK-positive patients. As part of this study, we will be focusing on ALK-positive NSCLC with brain metastases;

however, the study has been modified to eliminate brainetastases as an eligibility criterion.

Metastatic involvement of the CNS is a frequent complication in patients with lung cancer.[25] Up to 40% of patients with NSCLC ultimately develop brain metastases during the course of their disease.[26] In recent years, CNS metastases have also been recognized as an emerging complication in patients with ALK-positive NSCLC. In the PROFILE 1007 trial, for example, approximately 35% of ALK-positive patients had brain metastases at the time of study entry.[14] Moreover, among patients treated with crizotinib, the CNS is among the most common sites of relapse on therapy.[13] Of note, such relapses often occur despite continued systemic disease control. Costa and colleagues recently demonstrated that treatment with crizotinib results in low CSF-to-plasma ratios, indicative of poor blood brain barrier penetration.[27] In turn, this may result in a primary pharmacokinetic failure of crizotinib therapy in the CNS. At present, management of progressive CNS metastases in these patients typically consists of radiation therapy and occasionally surgical resection, but both modalities have the potential for significant morbidity.

Alectinib is a lipophilic drug and not a P-glycoprotein (P-gp) substrate; thus, it has the potential to penetrate the blood-brain barrier and achieve higher concentrations in brain as compared to substrates of P-gp, such as crizotinib. This has been shown in the pre-clinical setting on the basis of the prolongation of survival in a mouse model with implanted CNS lesions and in a tissue distribution study with a single oral dose of [14C]-alectinib at 1 mg/kg to albino rats.[28]

In a phase I/II trial conducted in Japan (Study AF-001JP), which enrolled crizotinib-naïve patients, alectinib was generally well tolerated and safe.[29] In this trial, alectinib was associated with an objective response rate of nearly 94%. In a preliminary report of an ongoing phase I/II study in crizotinib-resistant patients, alectinib also appeared effective, with responses seen in ~55% of patients.[3] Importantly, alectinib has also demonstrated activity in patients with CNS metastases, including patients with leptomeningeal disease.[28]

Preliminary assessments of the CNS activity of alectinib have come from two active studies: Study AF-001JP in Japan and Study NP28761/AF-002JG in North America. In Phase II of Study AF-001JP, 14 of the 46 (30%) crizotinib-naïve patients had documented CNS lesions before enrollment into the trial. Three of these 14 patients were asymptomatic and had not received prior CNS radiation. At the clinical cutoff date of 18 March 2013, 5 of the 14 patients were off-study because of systemic disease progression or an adverse event. Nine patients remain in the study with duration of treatment ranging from 10 to 18 months (none of these patients presented signs or evidence of systemic disease or CNS progression).

Similarly, in Study NP28761/AF-002JG, among the 47 patients enrolled (data cutoff date: 12 September 2013), 21 patients (45%) were known to have brain metastases at baseline. Of these 21 patients, 11 (52%) achieved an ORR as determined by Independent Review Committee (IRC; data cutoff date: 12 September 2013).[30] Moreover, of these 21 patients, 17 remained on active study treatment and 4 discontinued study treatment because of systemic PD (1 patient had both systemic disease and CNS progression). No patient discontinued because of CNS progression alone. In addition, 2 patients with leptomeningeal carcinomatosis received benefit from alectinib treatment. One patient with leptomeningeal spread in Study NP28761/AF-002JG achieved PR after 6 weeks of treatment. Another patient with leptomeningeal carcinomatosis but without systemic lesions was treated under a single-patient Investigational New Drug (IND) application because of an inability to enter either of the two Phase II alectinib studies (because of the high intake of dexamethasone for symptom control). After 6 weeks of treatment, this patient achieved a CR as demonstrated by complete disappearance of gadolinium enhancement on magnetic resonance imaging (MRI) and clearance of the CSF on cytology. This patient has been able to reduce corticosteroids to physiological replacement dosing only.

Bevacizumab is a recombinant, humanized monoclonal antibody directed against vascular endothelial

growth factor (VEGF), a key factor in tumor-associated angiogenesis. Although bevacizumab has received FDA approval in several tumor types, including NSCLC (Sattler et al, 2006), early concerns related to the risk of intracranial hemorrhage initially limited its use to patients with no evidence of brain metastases. More recently, however, bevacizumab was shown to be safe and effective in patients with recurrent glioblastoma, a primary brain tumor.[31] Several retrospective and prospective studies have also suggested that the risk of intracranial hemorrhage following treatment with angiogenesis inhibitors is relatively similar in patients with and without brain metastases.[32-34]

In NSCLC, the safety of bevacizumab in patients with treated CNS metastases was demonstrated in the phase II PASSPORT trial.[34] In this trial, patients with advanced, non-squamous NSCLC received bevacizumab in combination with first-line or second-line chemotherapy. Among 106 evaluable patients, there were no episodes of grade ≥ 2 CNS hemorrhage. More recently, preliminary data from a phase II, non-comparative study of bevacizumab in NSCLC patients with untreated brain metastases were presented.[35] In this two-arm trial, patients were treated with first-line carboplatin/paclitaxel/bevacizumab or second-line erlotinib/bevacizumab. Among patients receiving first-line carboplatin/paclitaxel/bevacizumab (n=67), approximately 60% experienced intracranial objective responses, while an additional 28% experienced stable disease in the CNS. Among those patients receiving erlotinib/bevacizumab (n=24), the intracranial disease control rate was nearly 70% (objective response rate 20%; stable disease 50%). Importantly, only 1 (1.1%) patient developed an intracranial hemorrhage across the entire study population.

## 2.5 Correlative Studies Background

Patient-derived biopsies have emerged as powerful tools for elucidating molecular mechanisms of resistance to crizotinib and other next-generation ALK TKIs (*e.g.,* ceritinib, alectinib). To date, several different mechanisms of acquired resistance have been identified among ALK-positive patients (Figure 3). For example, secondary mutations in the *ALK* tyrosine kinase domain have been found in approximately 30% of patients.[17-19] These resistance mutations are distributed throughout the *ALK* tyrosine kinase domain and confer differential sensitivities to next-generation ALK inhibitors *in vitro*. The most common *ALK* secondary mutations following treatment with crizotinib are G1269A and the gatekeeper mutation L1196M.[20] In addition to these *ALK* resistance mutations, *ALK* gene amplification has been identified in approximately 10% of crizotinib-resistant patients.[17]

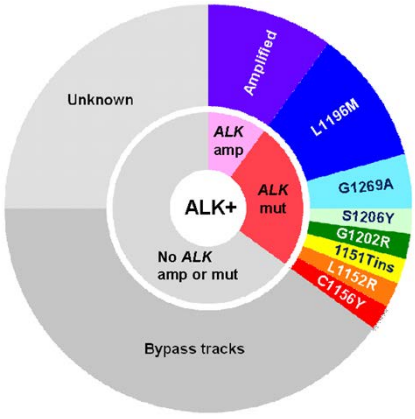



**Figure 1:** Mechanisms of Acquired Resistance to Crizotinib in ALK-Positive Lung Cancer

It is now appreciated that acquired resistance to crizotinib can also occur as a result of up-regulation of bypass signaling pathways. Specifically, in crizotinib-resistant biopsy specimens, ligand-dependent EGFR activation (~40%) and *c-KIT* gene amplification (15%) have been observed.[17] Moreover, multiple different mechanisms of resistance have been identified in the same patient. Still, approximately one-third of crizotinib-resistant patients have no known mechanisms of resistance identified to date.

Notably, molecular mechanisms of resistance may vary in response to different ALK inhibitors. For example, nearly 50% of ALK-positive patients who acquired resistance to the second-generation ALK inhibitor ceritinib were found to have ALK resistance mutations at two residues, G1202 and F1174

(Friboulet). Notably, the G1202R resistance mutation was also observed in a case report of an ALK-positive patient with resistance to alectinib (Ou, JTO).

As part of this study, we aim to collect optional pre- and post-treatment biopsies from participants. These biopsies will be evaluated for molecular mechanisms of resistance. Specifically, we will evaluate for ALK resistance mutations, ALK amplification, and activation of bypass signaling pathways. Due to the evolving nature of the field, not all of the proteins or genes of interest leading to resistance can be pre-specified in this document. Molecular techniques may include but will not necessarily be limited to: targeted next-generation sequencing, FISH studies, and whole-exome sequencing.

## 3. PARTICIPANT SELECTION

Participants must meet the following eligibility criteria for study entry:

### 3.1 Eligibility Criteria

- Histologically or cytologically confirmed advanced (stage IIIB or IV) non-squamous, non-small cell lung cancer.

- Molecular confirmation of an ALK rearrangement using ALK FISH, IHC or next-generation sequencing (NGS). For ALK FISH, rearrangements must be detected in >15% of tumor cells. If an ALK rearrangement has been detected by IHC or NGS, archival tissue must be available to confirm ALK positivity by FISH.

- Age ≥ 18 years old.

- Life expectancy > 12 weeks.

- ECOG performance status 0-2.

- Adequate hematologic function:
  - ANC ≥ 1500 cells/μL
  - Platelet count ≥ 100 x $10^9$/L
  - Hemoglobin ≥ 8 g/dL

- Adequate renal function:
  - An estimated Glomerular Filtration Rate (eGFR) calculated using the Modification of Diet in Renal Disease (MDRD) equation of at least 45 mL/min/1.73 m2

- Coagulation
  - International normalized ratio (INR) ≤ 1.5, and
  - PTT ≤ 1.5 x ULN

- For all females of childbearing potential, a negative pregnancy test must be obtained within 3 days before starting study treatment.

- For women who are not postmenopausal (≥ 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 patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception. Examples of non-hormonal 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. Alternatively, two methods (e.g., two barrier methods such as a condom and a cervical cap) may be combined to achieve a failure rate of < 1% per year. Barrier methods must always be supplemented with the use of a spermicide.

- For men: agreement to remain abstinent or use a condom plus an additional contraceptive method that together 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 patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

- Able and willing to provide written informed consent prior to performing any study-related procedures and to comply with the study protocol, including patients must be willing and able to use the electronic patient-reported outcome (ePRO) device.

- At least one measurable lesion based upon RECIST version 1.1.

## 3.2 Exclusion Criteria

Participants who meet any of the following criteria will be excluded from study entry:

- Squamous cell histology or mixed, predominantly squamous adenosquamous carcinoma

- Previous history of haemoptysis (expectoration of more than 2.5 mL of blood), within three months prior to enrolment.

- Tumour infiltrating into large vessels or infiltrating into the proximal tracheobronchial network, visible on medical imaging. The investigator or radiologist must rule out tumours that conjoin, surround or extend into the immediate area of a large vessel (e.g.: pulmonary artery, superior vena cava).

- Unstable, symptomatic brain metastases. Asymptomatic CNS metastasis noted on baseline scans are acceptable after discussion and approval from the Overall PI of the study.

- History of hemorrhagic CNS metastases

- History of intracranial hemorrhage (either by clinical history or neuroimaging)

- History of or genetic predisposition to a bleeding diathesis or coagulopathy

- Therapeutic anticoagulation, including but not limited to: low-molecular weight heparin (LMWH), heparin, or warfarin. Anticoagulants must be discontinued 10 days prior to the first administration of bevacizumab. Prophylactic use of anticoagulants is allowed.

- Current or recent (within 10 days of first dose of bevacizumab) use of aspirin (> 325 mg/day) or other nonsteroidal anti-inflammatories known to inhibit platelet function. Prophylactic use of anticoagulants is allowed.

- Clinically significant heart disease (i.e., active), stroke or myocardial infarction within 6 months prior to enrolment, unstable angina pectoris, congestive heart failure of grade > II according to the New York Heart Association (NYHA), or cardiac arrhythmia requiring specific treatment during the study and that may interfere with the follow-up of the study treatment or poorly controlled by treatment.

- Arterial or venous thromboembolic events within 6 months of study enrolment.

