Title: Phase 2 Trial of Brigatinib after Treatment with Next-Generation ALK inhibitors in Refractory ALK Rearranged NSCLC

Protocol Number: ARI-AT-002

Study Collaborator: Takeda Oncology

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Version	Main Changes
1	Original
2	• Removal of Co-Investigators, updates to study collaborators and contact information, addition of IND #; • Clarifications, formatting, and spelling updates throughout; • Section 1.3.5 updated with new findings; • Mechanism of resistance added to exploratory findings; • Inclusion 7 updated to allow study entry for subjects who cannot undergo a biopsy; • Exclusion criteria 2 added to exclude patients who received prior brigatinib treatment; • Addition of ctDNA blood sample collection at C1D1 and D1 of odd cycles; • SAE and pregnancy reporting process updated; • Addition of overdose reporting; • Updates to section 9.2: Required documentation for site opening; • Updates to enrollment procedures; • Updates to section 9.4 due to change in EDC system and monitoring of data. • Addition of Criterium Project manager's role throughout the protocol. • Removal of Unanticipated problems; • Updated Appendix B Model Patient Diary.
3	• Background and Rationale updated with new data • Updates throughout removing references to UNC and LCCC 1523 to reflect the transition of responsibilities to ATOMIC and Duke Principal Investigator; • Change of the Protocol number to ARI-AT-002; • Update to study team and contact information; • Addition of protocol signature page; • Clarifications, formatting, and spelling updates throughout; • New background information added; • Update to Inclusion 7; • Update to Exclusion 6 to include wash out period; • Removal of therapy actions related to QTc Interval prolongation; • Update to treatment modifications due to pneumonitis; • Update to prohibited medications and medications to be used with caution due to updated safety profile; • Update to management of adverse events of note to reflect current safety profile; • Removal of treatment beyond disease progression; • Updates to Time and Events table and footnotes; • Clarification of tumor biopsy requirement; • Updates to SAE and Serious SAR reporting; • Updates to Data Safety Monitoring Plan;

	• Updated to data analysis plan • Removal of institution specific IRB reporting requirements; • Removal of single patient/subject exception. • Removal of appendix Drugs with a Risk of Torsades de Pointes
4	• Revision to title of protocol • The addition of 2 cohorts (one for patients who have only received alectinib and one for patients who have tolerated brigatinib and experienced disease progression and then will receive brigatinib 240 mg daily • Increased number of patients enrolled to 120 (40 per cohort) • Addition of information from the updated IB which included updated information about the randomized phase 2 trial • Updated information about the drug-drug interactions • Additional changes were administrative to clarify questions investigators have had over eligibility or tests. • Inclusion criteria for previous therapies revised to reflect cohorts A, B, C • Dose administration for Cohort C added • Toxicities and dose modifications for Cohort C were added • Contact information was updated for safety reporting • Product complaint/medication error instructions were added • Length of study revised to two years from amendment approval
5	• Inclusion criteria 3.1.11 – Revised contraception language; removed hormonal contraception as an effective method of birth control • Appendix C - Added information regarding co-administration of brigatinib with CYP3A substrates • Pregnancy reporting language updated.
5.1	• Page 2 (Study Contacts) adds Principal Investigator of Canada site. • Section 9.7 (Record Retention) updated to comply with Canadian law. • Appendix B and C removed from protocol by University Health Network Research Ethics Board request, to be presented as auxiliary material for the patient.
6	• Corrected Table of Content including page numbering. • Administrative changes throughout to correct vertical spacing (reduced number of pages to this document); section formatting and numbering; sections headings; and page numbering in footer. • Clarified that no EOT visit is required with cohort changes from A or B to C in Sections (Section 3.2.4. 3.3.3 and 6.4). • Clarifies dose modification regarding Grade 4 Non- Hematologic Treatment Related AEs during Brigatinib 180mg Daily than Pneumonitis (Section 4.4.3). • Corrected section references related to Concomitant Medications/ Juices/Herbal Supplements (within Section 4.6). • Clarifies timeframe of Duration of Follow-up (Section 4.7, see also footnote 4 Section 6.1).