- Poorly controlled arterial hypertension (systolic > 150 mm Hg and/or diastolic > 100 mm Hg), with or without antihypertensive medication. Patients presenting with high blood pressure are eligible if the dose or adjustment of anti-hypertensives lowers blood pressure to meet the inclusion criteria of the study.

- Invasive surgical intervention (including biopsy by surgical route), major traumatic injury during the 28 days prior to the start of treatment, or scheduled invasive surgical intervention during the study treatment.

- Minor surgical intervention, including placement of a permanent catheter within 24 hours prior to the first infusion of bevacizumab.

- Non-healing wound, active peptic ulcer or bone fracture.

- Previous history of abdominal fistula, tracheoesophageal fistula or other fistula with grade 4 severity, gastrointestinal perforation or intra-abdominal abscess within 6 months prior to enrolment.

- Proteinuria at baseline. Subjects unexpectedly found to have ≥2+ proteinuria on a urine dipstick at baseline should undergo a 24-hour urine which must be an adequate collection and must demonstrate <2 g of protein/24 hr to allow participation in the study.

- Patients who have received previous anti-angiogenic treatment (experimental or marketed: bevacizumab, thalidomide, CP-547632, sunitinib, sorafenib or others).

- Patients previously treated with alectinib

- Radical radiotherapy to the thorax with curative intent within 28 days of initiation of study drug treatment; palliative radiotherapy for bone lesions outside of the thorax or brain within 14 days of the first dose of study treatment; palliative radiotherapy to the brain or thorax within 28 days of the first dose of study drug treatment.

- Cytotoxic chemotherapy within 21 days prior to enrolment.

- Treatment with crizotinib within 7 days prior to enrolment. For all other ALK TKIs, the washout period should 3 days prior to enrolment. A shorter washout period may be considered after discussion with the Overall Investigator.

- Any GI disorder that may affect absorption of oral medications, such as mal-absorption syndrome or status post major bowel resection.

- Liver disease characterized by: ALT or AST > 3 × ULN (≥ 5 × ULN for patients with concurrent liver metastasis)

  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 hepatitis

- National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) (version 4.0) Grade 3 or higher toxicities due to any prior therapy (e.g. radiotherapy) (excluding alopecia), which have not shown improvement and are strictly considered to interfere with current study medication.

- History of organ transplant.

- Co-administration of anti-cancer therapies other than those administered in this study.

- Patients with baseline QTc > 470 ms or patients with symptomatic bradycardia.

- History of hypersensitivity to any of the additives in the alectinib drug formulation (lactose monohydrate, microcrystalline cellulose, sodium starch glycolate, hydroxypropyl cellulose, sodium lauryl sulfate [SLS], magnesium stearate).

- Documented allergy or hypersensitivity to monoclonal antibodies (bevacizumab), to Chinese hamster ovarian cells of the or to any other humanised or recombinant antibodies.

- A history of drug-induced pneumonitis or hypersensitivity pneumonitis from prior ALK TKI therapy.

- Pregnant or lactating women.

- Known HIV positivity or AIDS-related illness.

- Any clinically significant concomitant disease or condition that could interfere with, or for which the treatment might interfere with, the conduct of the study or the absorption of oral medications or that would, in the opinion of the Principal Investigator, pose an unacceptable risk to the patient in this study.

# 4. REGISTRATION PROCEDURES

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

Institutions will register eligible participants with the DF/HCC Quality Assurance Office for Clinical Trials (QACT) central registration system. Registrations must occur prior to the initiation of protocol therapy. Any participant not registered to the protocol before protocol therapy begins will be considered ineligible and registration will be denied.

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

Following registration, participants may begin protocol therapy. Issues that would cause treatment delays should be discussed with the Overall Principal Investigator (PI). If a participant does not receive protocol therapy following registration, the participant's registration on the study must be canceled. Notify the QACT Registrar of registration cancellations as soon as possible.

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

The QACT registration staff is accessible on Monday through Friday, from 8:00 AM to 5:00 PM Eastern Standard Time. In emergency situations when a participant must begin protocol therapy during off-hours or holidays, call the QACT registration line at 617-632-3761 and follow the instructions for registering participants after hours.

The registration procedures are as follows:

- Obtain written informed consent from the participant prior to the performance of any protocol specific procedures or assessments.

- Complete the QACT protocol-specific eligibility checklist using the eligibility assessment documented in the participant's medical record and/or research chart. **To be eligible for registration to the protocol, the participant must meet all inclusion and exclusion criterion as described in the protocol and reflected on the eligibility checklist.**

  Reminder: Confirm eligibility for ancillary studies at the same time as eligibility for a treatment protocol. Registration to both treatment and ancillary protocols will not be completed if eligibility requirements are not met for all studies.

- Fax the eligibility checklist(s) and all pages of the consent form(s) to the QACT at 617-632-2295. For Phase I protocols, attach participant dose level assignment confirmation from the sponsor.

- The QACT Registrar will (a) review the eligibility checklist, (b) register the participant on the protocol, and (c) randomize the participant when applicable.

- An email confirmation of the registration and/or randomization will be sent to the Overall PI, study coordinator(s) from the Lead Site, treating investigator and registering person immediately following the registration and/or randomization.

### 4.3 General Guidelines for Other Investigative Sites

N/A

### 4.4 Registration Process for Other Investigative Sites

N/A

## 5. TREATMENT PLAN

For this study, the terms "study drug(s)" will refer to the combination of alectinib and bevacizumab.

In the phase I portion of this study, eligible participants with ALK-positive NSCLC will be treated with the combination of alectinib and bevacizumab in order to identify the recommended phase II doses of this combination. As we expect minimal overlapping toxicities between alectinib and bevacizumab, dose cohort 1 will be the combination of alectinib at its recommended phase II dose (600 mg twice daily) and bevacizumab at it's highest tolerated dose (15 mg/kg IV every 21 days) investigated in this indication.[22] This dose of bevacizumab has been used in combination with other TKIs (e.g., erlotinib) and standard platinum-based chemotherapy doublets (e.g, carboplatin and paclitaxel) with acceptable side effect profiles.[23,35,36] Participants will be treated using a 3+3 design. Three patients will be treated per cohort for one cycle (21 days per cycle) beginning with dose cohort 1. If no DLTs are observed with dose cohort 1, we will enroll an additional 3 participants (6 total) and proceed with the phase II portion of the trial if one or less experience a DLT. In subsequent dose cohorts, if one of three patients experiences a DLT, another 3 patients will be treated at the same dose level for one cycle. If no additional DLTs are observed, we will proceed with the phase II portion of the trial. If more than one of 3 patients develops a DLT in any cohort, another 3 patients will be treated in the next lowest lower dose cohort. We will continue until identification of the recommended phase II doses for the combination of alectinib and bevacizumab. The recommended phase II doses for the combination of alectinib and bevacizumab will be defined as either a) the highest dosage cohort in which less than 1/3 of patients experience a DLT or b) alectinib at the previously defined recommended phase II dose (600 mg twice daily PO) as a single agent plus bevacizumab at the highest tolerated dose (15 mg/kg IV every 21 days) investigated in this indication – whichever is the lower dose.

In the phase II portion of this study, we will evaluate the combination of alectinib plus bevacizumab in ALK-positive patients with untreated or progressive, asymptomatic brain metastases. Eligible participants will receive alectinib plus bevacizumab at the recommended phase II doses determined in the phase I portion of the study.

### 5.1 Treatment Regimen

One treatment cycle will consist of 21 consecutive days. A 3-day window period will be authorized throughout the study period.

Alectinib will be administered twice daily on an outpatient basis. Bevacizumab will be administered as an infusion every 3 weeks.

Reported 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 participant's malignancy.

Please see Table 5.1 and Table 5.2 for the Dose Escalation Schedule and Regimen Description, respectively.

**Table 5.1**

| **Dose De-escalation Schedule** | | |
|---|---|---|
| **Dose Level** | **Dose** | |
| | ***Alectinib*** | ***Bevacizumab*** |
| Level 1: Starting Dose | 600 mg BID | 15 mg/kg IV every 3 weeks |
| Level minus 1 | 600 mg BID | 7.5 mg/kg IV every 3 weeks |
| Level minus 2 | 450 mg BID | 7.5 mg/kg IV every 3 weeks |

**Table 5.2**

| **Regimen Description** | | | | | |
|---|---|---|---|---|---|
| ***Agent*** | ***Premedications; Precautions*** | ***Dose*** | ***Route*** | ***Schedule*** | ***Cycle Length*** |
| Alectinib | Should be taken within 30 minutes of a meal | Dose as appropriate for assigned dose level | Oral | Days 1-21 | 21 days (3 weeks) |
| Bevacizumab | Do NOT administer or mix with glycolated solutions. | Dose as appropriate for assigned dose level | IV infusion lasting 30-90 minutes* | Day 1 | |
| * The initial dose of bevacizumab will be administered in 90 (± 15) minutes. If the first infusion is tolerated well and there are no associated adverse events (fever or shivering), the second infusion may be administered in 60 (± 10) minutes. If the infusion is tolerated well in 60 minutes, all subsequent administrations may be performed in 30 (± 10) minutes. | | | | | |
| | | | | | |

## 5.2 Agent Administration

### 5.2.1 Alectinib

Alectinib comes in a capsule dosage form containing the following active ingredient:

[Chemical name] 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

Each capsule contains 150 mg of alectinib (as free base) along with lactose monohydrate, carmellose calcium, hydroxypropyl cellulose, SLS, and magnesium stearate. Alectinib capsules should be stored in accordance with the storage instructions on the label.

Alectinib capsules should be administered orally BID with food (within 30 minutes after a meal, in the morning and evening).

If a patient misses a dose, it can be taken within 6 hours of the scheduled time. If the time is greater than 6 hours, or if the patient vomits the dose, the patient should wait until the next scheduled time and take the next scheduled dose. Patients should not take two doses at the same time to make up for a missed dose.

Guidelines for dosage modifications and treatment interruptions or discontinuation due to specified adverse events are provided in Section 6.

For further details, see the alectinib Investigator's Brochure.

#### 5.2.2 Bevacizumab

Bevacizumab will be administered on day 1 of each cycle. The bevacizumab dose will be per the assigned dose cohort level (Phase I) or the recommended phase II dose (Phase II).

The initial dose of bevacizumab will be administered in 90 (± 15) minutes. If the first infusion is tolerated well and there are no associated adverse events (fever or shivering), the second infusion may be administered in 60 (± 10) minutes. If the infusion is tolerated well in 60 minutes, all subsequent administrations may be performed in 30 (± 10) minutes.

Do not administer by direct intravenous or bolus injection

In case of extravasation of the study treatment, the following procedures will be followed:

- Stop the infusion
- If the volume of the remaining product is significant, restart the infusion at another site on the same arm.

Treat the infiltration according to the guidelines of the centre for infiltration of a non-caustic product.

**Note: During the COVID-19 pandemic, bevacizumab infusions may be held in the absence of toxicity at the discretion of the investigation in order to minimize patient exposures in the clinic.

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

Safety will be assessed using Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Select Adverse Events will be closely monitored, including intracranial hemorrhage, bleeding, arterial/venous thrombotic events, hypertension, interstitial lung disease (ILD), hepatobiliary tests elevations, hematologic abnormalities, GI disorders, skin disorders, vision disorders, abnormal renal function, proteinuria, muscular adverse events and CPK increases.

For the purposes of this protocol, the DLT determination period will be 21 days (1 cycle). DLTs are defined as drug-related toxicities that meet any one of the following criteria:

Non-hematologic toxicities:

- Grade ≥ 2 intracranial hemorrhage

- Any grade ≥ 3 non-hematologic toxicity (except for the following):
    - Alopecia;
    - Grade 3 or 4 hypophosphatemia;
    - Grade 3 or 4 hyperuricemia without signs or symptoms of gout;
    - Transient electrolyte abnormalities that resolve to ≤ grade 1 in less than 2 days
    - Diarrhea, nausea, vomiting, and hypertension that recovers to grade 2 or lower with appropriate treatment;
    - Grade 3 AST or ALT elevations when grade 2 AST or ALT elevations were present at baseline (unless grade 3 AST or ALT elevations are present for 7 days or grade 4 AST or ALT elevations are observed)
- Adverse events that require interruption of treatment for a total of ≥ 7 days

Hematologic toxicities:

- Febrile neutropenia not related to the underlying study disease (fever, >101 ºF; absolute neutrophil count <500);
- Prolonged grade 4 neutropenia (>7 days);
- Grade 3 neutropenia with grade ≥ 3 infection;
- Thrombocytopenia ≥ grade 3 with bleeding or grade 4 lasting ≥ 7 days

Management and dose modifications associated with the above adverse events are outlined in Section 6.

## 5.4 General Concomitant Medication and Supportive Care Guidelines

### 5.4.1 Permitted Therapy

Concomitant medication includes any medication (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by a patient from 28 days prior to screening to the study completion/discontinuation visit. All concomitant medications should be reported to the investigator and recorded on the CRFs.

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

- For medications that are substrates of P-gp transporter or breast cancer resistance protein transporter, the investigator should use caution and monitoring when considering concomitant use of alectinib. Alectinib has been shown to have potential for inhibition of these transporters. Substrates with a narrow therapeutic index (e.g., methotrexate, digoxin) should be avoided. If co-administration cannot be avoided, it is recommended that drug levels and/or signs for toxicity are carefully monitored (see Appendix B).

Caution should be exercised when the following are administered with bevacizumab:

- Aspirin and NSAIDS: Since the most serious toxicities observed with bevacizumab to date are hemorrhages, thromboses, and gastrointestinal perforations, the use of **aspirin** and **NSAIDs** must be limited.
    - Participants who require long-term administration of aspirin (>325 mg/day) or non-steroidal anti-inflammatory drugs that inhibit platelet function at doses used to treat chronic inflammatory diseases will not be included in the study (see inclusion and exclusion criteria).
    - Administration of low doses of aspirin (≤ 325 mg/day), occasional administration of nonsteroidal anti-inflammatory drugs or nonsteroidal anti-inflammatory drugs inhibiting platelet function is authorised. Patients presenting with a venous thromboembolic

accident during the trial will be withdrawn from bevacizumab treatment as described in section 6.

### 5.4.2 Prohibited Therapy

Use of the following therapies (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) is prohibited during the study and for at least 14 days prior to initiation of study treatment, unless otherwise specified below. Exceptions to the below listed concomitant therapies restrictions (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) may be made if the rationale is discussed and documented between the investigator and the Sponsor/Principal Investigator.

- Anticoagulants (e.g., LMWH, Coumadin) are prohibited within 10 days of the first administration of bevacizumab and for the entire duration of treatment.
- Anti-platelet agents (e.g., ticlopidine, clopidogrel)

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 can be given. In addition, the investigator should contact the Sponsor/Principal Investigator if questions arise regarding medications not listed above.

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

### 5.4.3 Supportive Care Guidelines

Patients should receive full supportive care including transfusions of blood and blood products, antibiotics, analgesia etc, according to local practice/institutional guidelines where appropriate. Anti-emetic medication should be prescribed according to local practice

Treatments received prior to the study entry and that are not prohibited by the protocol will be continued by the patients during the study, depending on their doctor's recommendations. All concomitant medication(s) must be reported in the case report form.

Palliative radiation therapy will be permitted for participants with symptomatic bone metastases provided that the participant continues to derive clinical benefit from study drugs in the opinion of the Investigator. Alectinib should be held for at least 72 hours before the initiation of radiation and resumed no sooner than 72 hours after the completion of radiation.

**In the event of progression of disease in the CNS, cerebral radiotherapy is permitted where appropriate.** Bevacizumab should be held for 14 days following completion of radiation. Alectinib should be held for at least 72 hours before cranial radiation and resumed no sooner than 72 hours after the completion of cranial radiation.

## 5.5 Criteria for Taking a Participant Off Protocol Therapy

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

criteria applies:

- Disease progression. **Note:** In some cases, despite disease progression by RECIST criteria, participants may be continued on study drugs if deemed beneficial by the participant and investigators. Depending on the participant's prior tolerance of therapy, he/she may continue alectinib/bevacizumab or single-agent alectinib or bevacizumab at the same doses/schedules following disease progression (if determined appropriate by the investigator).

- Intercurrent illness that prevents further administration of treatment

- Unacceptable adverse event(s)

- Participant demonstrates an inability or unwillingness to comply with the oral medication regimen and/or documentation requirements

- Participant decides to withdraw from the protocol therapy

- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the treating investigator

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

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

In the event of unusual or life-threatening complications, treating investigators must immediately notify the Overall PI, Justin Gainor, MD at 617-724-4000 or pager 16567.

## 5.6 Duration of Follow Up

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

## 5.7 Criteria for Taking a Participant Off Study

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

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

The reason for taking a participant off study, and the date the participant was removed, must be documented in the case report form (CRF).

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

### 5.8 Replacement Policy

Subjects who receive bevacizumab and at least 75% of planned alectinib doses in Cycle 1 will be considered to have had sufficient study drug exposure to support dose determination. Patients who did not receive bevacizumab and/or 75% of planned alectinib doses in Cycle 1 may be replaced, unless the reason for the early withdrawal is drug toxicity or drug-related death. Enrollment of a new patient to the current cohort will be considered if there is less than the required number of evaluable patients or if the Sponsor deems it necessary to add patients for determination of the recommended phase II doses. Enrollment of new patients may be considered until at least the minimum number (3) or at most the maximum number (6) of evaluable patients is achieved within the cohort. All patients who receive at least part of one dose will be included in the safety analysis. Any patient who either completed one cycle of study treatment or experienced a DLT during the first treatment cycle is evaluable for MTD.

## 6. DOSING DELAYS/DOSE MODIFICATIONS

### 6.1 Toxicity Related to Bevacizumab

- ***No** intra-patient **dose** modification of bevacizumab is permitted during this study. In the Phase I portion of the study, however, DLTs may result in subsequent patient cohorts receiving a lower dose level of bevacizumab as outlined in Section 5*

- In general, the occurrence of toxicity related to bevacizumab (haemorrhage, thromboembolic accidents, arterial hypertension, proteinuria, gastrointestinal perforation, complication of the healing of wounds, fistula or intra-abdominal abscess, congestive heart failure or allergic reaction), will require temporary discontinuation of treatment with bevacizumab.

- ***Treatment with bevacizumab must be permanently discontinued in case of treatment-related intracerebral hemorrhage, arterial thromboembolic accident, gastrointestinal perforation and grade 4 proteinuria (nephrotic syndrome).***

- In the case of permanent discontinuation of alectinib for toxicity reasons, bevacizumab can be administered until progression of the disease at the discretion of the treating investigator, except in case of unacceptable toxicity or the decision of the patient or the investigator.

**Allergic reaction related to the administration of bevacizumab/hypersensitivity (e.g. fever, rash, urticaria, bronchospasm)**

Grades 1, 2

- In case of occurrence of reactions related to the infusion, premedication will be administered with the subsequent infusion, but the infusion time will not be reduced for the subsequent infusion. If the subsequent infusion that is preceded by premedication is tolerated well, the next administration can be reduced to 30 ± 10 minutes as long as the premedication is still used. If AEs related to the infusion occur with the infusion over 60 minutes, all subsequent infusions will be administered over 90 ± 15 minutes (with premedication). Similarly, if AEs related to the infusion appear with the infusion over 30 minutes, all subsequent infusions will be administered over 60 ± 10 minutes

(with premedication).

Grade 3:

- In patients that had a grade 3 reaction, the infusion of bevacizumab will be discontinued and not resumed that same day. The permanent discontinuation of bevacizumab or another administration with premedication and infusion over 90 ± 15 minutes will be left to the discretion of the investigator. If the reaction reappears again during the 90-minute infusion, the investigator may test an infusion with a longer flow and gradually increase the flow to achieve an infusion time of 90 minutes. Upon resuming bevacizumab, the patient must be monitored according to the usual routine of the centre, for a duration at least equal to the duration of the reaction.

Grade 4:

- Permanent discontinuation of bevacizumab.

**Note: During the COVID-19 pandemic, bevacizumab infusions may be held in the absence of toxicity at the discretion of the investigation in order to minimize patient exposures in the clinic

**Table 6.1. Modifications of the administration of bevacizumab in case of adverse events**

| CTCAE Grade | Conduct to follow |
|---|---|
| **Hypertension** | |
| Grade 1 or 2 | No treatments modifications with bevacizumab |
| Grade 3 | If not controlled at ≤ 150 mmHg with antihypertensive treatment, do not administer bevacizumab. |
| Grade 4 | Discontinue bevacizumab. |
| **Signs of Posterior Reversible Leukoencephalopathy Syndrome (PRLS)** | |
| Any grade (confirmed on an MRI) | Discontinue bevacizumab |
| **Haemorrhaging of the CNS** | |
| Any grade | Discontinue bevacizumab |
| **Pulmonary haemorrhage** | |
| Any grade | Discontinue bevacizumab |
| **Non-pulmonary, non-CNS haemorrhage** | |
| Grade 1 | No dose modifications. |

| | |
|---|---|
| Grade ≥ 2 | Discontinue bevacizumab |
| **Venous thrombosis** | |
| Any grade | Discontinue bevacizumab. |
| **Arterial thromboembolic event** (angina pectoris, myocardial infarction, ischemic heart attack, arterial thromboembolic attack or any other arterial thromboembolic event) | |
| Any grade | Discontinue bevacizumab |
| **Proteinuria** | |
| Grade 1 or 2 | No dose modifications |
| Grade 3 | Suspend bevacizumab until resolution of grade to ≤ 2 |
| Grade 4 (nephrotic syndrome) | Discontinue bevacizumab |
| **GI Perforation** Grade ≥ 2 (Requiring medical or surgical intervention) | Discontinue bevacizumab |
| **Intestinal obstruction** | |
| Grade 1 | Keep the patient in the study for partial obstruction NOT requiring medical/surgical intervention. |
| Grade 2 | Suspend bevacizumab for partial obstruction requiring medical/clinical intervention. The administration of treatment will resume after full resolution. |
| Grade 3 or 4 | Discontinue bevacizumab for total obstruction. If surgical intervention is needed, the patient will resume treatment after wounds are healed and the assessment of investigator. |
| **Dehiscence of wounds requiring medical or surgical treatment** (if the wound comes from incision of a cavity) | |
| Any grade | Discontinue bevacizumab |
| **Left ventricular systolic dysfunction** | |
| Grade 1 or 2 | No dose modifications |
| Grade 3 | Suspend bevacizumab until resolution of grade ≤ 1 |
| Grade 4 | Discontinue bevacizumab |
| **Fistula** | |
| **TE Fistule** | Discontinue bevacizumab |

| | |
|---|---|
| Any Grade | |
| **Any other events of Grade 3/ 4 that may be related to bevacizumab according to the investigator** | |
| Grade 3<br><br>Grade 4 | Discontinue bevacizumab until resolution of grade ≤ 1.<br><br>Discontinue bevacizumab |

### 6.2 Adverse Events Relating to ALK Inhibitors and/or the Tyrosine Kinase Inhibitor Class and Alectinib Data

See Table 6.2 for an overview of the management of AEs related to alectinib.

Of note, participants may remain on alectinib despite discontinuation of bevacizumab, provided they do not meet criteria for discontinuation of alectinib as well.

**Table 6.2: Modification of the administration of alectinib in case of adverse events**

| Event | Action to be Taken |
|---|---|
| Interstitial lung disease | ● Patients should be monitored for pulmonary symptoms indicative of pneumontis<br>● Alectinib should be permanently discontinued in patients diagnosed with interstitial lung disease |
| Hepatotoxicity | ● If ALT or AST > 3 x baseline, repeat testing of ALT, AST, ALP and total bilirubin within 48-72 hours, w/ inquiry about symptoms. If upon repeat testing the transaminases remain > 3 × baseline, but are not > 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.<br>● At any time during study treatment, if symptoms compatible with liver injury are observed, liver enzymes should be measured as soon as possible.<br>● Alectinib should be permanently discontinued if any of the following occurs:<br>- First observation of ALT or AST > 8 x ULN<br>- ALT or AST > 5 x ULN for > 2 weeks<br>- First observation of ALT or AST > 3 x ULN and total bilirubin > 2 x ULN<br>- First observation of ALT or AST >3 x ULN and the |

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| | appearance of jaundice or signs of hepatic dysfunction or other symptoms (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash or eosinophilia [>5%]).<br>● Following alectinib 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.<br>● Resumption of alectinib is not allowed in patients discontinuing because of any of the above criteria. |

| Event | Action to be Taken |
|---|---|
| Gastrointestinal tract AEs (e.g., nausea, vomiting, diarrhea, stomatitis) | ● The events are expected to be minimized by taking alectinib with meals. In case GI events occur, appropriate measures should be taken in accordance with local clinical practice guidelines. If GI toxicities are observed and are not tolerable, treatment with alectinib should be temporarily interrupted until recovery to Grade 1 or lower. |
| Skin disorder AEs (e.g., photosensitivity, rash) | ● Participants should be advised to avoid prolonged sun exposure while taking alectinib and for at least 5 days after discontinuation. Participants 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. |
| Vision disorders | ● Investigators should consider referring participants for an ophthalmological evaluation according to local clinical practice guidelines, particularly if vision disorders persist or worsen in severity. Investigators should also advise patients to exercise caution when driving or operating machinery due to the risk of developing a vision disorder. |
| 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. |

| Event | Action to be Taken |
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| Abnormal kidney function AEs | ● If, at any time during study treatment, eGFR decreases more than 50% of the baseline visit value, the patient 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, |

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| | concomitant medications affecting renal function as appropriate, etc).<br>● Any eGFR decrease of more than 50% of the baseline visit value requires repeat testing. If, at the repeat test, the eGFR decrease is still more than 50% over the baseline visit value, the treatment with alectinib should be interrupted.<br>● Alectinib treatment may be resumed with caution if the eGFR value has increased to approximately the baseline visit value. |

| Event | Action to be Taken |
|---|---|
| Severe myalgia and/or CPK Elevations | ● Myopathy should be considered in any patient with diffuse myalgia, muscle tenderness or weakness, and/or marked elevation of CPK levels. Patients should promptly report unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever. CPK levels should be assessed in patients reporting these symptoms.<br>● At the first occurrence of any asymptomatic CPK values (> 10 x ULN, symptomatic CPK > 5 x ULN, or in the presence of severe muscular symptoms with CPK > ULN but ≤ 5 x ULN) at any time during study treatment, the patient 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. |

| Event | Action to be Taken |
|---|---|
| Other AEs (including bradycardia, anemia, ALP increases, dysgeusia) or laboratory abnormalities | ● Grade 3 or 4:<br>- Temporarily interrupt alectinib for a maximum of 3 week<br>- If improvement to Grade ≤ 1 or baseline does not occur within 3 weeks, permanently discontinue alectinib.<br>- First episode: If improvement to Grade ≤ 1 or baseline within 21 days, decrease the current dose of alectinib by 150 mg BID.<br>- Second episode: If improvement to Grade ≤ 1 or baseline within 21 days, decrease the current dose of alectinib by another 150 mg BID.<br>- Third episode: permanently discontinue alectinib.<br>● Grade 2 (except any symptoms and signs that can be corrected with supportive care)<br>- Temporarily interrupt alectinib and resume if recovering to Grade ≤ 1 or baseline if clinically indicated.<br>- First episode: If improvement to Grade ≤ 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 BID when resuming treatment.<br>- Second episode: If improvement to Grade ≤ 1 or baseline within 10 days, decrease the current dose of alectinib by 150 mg BID. If improvement occurs after 10 days, decrease the current dose of alectinib by 300 mg BID when resuming |

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| | treatment.<br>- Third episode: permanently discontinue alectinib.<br>● Grade 1: no action required |

## 7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of reported and/or potential AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting **in addition** to routine reporting.

### 7.1 Adverse Events

#### 7.1.1 Adverse Events Lists

**Adverse Events Relating to ALK Inhibitors and/or the Tyrosine Kinase Inhibitor Class and Alectinib Data**

AEs associated with alectinib or ALK inhibitors as a class are outlined below. A more detailed safety profile of alectinib is provided in the alectinib Investigator's Brochure.

**Interstitial Lung Disease**
Interstitial lung disease cases, some of which have been associated with fatal outcomes, have been reported with other ALK inhibitors, such as ceritinib and crizotinib.

See section 6.2 for management and follow-up.

**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
patients 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 patients treated in
alectinib clinical trials.
In patients treated with other ALK inhibitors, 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.

**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 crizotinib and ceritinib.
Cases of anemia have been reported in patients treated with alectinib; the majority of the events were Grade 1 or 2.
See section 6.2 for management and follow-up.

**Gastrointestinal Disorders**
GI disorders such as nausea, vomiting, constipation, diarrhea and stomatitis have been reported with alectinib. Similar GI disorders have been observed with other ALK inhibitors, including crizotinib and ceritinib. SLS (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.

**Skin Disorders**
Results of an in vitro phototoxicity study indicated that alectinib may have phototoxic potential.
Skin rash has been reported with a majority of TKIs including those targeting the ALK receptor (Hartmann et al. 2009). 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.

**Vision Disorders**
In the rat quantitative whole body autoradiography study, 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.

Vision disorders, including diplopia, photopsia, blurred vision, visual impairment, and vitreous floaters, have been reported with several TKIs, including crizotinib. Vision disorders, such as dry eye, blepharitis, conjunctivitis, blurred vision, and vision impaired, have been reported with alectinib and were generally Grades 1 and 2.

See section 6.2 for management and follow-up.

**Edema**
Crizotinib is associated with the development of lower extremity edema. Events of edema have been reported with alectinib, mostly Grade 1 or 2.

**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 [Cmax]: 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 Ca2+ channel inhibition. Events of bradycardia have been reported with alectinib.
Events of bradycardia have been reported with alectinib. Data based on ECG and pulse measurements from the ongoing alectinib clinical trials show a decrease in heart rate during alectinib treatment, which is mainly asymptomatic. In patients 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 also 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.

**Abnormal Renal Function (Serum Creatinine increased, Acute Kidney Injury)**
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. Serum creatinine increases and acute kidney injury with fatal outcome has been observed with uncommon frequency in patients treated in alectinib clinical trials.
Serum creatinine increases and/or decreases in GFR, renal failure and/or renal impairment have been reported for other ALK inhibitors (crizotinib, ceritinib).

Serum creatinine increases and/or decreases in GFR, renal failure and/or renal impairment have been reported for other ALK inhibitors (crizotinib, ceritinib).
See section 6.2 for management and follow-up.

**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.

**Dysgeusia**
Events of dysgeusia have been reported in clinical trials with alectinib, and were generally of Grade 1 and 2 severity. All patients who experienced dysgeusia, continued alectinib treatment without any modification. In patients treated with other ALK inhibitors, such as crizotinib and ceritinib, dysgeusia has been reported.

See section 6.2 for management and follow-up.

**Alkaline Phosphatase (ALP) Increase**

Cases of increased blood ALP have been observed after alectinib administration. The majority of the cases were of Grade 1 and Grade 2 severity. In patients treated with other ALK inhibitors, increased blood ALP has been reported.

See section 6.2 for management and follow-up.

7.1.1.1 Adverse Event List for Bevacizumab

**Hypertension**: An increased incidence of hypertension has been observed in patients treated with bevacizumab. Grade 4 and 5 hypertensive events are rare. Clinical sequelae of hypertension are rare but have included hypertensive crisis, hypertensive encephalopathy, and reversible posterior leukoencephalopathy syndrome (RPLS). There is no information on the effect of bevacizumab in patients with uncontrolled hypertension at the time of initiating bevacizumab therapy. Therefore, caution should be exercised before initiating bevacizumab therapy in these patients. Monitoring of blood pressure is recommended during bevacizumab therapy. Optimal control of blood pressure according to standard public health guidelines is recommended for patients on treatment with or without bevacizumab. Temporary interruption of bevacizumab therapy is recommended in patients with hypertension requiring medical therapy until adequate control is achieved. If hypertension cannot be controlled with medical therapy, bevacizumab therapy should be permanently discontinued. Bevacizumab should be permanently discontinued in patients who develop hypertensive crisis or hypertensive encephalopathy.

**Proteinuria**: An increased incidence of proteinuria has been observed in patients treated with bevacizumab compared with control arm patients. In the bevacizumab-containing treatment arms of clinical trials (across all indications), the incidence of proteinuria (reported as an adverse event) was up to 38% (metastatic CRC Study AVF2192g). The severity of proteinuria has ranged from asymptomatic and transient events detected on routine dipstick urinalysis to nephrotic syndrome; the majority of proteinuria events have been grade 1. NCI-CTC Grade 3 proteinuria was reported in up to 3% of bevacizumab-treated patients, and Grade 4 in up to 1.4% of bevacizumab-treated patients. The proteinuria seen in bevacizumab clinical trials was not associated with renal impairment and rarely required permanent discontinuation of bevacizumab therapy. Bevacizumab should be discontinued in patients who develop Grade 4 proteinuria (nephrotic syndrome). Patients with a history of hypertension may be at increased risk for the development of proteinuria when treated with bevacizumab. There is evidence from the dose-finding, Phase II trials (AVF0780g, AVF0809s, and AVF0757g) suggesting that
Grade 1 proteinuria may be related to bevacizumab dose.

**Thromboembolic Events**: Both venous and arterial thromboembolic (TE) events, ranging in severity from catheter-associated phlebitis to fatal events, have been reported in patients treated with bevacizumab in the colorectal cancer trials and, to a lesser extent, in patients treated with bevacizumab in NSCLC and breast cancer trials.

**Venous thromboembolism (including deep venous thrombosis, pulmonary embolism, and thrombophlebitis)**: In the pivotal Phase III trial in metastatic CRC, there was a slightly higher rate of venous TE events in patients treated with bevacizumab plus chemotherapy compared with chemotherapy alone (19% vs. 16%). In Study AVF2107g, a Phase III, pivotal trial in metastatic CRC, VTE events, including deep venous thrombosis, pulmonary embolism, and thrombophlebitis, occurred in 15.2% of patients receiving chemotherapy alone and 16.6% of patients receiving chemotherapy and bevacizumab.

The incidence of NCI-CTC Grade ≥ 3 venous VTE events in one NSCLC trial (E4599) was higher in the bevacizumab-containing arm compared to the chemotherapy control arm (5.6% vs. 3.2%). One event (0.2%) was fatal in the bevacizumab-containing arm; no fatal events were reported in the carboplatin/paclitaxel arm (see bevacizumab Investigator Brochure).

In metastatic CRC clinical trials, the incidence of VTE events was similar in patients receiving chemotherapy plus bevacizumab and those receiving the control chemotherapy alone. In clinical trials across all indications the overall incidence of VTE events was 2.8 - 17.3% in the bevacizumab-containing arms compared with 3.2 - 15.6% in the chemotherapy control arms. The use of bevacizumab with chemotherapy does not substantially increase the risk of VTE event compared with chemotherapy alone. However, patients with metastatic CRC who receive bevacizumab and experienced a VTE event may be at higher risk for recurrence of VTE event.

**Arterial Thromboembolic Events:** An increased incidence of ATE events was observed in patients treated with bevacizumab compared with those receiving control treatment. ATE events include cerebrovascular accidents, myocardial infarction, transient ischemic attacks (TIAs), and other ATE events. In a pooled analysis of data from five randomized Phase II and III trials (mCRC [AVF2107g, AVF2192g, AVF0780g]; locally advanced or metastatic NSCLC [AVF0757g]; and metastatic breast cancer [AVF2119g]), the incidence of ATE events was 3.8% (37 of 963) in patients who received chemotherapy and bevacizumab compared with 1.7% (13 of 782) in patients treated with chemotherapy alone. ATE events led to a fatal outcome in 0.8% (8 of 963) of patients treated with chemotherapy and bevacizumab and 0.5% (4 of 782) of patients treated with chemotherapy alone. Cerebrovascular accidents (including TIAs) occurred in 2.3% of patients treated with chemotherapy and bevacizumab and 0.5% of patients treated with chemotherapy alone. Myocardial infarction occurred in 1.4% of patients treated with chemotherapy plus bevacizumab compared with 0.7% of patients treated with chemotherapy alone (see the bevacizumab Investigator Brochure for additional details).

Aspirin is a standard therapy for primary and secondary prophylaxis of arterial thromboembolic events in patients at high risk of such events, and the use of aspirin ≤ 325 mg daily was allowed in the five randomized studies discussed above. Use of aspirin was assessed routinely as a baseline or concomitant medication in these trials, though safety analyses specifically regarding aspirin use were not preplanned. Due to the relatively small numbers of aspirin users and arterial thromboembolic events, retrospective analyses of the ability of aspirin to affect the risk of such events were inconclusive. However, similarly retrospective analyses suggested that the use of up to 325 mg of aspirin daily does not increase the risk of grade 1-2 or grade 3-4 bleeding events, and similar data with respect to metastatic colorectal cancer patients were presented at ASCO 2005 (Hambleton et al., 2005). Further analyses of the effects of concomitant use of bevacizumab and aspirin in colorectal and other tumor types are ongoing.

**Gastrointestinal perforation:** Patients with metastatic carcinoma may be at increased risk for the development of gastrointestinal perforation and fistula when treated with bevacizumab and chemotherapy. Bevacizumab should be permanently discontinued in patients who develop gastrointestinal perforation. A causal association of intra-abdominal inflammatory processes and gastrointestinal perforation to bevacizumab treatment has not been established. Nevertheless, caution should be exercised when treating patients with intra-abdominal inflammatory processes with bevacizumab. Gastrointestinal perforation has been reported in other trials in non-colorectal cancer populations (e.g., ovarian, renal cell, pancreas, breast, and NSCLC) and may be higher in incidence in some tumor types.

**Fistula**: Bevacizumab use has been associated with serious cases of fistulae including events resulting in death. Fistulae in the GI tract are common (1%–10% incidence) in patients with metastatic CRC, but uncommon (0.1 - 1%) or rare (0.01%–0.1%) in other indications. In addition, fistulae that involve areas of the body other than the GI tract (e.g., tracheoesophageal, bronchopleural, urogenital, biliary) have been

reported uncommonly (0.1%–1%) in patients receiving bevacizumab in clinical studies and postmarketing reports. Events were reported at various timepoints during treatment, ranging from 1 week to > 1 year following initiation of bevacizumab, with most events occurring within the first 6 months of therapy. Bevacizumab should be permanently discontinued in patients with tracheoesophageal fistulae or any Grade 4 fistula. Limited information is available on the continued use of bevacizumab in patients with other fistulae. In cases of internal fistula not arising in the GI tract, discontinuation of bevacizumab should be considered.

**Wound healing complications:** Wound healing complications such as wound dehiscence have been reported in patients receiving bevacizumab. In an analysis of pooled data from two trials in metastatic colorectal cancer, patients undergoing surgery 28-60 days before study treatment with 5-FU/LV plus bevacizumab did not appear to have an increased risk of wound healing complications compared to those treated with chemotherapy alone.[37] Surgery in patients currently receiving bevacizumab is not recommended. No definitive data are available to define a safe interval after bevacizumab exposure with respect to wound healing risk in patients receiving elective surgery; however, the estimated half life of bevacizumab is 21 days. Bevacizumab should be discontinued in patients with severe wound healing complications.

If patients receiving treatment with bevacizumab require elective major surgery, it is recommended that bevacizumab be held for 4–8 weeks prior to the surgical procedure. Patients undergoing a major surgical procedure should not begin or restart bevacizumab until 4 weeks after that procedure (in the case of high-risk procedures such as liver resection, thoracotomy, or neurosurgery, it is recommended that chemotherapy be restarted no earlier than 6 weeks and
bevacizumab no earlier than 8 weeks after surgery).

**Hemorrhage**: Overall, Grade 3 and 4 bleeding events were observed in 4.0% of 1132 patients treated with bevacizumab in a pooled database from eight Phase I, II, and III clinical trials in multiple tumor types (bevacizumab Investigator Brochure). The hemorrhagic events that have been observed in bevacizumab clinical studies were predominantly tumor-associated hemorrhage (see below) and minor mucocutaneous hemorrhage.

**Tumor-Associated Hemorrhage:** Major or massive pulmonary hemorrhage or hemoptysis has been observed primarily in patients with NSCLC. Life-threatening and fatal hemoptysis was identified as a bevacizumab-related adverse event in NSCLC trials. These events occurred suddenly and presented as major or massive hemoptysis. Among the possible risk factors evaluated (include squamous cell histology, treatment with anti-rheumatic/anti-inflammatory drugs, treatment with anticoagulants, prior radiotherapy, bevacizumab therapy, previous medical history of atherosclerosis, central tumor location, and cavitation of tumors during therapy), the only variables that showed statistically significant correlations with bleeding were bevacizumab therapy and squamous cell histology.

Of patients experiencing pulmonary hemorrhages requiring medical intervention, many had cavitation and/or necrosis of the tumor, either preexisting or developing during bevacizumab therapy. Patients developing lung cavitation on treatment should be assessed by the treating physician for risk-benefit. In Study E4599, in which squamous cell carcinoma was excluded, the rate of any type of Grade ≥ 3 hemorrhage was 1.0% in the control arm (carboplatin and
paclitaxel) versus 4.1% in the carboplatin and paclitaxel plus bevacizumab arm.[23]

GI hemorrhages, including rectal bleeding and melena have been reported in patients with CRC, and have been assessed as tumor-associated hemorrhages.

Tumor-associated hemorrhages were also seen rarely in other tumor types and locations, including a case of CNS bleeding in a patient with hepatoma with occult CNS metastases and a patient who developed continuous oozing of blood from a thigh sarcoma with necrosis. A recent review examined the risk of CNS hemorrhage in association with anti-VEGF therapy. Among 669 patients treated on Phase I and II studies of bevacizumab that excluded brain metastases, only 1 case (0.2%) of CNS bleeding was reported.[38]

**Mucocutaneus Hemorrhage:** Across all bevacizumab clinical trials, mucocutaneous hemorrhage has been seen in 20%-40% of patients treated with bevacizumab. These were most commonly NCI-CTC Grade 1 epistaxis that lasted less than 5 minutes, resolved without medical intervention and did not require any changes in bevacizumab treatment regimen. There have also been less common events of minor mucocutaneous hemorrhage in other locations, such as gingival bleeding and vaginal bleeding.

**Reversible Posterior Leukoencephalopathy Syndrome:** There have been rare reports of bevacizumab-treated patients developing signs and symptoms that are consistent with RPLS, a rare neurological disorder that can present with the following signs and symptoms (among others): seizures, headache, altered mental status, visual disturbance, or cortical blindness, with or without associated hypertension. Brain imaging is mandatory to confirm the diagnosis of RPLS. In patients who develop RPLS, treatment of specific symptoms, including control of hypertension, is recommended along with discontinuation of bevacizumab. The safety of reinitiating bevacizumab therapy in patients previously experiencing RPLS is not known.[39]

**Congestive heart failure:** In clinical trials, CHF was observed in all cancer indications studied to date, but predominantly in patients with metastatic breast cancer. In the Phase III clinical trial of metastatic breast cancer (AVF2119g), 7 (3%) bevacizumab-treated patients experienced CHF, compared with two (1%) control arm patients. These events varied in severity from asymptomatic declines in left ventricular ejection fraction (LVEF) to symptomatic CHF requiring hospitalization and treatment. All the patients treated with bevacizumab were previously treated with anthracyclines (doxorubicin cumulative dose of 240□-360 mg/m2). Many of these patients also had prior radiotherapy to the left chest wall. Most of these patients showed improved symptoms and/or left ventricular function following appropriate medical therapy.

In a randomized, Phase III trial of patients with previously untreated metastatic breast cancer (E2100), the incidence of LVEF decrease (defined as NCI-CTC Grade 3 or 4) in the paclitaxel □□bevacizumab arm was 0.3% versus 0% for the paclitaxel alone arm. No information is available on patients with preexisting CHF of New York Heart Association (NYHA) Class II□IV at the time of initiating bevacizumab therapy, as these patients were excluded from clinical trials. Prior anthracyclines exposure and/or prior radiotherapy to the chest wall may be possible risk factors for the development of CHF. Caution should be exercised before initiating bevacizumab therapy in patients with these risk factors. A Phase II trial in patients with refractory acute myelogenous leukemia reported 5 cases of cardiac dysfunction (CHF or LVEF decrease to <□40%) among
48 patients treated with sequential cytarabine, mitoxantrone, and bevacizumab. All but 1 of these patients had significant prior exposure to anthracyclines as well.[40]

Two additional studies investigated concurrent administration of anthracyclines and bevacizumab. In 21 patients with inflammatory breast cancer treated with neoadjuvant docetaxel, doxorubicin, and bevacizumab, no patients developed clinically apparent CHF; however, patients had asymptomatic decreases in LVEF to < 40%.[41] In a small Phase II study in patients with soft tissue sarcoma, 2 of the 17 patients treated with bevacizumab and high-dose doxorubicin (75 mg/m2) developed CHF (one Grade 3 event after a cumulative doxorubicin dose of 591 mg/m2, one Grade 4 event after a cumulative doxorubicin dose of 420 mg/m2); an additional 4 patients had asymptomatic decreases in LVEF.[42] Other

studies in patients with various tumor types and either a history of anthracycline exposure or concomitant use with bevacizumab are ongoing. Patients receiving concomitant anthracyclines or with prior exposure to anthracyclines should have a baseline MUGA scans or echocardiograms (Echo's) with a normal LVEF.

**Neutropenia:** Increased rates of severe neutropenia, febrile neutropenia, or infection with severe neutropenia (including some fatalities) have been observed in patients treated with some myelotoxic chemotherapy regimens plus bevacizumab in comparison to chemotherapy alone.

**Additional Adverse Events:** See the bevacizumab Investigator Brochure for additional details regarding the safety experience with bevacizumab.

## 7.2 Safety Reporting of Adverse Events

**Specifications of Safety Variables**
Safety assessments will consist of monitoring and reporting adverse events (AEs) and serious adverse events (SAEs) that are considered related to alectinib and/or bevacizumab, all events of death, and any study specific issue of concern.

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

**Adverse Events**
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 NSCLC 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.

Preexisting 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.

**Serious Adverse Events**
An AE should be classified as an 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).

## *METHODS AND TIMING FOR ASSESSING AND RECORDING SAFETY VARIABLES*

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

### Adverse Event Reporting Period

The study period during which all AEs and SAEs must be reported begins after informed consent is obtained and initiation of study treatment and ends 30 days following the last administration of study treatment or study discontinuation/termination, whichever is earlier. After this period, investigators should only report SAEs that are attributed to prior study treatment.

### Assessment of Adverse Events

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 the study drugs (see following guidance), 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 the study drugs, 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 the study drugs; and/or the AE abates or resolves upon discontinuation of the study drugs or dose reduction and, if applicable, reappears upon re-challenge.

**No**
Evidence exists that the AE has an etiology other than the study drugs (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to study drug 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 or current Investigator Brochure.

Unexpected adverse events are those not listed in the Package Insert (P.I.) or current Investigator Brochure (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.

## *PROCEDURES FOR ELICITING, RECORDING AND REPORTING ADVERSE EVENTS*

**Eliciting 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?"

**Specific Instructions for Recording Adverse Events**
Investigators should use correct medical terminology/concepts when reporting AEs or SAEs. Avoid colloquialisms and abbreviations.

**a. 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 ok to report the information that is currently available. If a diagnosis is subsequently established, it should be reported as follow-up information.

**b. Deaths**
All deaths that occur during the protocol-specified AE reporting period, regardless of attribution, will be reported to the appropriate parties. When recording a death, the event or condition that caused or contributed to the fatal outcome should be reported as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, report "Unexplained Death".

c. **Preexisting Medical Conditions**
A preexisting medical condition is one that is present at the start of the study. Such conditions should be reported as medical and surgical history. A preexisting 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 preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

**d. Hospitalizations for Medical or Surgical Procedures**
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 preexisting 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.

e. **Pregnancy**

If a female subject or a female partner of a male subject, becomes pregnant while receiving investigational therapy or within 90 days after the last dose of study drug, a report should be completed and expeditiously submitted to the 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 the study drugs should be reported as an SAE.

**f. 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 study drug 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.

**g. Reconciliation/Case Transmission Verification of Single Case Reports**

The Sponsor agrees to conduct reconciliation to ensure that all single case reports have been adequately received by Genentech. Genentech and the Sponsor 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 Sponsor and Genentech 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.

Following Case Transmission Verification, single case reports which have not been received by Genentech/Roche shall be forwarded by the Sponsor to Genentech/Roche within five (5) calendar days from request by Genentech/Roche.

At the end of the study, a final cumulative Case Transmission Verification report will be sent to Genentech/Roche.

Case transmission verification/ queries on CTV should be sent to:
ctvist_drugsafety@gene.com

**h. AEs of Special Interest (AESIs)**

AEs of Special Interest are defined as a potential safety problem, identified as a result of safety monitoring of the Product.

Adverse events of special interest for this study include 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:

    - o Treatment-emergent ALT or AST > 3 x ULN in combination with total bilirubin > 2 x ULN

    - o Treatment-emergent ALT or AST > 3 x ULN in combination with clinical jaundice

- 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 patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected

## 7.3 Expedited Adverse Event Reporting

7.3.1 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.

7.3.2 DF/HCC Expedited Reporting Guidelines

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

## 7.4 Expedited Adverse Event Reporting – Genentech

Investigators must report all SAEs, AESIs,Special Situation Reports (including pregnancy reports) and Product Complaints with an AE should be sent to Genentech within the timelines described below. The completed Medwatch/case report should be sent immediately upon completion to Genentech Drug Safety at:

**Fax: 650-238-6067**
**Email: usds_aereporting-d@gene.com**

- Fax Cover Sheets are available in Appendix C.
- Relevant follow-up information should be submitted to Genentech Drug Safety as soon as it becomes available.
- Serious AE reports that are related to the study drugs will be transmitted to Genentech within fifteen (15) calendar days of the Awareness Date.
- Serious AE reports that are unrelated to the study drugs will be transmitted to Genentech within thirty (30) calendar days of the Awareness Date.
- AESIs will be transmitted to Genentech within fifteen (15) calendar days of the Awareness Date.
- Pregnancy reports
  While such reports are not serious AEs or Adverse Drug Reactions (ADRs) per se, as defined herein, any reports of pregnancy (including pregnancy occurring in the partner of a male study subject), where the fetus may have been exposed to the Product, shall be transmitted to Genentech within thirty (30) calendar days of the awareness date. Pregnancies will be followed up until the outcome of the pregnancy is known, whenever possible, based upon due diligence taken to obtain the follow-up information.

Pregnancies in Female Partners of Male Patients
Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 30 days after the last dose of study drug. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to Genentech within thirty (30) calendar days of the awareness date.

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

  In addition, reasonable attempts should made to obtain and submit the age or age group of the patient, in order to be able to identify potential safety signals specific to a particular population
- .Product Complaints

  All Product Complaints (with or without an AE) shall be forwarded to Genentech within fifteen (15) calendar days of the awareness date.

  A Product Complaint is defined as any written or oral information received from a complainant that alleges deficiencies related to identity, quality, safety, strength, purity, reliability, durability, effectiveness, or performance of a product after it has been released and distributed to the commercial market or clinical trial.

  All Product Complaints without an AE or special situation should be reported to:

  Product Complaints Hotline Number: (800) 334-0290

*Note: Investigators should also report events to their IRB as required (see Section 7.6).*

**MedWatch 3500A Reporting Guidelines**

In addition to completing appropriate patient demographic and suspect medication information, the report should include the following information within the Event Description 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 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 patient identifiers (i.e. D.O.B. initial, patient number), protocol description and number, if assigned, brief adverse event description, and notation that additional or follow-up information is being submitted (The patient 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 patient 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.

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

## 7.5 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 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 the study drug(s). An unexpected adverse event is one that is not already described in the study drug's 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 the study drug. An unexpected adverse event is one that is not already described in the study drug 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 written IND Safety Reports submitted to the FDA by the Investigator must also be faxed to Genentech Drug Safety:**
Fax: (650) 225-4682 or (650) 225-4630

For questions related to safety reporting, please contact Genentech Drug Safety:
Tel: (888) 835-2555
Fax: (650) 225-4682 or (650) 225-4630

**IND Annual Reports**

***Copies to Genentech:***
All IND annual reports submitted to the FDA by the Sponsor-Investigator should be copied to Genentech. Copies of such reports should be emailed to Genentech at: Genentech Drug Safety CTV mail box: ctvist_drugsafety@gene.com

**Aggregate Reports**

The Sponsor will forward a copy of the Final Study Report to Genentech/Roche upon completion of the Study. Copies of such reports should be emailed to Genentech at: Genentech Drug Safety CTV mail box: ctvist_drugsafety@gene.com

The Sponsor will be responsible for the preparation of their own Development Safety Update Report (DSUR) for the Study and for the submission of the report to the regulatory authorities and Ethics Committees of the concerned Member States, where applicable. The Sponsor agrees to share a copy of their own DSUR with Genentech/Roche as soon as reasonably possible after completion. Genentech/Roche agrees to forward to the Sponsor an executive summary of the Genentech/Roche DSUR upon request. Furthermore, Genentech/Roche agrees that the Sponsor may cross-reference the executive summary of the Genentech/Roche DSUR, as applicable.

Note: Investigators should also report events to their IRB as required.

***Study Close-Out***
Any study report submitted to the FDA by the Sponsor-Investigator should be copied to Genentech. 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. Copies of such reports should be emailed to Genentech at: Genentech Drug Safety CTV mail box: ctvist_drugsafety@gene.com

**Queries**

Queries related to the Study will be answered by the Sponsor. However, responses to all safety queries from regulatory authorities or for publications will be discussed and coordinated between the Parties. The Parties agree that Genentech/Roche shall have the final say and control over safety queries relating to the Product. The Sponsor agrees that it shall not answer such queries from regulatory authorities and other sources relating to the Product independently but shall redirect such queries to Genentech/Roche.

Both Parties will use all reasonable effort to ensure that deadlines for responses to urgent requests for information or review of data are met. The Parties will clearly indicate on the request the reason for urgency and the date by which a response is required.

**Safety Crisis Management**

In case of a safety crisis, e.g., where safety issues have a potential impact on the indication(s), on the conduct of the Study, may lead to labeling changes or regulatory actions that limit or restrict the way in which the Product is used, or where there is media involvement, the Party where the crisis originates will contact the other Party as soon as possible.

The Parties agree that Genentech/Roche shall have the final say and control over safety crisis management issues relating to the Product. The Sponsor agrees that it shall not answer such queries from media and other sources relating to the Product but shall redirect such queries to Genentech/Roche.

## 7.6 Reporting to the Institutional Review Board (IRB)

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

## 7.7 Expedited Reporting to Hospital Risk Management

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

## 7.8 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 <u>also</u> be reported in routine study data submissions.**

7.9 Overall PI/Sponsor of the Study, will be responsible for the expedited reporting of safety reports originating from the study to the EMA through Eudravigilance Clinical Trial Module (EVCTM), where applicable. Overall PI/Sponsor of the Study will be responsible for the distribution of safety information to its own investigators, where relevant, in accordance with local regulations.

# 8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the study agents can be found in Section 7.1.

## 8.1 Alectinib

### 8.1.1 Description

Alectinib is a second-generation ALK tyrosine kinase inhibitor.

[Chemical name] 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**

Each capsule contains 150 mg of alectinib (as free base) along with lactose monohydrate, carmellose calcium, hydroxypropyl cellulose, SLS, and magnesium stearate.

### 8.1.3 **Storage and Stability**

Alectinib capsules should be stored in accordance with the storage instructions on the label.

### 8.1.4 **Compatibility**

N/A

### 8.1.5 **Handling**

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

The Investigator (or assigned designee, i.e., study pharmacist) will dispense the proper number of each strength capsule to the participant to satisfy dosing requirements for the study. The containers provided to the participant should be labeled with proper instructions for use. The lot numbers, dosing start dates and the number of capsules for each dosage strength must be recorded on the drug accountability pages of record for the site. The participant must be instructed to return all unused alectinib in the provided packaging at each subsequent visit.

### 8.1.6 **Availability**

Alectinib will be provided by Genentech/Roche.

### 8.1.7 **Preparation**

N/A

### 8.1.8 **Administration**

See Section 5.2.1

### 8.1.9 **Ordering**

Investigative site(s) will order alectinib directly through Genentech/Roche. Shipments will be at appropriate intervals, depending on patient accrual. The site(s) must use an appropriate dispensing log/accountability form provided by the Sponsor, or an acceptable substitute approved by the Sponsor. Each time study medication is dispensed for a participant, the following information must be recorded: the patient's initials, the patient's study number, the number of capsules dispensed with the corresponding lot number, and the initials of the person dispensing the drug. These logs are to be maintained by the study pharmacist in the pharmacy throughout the duration of the study. The Investigator is responsible for ensuring that the patient diary card(s) and study drug provided to the

participant and returned from the participant are accounted for and noted in source documentation.

### 8.1.10 **Accountability**

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

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

### 8.1.11 **Destruction and Return**

If the investigational product is to be destroyed on site, it is the investigator's responsibility to ensure that arrangements have been made for disposal, and that procedures for proper disposal have been established according to applicable regulations, guidelines, and institutional procedures. Appropriate records of the disposal must be maintained.

Consult with the Principal Investigator for instructions on disposal of unused alectinib capsules.

## 8.2 Bevacizumab

### 8.2.1 **Description**

Bevacizumab is a recombinant monoclonal antibody targeting vascular endothelial growth factor (VEGF)

### 8.2.2 **Form**

Pharmaceutical form: solution for dilution for infusion

Bevacizumab 25 mg per mL
Trehalose dihydrate
Sodium phosphate
Polysorbate 20
Water for injection
Clear to slightly opalescent liquid, colourless to pale brown

### 8.2.3 **Storage and Stability**

Chemical and physical stability during use has been demonstrated for 48 hours between 2°C and 30°C in an injectable solution of sodium chloride at 9 mg/mL (0.9%). From a microbiological point of view, immediate use is recommended. If the product is not used immediately after reconstitution, the storage period and conditions are the responsibility of the user and must not normally exceed 24 hours in the refrigerator between 2°C and 8°C, unless the dilution has been performed in controlled, aseptic conditions.

Do not freeze.

Store the vial in the outer packaging away from light.

### 8.2.4 **Compatibility**

No incompatibility between bevacizumab and infusion bags or devices made of polyvinyl chloride or polyolefin has been observed.

### 8.2.5 **Handling/Preparation**

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

Bevacizumab must be prepared by a health professional observing aseptic precautions. Take the volume of bevacizumab needed for the preparation of one dose of 15 mg/kg of body weight every 3 weeks and dilute it with an injectable solution of sodium chloride at 9 mg/mL (0.9%) up to a total volume of 100 mL. Dispose of any unused amount remaining in the vial, since the product does not contain a preservative. Medicinal products intended for parenteral route must be visually examined, looking for particles and colour deviations, before their administration.

No incompatibility between bevacizumab and infusion bags or devices made of polyvinyl chloride or polyolefin has been observed.

When bevacizumab has been mixed with a sterile saline solution bag, the solution must be administered within 8 hours.

Bevacizumab must not be administered or mixed with glycated solutions (see investigator's brochure).

A mechanism regulating the speed of the infusions will be used for all infusions. When the bag is empty, a volume of 50 mL of sodium at 0.9% will be added or another bag will be added, and the infusion will be continued for a volume equal to that of the tube in order to ensure the complete administration of bevacizumab. Saline solution, which will then be injected to empty the tube, will not influence the infusion time of the study treatment.

### 8.2.6 **Availability**

Bevacizumab will be provided by Genentech/Roche.

### 8.2.7 **Administration**

See Section 5.2.2

### 8.2.8 **Ordering**

Investigative site(s) will order bevacizumab directly through Genentech/Roche. Shipments will be at appropriate intervals, depending on patient accrual. The site(s) must use an appropriate dispensing log/accountability form provided by the Sponsor, or an acceptable substitute approved by the Sponsor.

### 8.2.9 **Accountability**

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

Bevacizumab dispensing record/inventory logs and copies of signed packing lists must be maintained

at the investigational site. Batch numbers for bevacizumab must be recorded in the drug accountability records.

### 8.2.10 **Destruction and Return**

If the investigational product is to be destroyed on site, it is the investigator's responsibility to ensure that arrangements have been made for disposal, and that procedures for proper disposal have been established accordingto applicable regulations, guidelines, and institutional procedures. Appropriate records of the disposal must be maintained.

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

## 9. STUDY CALENDAR AND ASSESSMENTS

Baseline evaluations are to be conducted within 2 weeks prior to start of protocol therapy. Scans must be done ≤4 weeks prior to the start of therapy. In the event that the participant's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

Assessments must be performed prior to administration of any study agent. Study assessments and agents should be administered within ± 3 days of the protocol-specified date, unless otherwise noted.

**Table 9-1: Study Calendar**

| **Assessment** | **Baseline** | **Cycle 1 Day 1** | **Cycle 1 Day 15** | **Cycle 2-10 Day 1** | **Subsequent Cycles Day 1** | **End of Treatment** | **30 Day Safety Follow-up** |
|---|---|---|---|---|---|---|---|
| Informed Consent | X | | | | | | |
| Demographics | X | | | | | | |
| Inclusion/Exclusion Criteria | X | | | | | | |
| Relevant Medical History & Current Medical Conditions | X | | | | | | |
| Diagnosis & Extent of Cancer | X | | | | | | |
| Prior Antineoplastic Therapy | X | | | | | | |
| Documentation of ALK status | X | | | | | | |
| Concomitant Medications | X | Continuous | | | | | X |
| Vital signs | X | X | X | X | X | X | |
| ECOG Performance Status | X | X | X | X | X | X | |
| Physical Exam | X | X | X | X | X | X | |
| Hematology/Chemistry[1] | X | X | X | X | X | X | |
| Coagulation | X | | | | | X | |
| ECG | X | X | | X[2] | X[2] | X | |
| Urinalysis | X | X | | X | X | X | |
| Pregnancy Test | X | | | | | | |
| Disease Assessments | X[3] | | | X[3, 7] | X[4,7] | X | |
| Patient Reported Outcomes[5] | X | X | | X | X | X | X |
| Tumor Biopsies (Optional)[6] | X | | | | | X | |
| Adverse Events[7] | X | Continuous | | | | | X |

1. ALT, AST and total bilirubin should also be obtained on cycle 1, day 15.

2. ECGS will be performed at baseline, cycle 1 day 1, cycle 2 day 1, cycle 8 day 1 (week 24), cycle 18 day 1 (week 56), end of treatment visit, and as clinically indicated throughout the study.

3. Baseline disease assessments will include CTs of the chest and abdomen (if clinically indicated, a CT of the pelvis should also be performed) and a brain MRI. Please see Section 9.1 for specifics on MRI slice thickness. Repeat disease assessments (including a brain MRI) should take place every 2 cycles for the first 10 cycles of study treatment. Note: Participants in the phase I portion of the study will not be required to have brain MRIs performed beyond screening, provided that the baseline brain MRI is negative for intracranial metastases.

4. After cycle 10, disease assessments will take place every 4 cycles.

5. Patient reported outcome (PROs) questionnaires will include: EORTC QLQ-C30 and QLQ-BN20.

6. Optional biopsies will be performed at baseline and upon disease progression on alectinib/bevacizumab. When possible, a core biopsy is preferred, though not required, over a fine-needle aspiration or cytology specimen.

7. For patients who are holding bevacizumab or who have permanently discontinued bevacizumab, study assessments (vitals, exam, and laboratories) can be performed every 6 weeks. Virtual visits are permitted during the COVID-19 pandemic.

## 9.1 Study Assessments

- **Informed consent:** Informed consent, documented by a signed consent form, must be obtained prior to any screening activities not otherwise part of the participant's care. A note documenting the informed consent procedure should be included in the participant's medical record. Signed, informed consent should be obtained with 28 days of treatment start.

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

- **Relevant Medical History & Current Medical Conditions:** Medical and surgical history includes diagnoses, therapies, and medical/surgical treatments.

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

- **Prior Antineoplastic Therapy:** Prior cancer therapy history consists of the specific oncologic regimens a patient has received, the dates of the regimen and the best response to the regimen, and the reason for failure or intolerance to each regimen. Stem cell transplant or experimental or investigational therapy history must also be recorded. In particular, focus will be placed on prior CNS-directed therapies, such as radiation or surgical procedures.

- **Documentation of an ALK Rearrangement:** ALK status to be determined using ALK FISH, IHC or next-generation sequencing (NGS). For ALK FISH, positivity is defined as >15% positive tumor cells. Local ALK testing is acceptable, provided that archival tissue is available for patients deemed ALK positive on the basis of IHC or NGS.

- **Concomitant Medications:** Concomitant medications for all ongoing medical history conditions or AEs must be reported from the date the informed consent is signed until at least 30 Days After the End of Treatment, and for all concomitant medications related to serious or study drug-related toxicities until the medication is no longer taken or until patient contact discontinues. Special focus will be placed on use and dose of corticosteroids over time.

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

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

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

- **Hematology:** Hematology assessments of the parameters listed in Table 9-1 will be tested as per the schedule of assessments (Table 9-1).

**Table 9-2: Local Clinical Laboratory Parameters Collection Plan**

| Test Category | Test Name |
|---|---|
| Hematology | Hgb, platelets, white blood cells (WBC), red blood cells (RBC), differential [basophils, eosinophils, lymphocytes, monocytes, neutrophils (% or absolute)] |
| Chemistry | Albumin, ALT, AST, calcium, creatinine, total bilirubin, direct bilirubin (only if total bilirubin is ≥ grade 2), blood urea nitrogen (BUN) or urea, magnesium, potassium, sodium, glucose, phosphate (inorganic phosphorus), alkaline phosphatase, and **creatine phosphokinase (CPK)** |
| Coagulation | International normalized ration (INR) and PTT. |
| Urinalysis | Macroscopic panel ()(color, total bilirubin, blood, glucose, ketones, leukocyte esterase, nitrite, pH, protein, specific gravity, urobilinogen) Microscopic panel (RBC, WBC, casts, crystals, bacteria, epithelial cells) |
| Pregnancy test | At screening visit, serum pregnancy test will be performed |

- **Chemistry:** Clinical chemistry assessments of the parameters listed in Table 9-2 will be tested as per the schedule of assessments (Table 9-1).

- **Coagulation:** Coagulation assessments of the parameters listed in Table 9-2 will be tested as per the schedule of assessments (Table 9-1).

- **Electrocardiogram:** 12-lead ECGs will be performed at baseline, cycle 1 day 1, cycle 2 day 1, cycle 8 day 1, cycle 18 day 1 and at end of treatment. ECGs will also be performed as clinically indicated throughout the study.

- **Urinalysis:** measurements will be performed as per Table 9-2 and according to the schedule of assessments (Table 9-1). **Pregnancy Test:** During screening, a serum pregnancy test will be completed.

- **Disease Assessments:** At screening, disease assessment must include imaging of the chest and abdomen. A CT of the pelvis should also be performed if clinically indicated. A gadolinium-enhanced brain MRI is also required at entry and as part of serial assessments (Note: Phase I participants with a brain MRI that is negative for intracranial metastases at baseline do not require serial brain MRIs as part of their disease assessments). MRI slices should be 1 mm for brain metastases measuring 5-10 mm in size. MRI slices of 1-5 mm are permitted for brain metastases measuring between 10 and 40 mm.

  Target and non-target lesions must be selected at study start and followed throughout the course of treatment for response assessment according to RECIST version 1.1 guidelines (See Section 10) and a modified RECIST for CNS response (Long 2012; Section 10). Imaging assessment is also required to be performed at the End of Treatment.

- **Patient-reported outcomes (PROs)**: PROs (EORTC QLQ-C30 and QLQ-BN20) will be

collected to more fully characterize the clinical profile of alectinib/bevacizumab. The instruments will be translated as required into the local language. To ensure instrument validity, the PROs scheduled for administration during a clinic visit should be completed prior to the performance of non-PRO assessments and the administration of study drugs.

- **Tumor Biopsies (Optional):** An optional baseline biopsy will be performed on participants at the time of study entry (i.e., prior to treatment with alectinib and bevacizumab). When possible, a core biopsy is preferred, though not required, over a fine-needle aspiration or cytology specimen. Among participants previously treated with other ALK inhibitors (e.g. crizotinib), tissue will be analyzed for molecular mechanisms of resistance. For example, specimens will be assessed for ALK gene amplification, secondary mutations in the ALK tyrosine kinase domain, and bypass tract activation.

  In addition, participants will undergo an optional biopsy at the time of disease progression on alectinib/bevacizumab. This will be evaluated for molecular mechanisms of resistance to alectinib/bevacizumab (e.g. secondary mutations in the ALK tyrosine kinase domain). Due to the evolving nature of the field, not all of the proteins or genes of interest leading to response or resistance can be pre-specified in this document.

- **Adverse Events:** Participants must be followed for all adverse events (AEs) from the start of study treatment until at least 30 Days After the End of Treatment, and for all serious or study drug-related toxicities until the AEs are resolved or are considered chronic or stable or until patient contact discontinues. Serious adverse events (SAEs) should be monitored and reported as described in Section 7.

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

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

## 10. MEASUREMENT OF EFFECT

Although response is not the primary endpoint of this trial, participants with measurable disease will be assessed by RECIST version 1.1 as well as a modified version of RECIST to include assessment of CNS responses (Long 2012). For the purposes of this study, participants should be reevaluated every 6 weeks (After cycle 10, this will be changed to every 9 weeks). In addition to a baseline scan, confirmatory scans should also be obtained ≥ 4 weeks following initial documentation of an objective response.

### 10.1 Antitumor Effect – Solid Tumors

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

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

### 10.1.1 **Disease Parameters**

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

Measurable CNS disease. Measurable CNS lesions with a minimum size of ≥ 5 mm if performed with a gadolinium-enhanced MRI with contingent slices of 1 mm.

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

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease.

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

Target lesions.

*Extra-CNS 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.

Lytic bone lesions or mixed lytic-blastic lesions, *with identifiable soft tissue components*, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered target lesions if the *soft tissue component* meets the definition of measurability as defined above. Cystic lesions thought to represent cystic metastases can

be considered as target lesions. However, if non-cystic lesions are present, these are preferred for selection as target lesions. Lesions in previously irradiated areas or areas subject to other loco-regional therapy are usually not considered measurable unless there has been demonstrated progression of that lesion.

*CNS Target Lesions*

**CNS metastases ≥ 5 mm in diameter will be considered measurable CNS targets, provided assessments were performed using gadolinium-enhanced MRIs with contingent slices of 1 mm. Up to 5 CNS lesions will be permitted as target lesions in addition to 5 extracranial lesions previously noted (Long 2012).** Target lesions should be selected on the basis of their size, be representative of all the involved organs, and should be lesions that can be followed with reproducible repeated measurements.

Non-target lesions.

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

### 10.1.2 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation, using a ruler, calipers, or digital measurement tool. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 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 when both methods have been used to assess the anti-tumor effect of a treatment.

### 10.1.3 Response Criteria

#### 10.1.3.1 Evaluation of Target Lesions

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

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

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

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

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

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

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

#### 10.1.3.2 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).

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

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

existing non-target lesions.

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

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

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

10.1.3.3 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The participant's best response assignment will depend on the achievement of both measurement and confirmation criteria.

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

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

| | | | | |
|---|---|---|---|---|
| Any | PD* | Yes or No | PD | |
| Any | Any | Yes | PD | |

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

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

## 11. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

### 11.1 Data Reporting

#### 11.1.1 Method

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

#### 11.1.2 Responsibility for Data Submission

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

### 11.2 Data Safety Monitoring

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

The DSMC will review each protocol up to four times a year or more often if required to review toxicity and accrual data. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; DLT information; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring 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.

### 11.3 Multicenter Guidelines

N/A

# 12. STATISTICAL CONSIDERATIONS

## 12.1 Study Design/Endpoints

This is a phase I/II trial evaluating the safety and tolerability of alectinib and bevacizumab in patients with advanced NSCLC harboring ALK rearrangements. In the phase I portion of this study, eligible participants with ALK-positive NSCLC will be treated with the combination of alectinib and bevacizumab. The primary objective is to identify the recommended phase II doses of this combination. Participants will be treated using a 3+3 design. As dose level 1 consists of the individual recommended phase II doses of alectinib and bevacizumab, we will follow a dose de-escalation protocol in the setting of DLTs (as outlined below). Three patients will be treated per cohort for one cycle (21 days per cycle) beginning with dose cohort 1. If no DLTs are observed with dose cohort 1, we will enroll an additional 3 patients (6 total) proceed with the phase II portion of the trial if one or less experience a DLT. In any other dose cohort, if one of three patients experiences a DLT, another 3 patients will be treated at the same dose level for one cycle. If no additional DLTs are observed, we will proceed with the phase II portion of the trial. If more than one of 3 patients develops a DLT in any cohort, another 3 patients will be treated in the next lowest dose cohort. We will continue until identification of the recommended phase II doses for the combination of alectinib and bevacizumab. The recommended phase II doses for the combination of alectinib and bevacizumab will be defined as either a) the highest dosage cohort in which less than 1/3 of patients experience a DLT or b) alectinib at the previously defined recommended phase II dose (600 mg twice daily PO) as a single agent plus bevacizumab at the highest tolerated dose (15 mg/kg IV every 21 days) investigated in this indication – whichever is the lower dose.

**Table 12.1 Dose De-Escalation Probabilities**

| True DLT prob | De-escalation Probability |
|---|---|
| 0.1 | 0.09 |
| 0.2 | 0.29 |
| 0.3 | 0.50 |
| 0.4 | 0.69 |
| 0.5 | 0.82 |
| 0.6 | 0.91 |

Additional secondary endpoints for the phase I portion of the study include safety, tolerability and dose-limiting toxicities of alectinib/bevacizumab. Toxicity will be assessed using CTCAE v4.0 criteria. All participants who receive any study drug will be evaluable for toxicity. Summary tables of adverse events and serious adverse events will be created.

In the phase II portion of this study, we will evaluate the combination of alectinib plus bevacizumab in ALK-positive patients with untreated or progressive, asymptomatic brain metastases. Eligible participants

will receive alectinib plus bevacizumab at the recommended phase II doses determined in the phase I portion of the study. Our primary objective will be to evaluate the safety and tolerability of alectinib and bevacizumab in this patient population. Toxicity will be assessed using CTCAE v4.0. All participants who receive any study drug will be evaluable for toxicity. Summary tables of adverse events and serious adverse events will be created. The focus of AE summaries will be on treatment emergent AEs – those with initial onset of increasing in severity after the first dose of study medicine. The number and percentage of participants who experience any AE, SAE, treatment-related AE, and treatment-related SAE will be summarized according to worst toxicity grades. These will be presented for the entire study period and potentially by cycle. The incidence and reasons for dose reductions, interruptions and discontinuations will be recorded for both the Phase I and II portions of the study.

Secondary objectives will be to assess the efficacy of this combination, with particular focus on control of brain metastases. Secondary endpoints will include CNS objective response rate (ORR), CNS disease control rate (DCR), extra-CNS ORR, extra-CNS DCR, and progression-free survival. Exploratory endpoints will include molecular profiling of pre- and post-alectinib/bevacizumab biopsy tissues to evaluate for potential mechanisms of resistance to therapy. Post-treatment biopsies will be optional.

## 12.2 Sample Size, Accrual Rate and Study Duration

For the phase I portion of the study, at least 3 participants will be treated at each dose level. However, not every dose level listed will be studied; thus, the exact sample size for this portion of the study cannot be clearly defined. It is expected that roughly 6-12 participants will enroll in the phase I portion of the study.

In the phase II portion of the study, we aim to further investigate the safety and preliminary preliminary efficacy of alectinib plus bevacizumab in ALK-positive patients. With protocol version 8.2.2017, the sample size of this cohort will decrease to 20 participants. The combination of alectinib/bevacizumab will be deemed unsafe if 2 or more patients are observed to have grade ≥2 CNS hemorrhagic events. Twenty patients are needed to guarantee that the discontinuation rate is not higher than 28% based upon the upper bound of the 95% exact binomial confidence interval.

ALK rearrangements are identified in approximately 4-6% of patients with NSCLC. At MGH alone, approximately 500 patients with NSCLC undergo genotyping annually. Additionally, MGH is a referral center for patients with ALK-positive NSCLC. Recently, data from the phase III global ALEX study has established the superiority of alectinib over crizotinib, establishing alectinib as a new standard of care. With this new data, we expect to enroll 1-2 patients per month.

## 12.3 Interim Monitoring Plan

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this study. Patients with cerebral hemorrhages and particular adverse events: gastrointestinal perforation, complication of wound healing, bleeding/hemorrhage, hypertension, proteinuria, thromboembolic accident (venous and arterial) will be followed until their resolution.

Each case of intracerebral hemorrhage will be reviewed by the DSMC in order to define whether it is clinically significant. The scoring of the intracerebral hemorrhage grade by the investigators, whatever the grade, will be confirmed or re-evaluated by the DSMC, based on clinical and radiological criteria sent the DSMC. The score assigned by the DSMC will be the only one taken into account for evaluation of the end of the study.

The study will stop early if out of the first 15 patients, 3 experience intracerebral hemorrhages. If the intracerebral hemorrhage rate is as low as 5%, the chance of observing 3 or more events is less than 0.05. If the intracerebral hemorrhage rate is as high as 25%, the probability of observing 3 or more events is more than 0.75. This rule has 95% confidence that the upper bound of the true intracerebral hemorrhage rate is less than 0.43.

### 12.4 Analysis of Primary Endpoints

See section 12.1.

### 12.5 Analysis of Secondary Endpoints

Secondary endpoints will be analyzed for exploratory purposes only.

**Safety -** Toxicity will be assessed using CTCAE v4.0 criteria. All participants who receive any study drug will be evaluable for toxicity. Summary tables of adverse events and serious adverse events will be created.

**CNS objective response rate** – CNS response rate will be evaluated using a modified RECIST criteria (Long et al, 2012). It will consist of complete responses and partial responses.

**CNS DCR** – CNS DCR will be evaluated using a modified RECIST criteria (Long et al, 2012). It will consist of complete responses, partial responses and stable disease.

CNS PFS – CNS PFS will be defined as the time from the start of study drug treatment to the date of first document progression in the CNS or death due to CNS disease.

**Overall objective response rate** – Overall ORR will be assessed by RECIST version 1.1. and will consist of intra- and extra-cranial complete responses and partial responses.

**Overall DCR** – Overall DCR is defined as either complete response, partial response or stable disease (SD) as assessed by RECIST v1.1.

**Progression-free survival (PFS)** - PFS will be defined as the time from the start date of study drug treatment to the date of first documented progression or death due to any cause.

**Select Tumor Genotyping (optional)** - Exploratory, hypothesis-generating analyses will be performed to correlate any findings from the various potential biomarker studies listed in Section 9 with the study endpoints above.

**Patient Reported Outcomes –** PROs of HRQoL, brain-metastasis-related symptoms, and health status will be measured using the EORTC QLQ-C30 and EORT QLQ-BN20.
Summary statistics (mean, standard deviation, median, and range) of linear transformed scores will be reported for all the items and subscales of the EORTC QLQ-C30 questionnaire, and the QLQ-BN2- according to the EORTC scoring manual guidelines. Completion and compliance rates will be summarized at each time-point with reasons for missing data. Only patients with a baseline assessment and at least one post-treatment assessment will be included in the analyses.

## 13. PUBLICATION PLAN

It is anticipated that the results of this study will first be reported in abstract form, followed by presentation in a peer-reviewed manuscript.

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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 (*e.g.*, light housework, office work). | 80 | Normal activity with effort; some signs or symptoms of disease. |
| | | 70 | Cares for self, unable to carry on normal activity or to do active work. |
| 2 | In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours. | 60 | Requires occasional assistance, but is able to care for most of his/her needs. |
| | | 50 | Requires considerable assistance and frequent medical care. |
| 3 | In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours. | 40 | Disabled, requires special care and assistance. |
| | | 30 | Severely disabled, hospitalization indicated. Death not imminent. |
| 4 | 100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair. | 20 | Very sick, hospitalization indicated. Death not imminent. |
| | | 10 | Moribund, fatal processes progressing rapidly. |
| 5 | Dead. | 0 | Dead. |

**Appendix B**

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

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

| PgP Substrates |
|---|
| aliskiren, ambrisentan, colchicine, dabigatran, digoxin, everolimus, fexofenadine, imatinib, lapatinib, maraviroc, nilotinib, posaconazole, pravastatin, ranolazine, saxagliptin, sirolimus, sitagliptin, talinolol, tolvaptan, topotecan |

This information in this appendix is adapted from Levien and Baker 2003[1], Zhang 2010[2], and FDA Guidance on Drug-Drug Interactions.

Also see:
• http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm

1 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 and www.prescribersletter.com.
2 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.

**Appendix C: Adverse Event Fax Cover Sheet**

Genentech
A Member of the Roche Group

AE / SAE FAX No: (650) 238-6067

| | |
|---|---|
| Genentech Study Number | |
| Principal Investigator | |
| Site Name | |
| Reporter name | |
| Reporter Telephone # | |
| Reporter Fax # | |

| | |
|---|---|
| Initial Report Date | [DD] / [MON] / [YY] |
| Follow-up Report Date | [DD] / [MON] / [YY] |

| | |
|---|---|
| Subject Initials<br>(Enter a dash if patient has no middle name) | [ ] - [ ] - [ ] |

SAE or Safety Reporting questions, contact Genentech Safety: (888) 835-2555

PLEASE PLACE MEDWATCH REPORT or SAFETY REPORT BEHIND THIS COVER SHEET

**Appendix D**
**Modification of Diet in Renal Disease (MDRD) Formula**

The estimating glomerular filtration rate (eGFR) will be calculated on the basis of the following formula (Miller 2009):
$eGFR = 175 \times SCRT^{-1.154} \times AGE^{-0.203}$ [x 0.742 if female] [x 1.212 if

African American] (conventional units)