	• Clarifies Section 6, including Schedule of Events (Section 6.1) and Treatment Assessments (Section 6.3), Assessment of Efficacy (Section 6.8) as follows: - collection of information regarding prior cancer therapy; - clarifies CT scans requirements. - Clarifies CT scan and brain MRI requirements and measurements. - Clarifies no EOT visit required with cohort changes from A or B to cohort C. - Clarifies timeframe of Duration of Follow-up. - Clarifies that biopsies are required for patients treated on cohorts A or B and enrolling in C. - Specifies prior cancer therapy to be captured. - Clarifies tissue acquisition requirements.
7	• Updated to maintain one protocol version for all participating sites (merging v5.1 and v6). • Adjusts left margins per ICH required minimum, and includes some right margin readjustments. • Updates References throughout to identify by authors (vs. numbers) • Page 2 (Study Contacts) adds Canadian Site PI and updates some other addresses • Section 1.1 updated with recent research findings regarding brigatinib, clarifies each cohort is evaluated independently • Section 1.2 adds Canadian health systems use of IHC testing method and recent FDA approval of loritinib for patients with disease progression. • Sections 1.3 and 1.4 adds current and clarifies brigatinib information. • EOT visit clarified that EOT not needed for cohort changes from A or B to C in Sections 3.2.4. 3.3.3 and 6.4. • Inclusion criteria Sections updated to confirm ALK positive status allows CLIA or test approved for use in Canada (3.1.2); correct subsection numbering (3.1.7 - 3.1.13); reference progressing on lorlatinib for cohort A (3.2.1); and clarify no EOT visit for cohort A or B participants entering cohort C; and biopsy required for cohort C participants (3.2.4). • Exclusion criteria Sections revisions include no washout for A or cohort B participants entering cohort C (3.3.6); adds “as determined by the investigator” to Clinically significant atrial arrhythmia (3.3.7); adds new section “Another primary malignancy for which the patient is currently receiving therapy” (3.3.8), and readjusts subsequent subsection numbers (3.3.9 - 3.3.13) • Section 6.1 (Time/Events Table) expands columns to 12 cycles adding new footnote 14 reference; updates “X” at Medical History (removes at C1D1 & D8), all D1 cycle visits (adds for physical exam/vital signs, ECOG, CBC/serum blood tests, and AEs); all D1 cycles for patient diary and concomitant meds (add “Review”); and brain MRI timepoints (moves to each 3rd cycle from each odd cycle – revised with protocol v6) visit.

	• Section 6.1 (Keynotes to footnotes) updates FN 9 to clarify ctDNA blood samples collected only while patient receives treatment and adds FN 14 allowing some telemedicine visits, at treating physician's discretion, for non-scan even cycle visits. • Section 6.2 revised that patient diary (Appendix B) is a stand-alone auxiliary patient document. • Section 6.3 (Treatment Assessments) updates include adds paragraph clarifying each odd day cycles (at 6.3.3) and each 3rd cycle (new 6.3.4) visit assessments; updates odd day cycles (6.3.3); adds new subsection for each 3rd cycle visit (6.3.4); and adds new subsection for non-scan even cycles allowing some telemedicine visits (6.3.5). • Section 6.4 (EOT Visit) revisions adds clarity for consistency with data collection across participating centers (new paragraph 2); for AEs, ctDNA blood sample collection; and for cohort C (previously cohort A or B) participants. • Section 6.5 (Post-treatment/Follow-up Assessments) adds clarity for recording data of EOT visit and long-term follow-ups. • Section 7.3 (Documentation of non-serious AEs or SARs) adds clarity for data recording with participants as both cohort A or B and cohort C. • Section 9.1, and throughout, updated references to IRB to include REB • Section 9.4 (Data Management) clarifies all data for each cohort is captured independently from time of entry into cohort. • Section 9.5.2 (Protocol Deviations) adds clarity for data capture and regulatory reporting of missed assessments with use of telemedicine visits. • Section 9.7 (Record Retention) adds Canada's required record retention period per protocol v5.1 • Section 10 (Appendices) removes Appendix B and Appendix C per protocol v5.1

ARI-AT-002: Phase 2 Trial of Brigatinib after Treatment with Second-Generation ALK inhibitors in Refractory ALK Rearranged NSCLC

Amendment 7: April 20, 2020

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Signature Page

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

Principal Investigator (PI) Name: _____

PI Signature: _____

Date: _____

PROTOCOL SIGNATURE PAGE

Study Protocol Number:	ARI-AT-002
Study Protocol Title:	Phase 2 Trial of Brigatinib after Treatment with Second-Generation ALK inhibitors in Refractory ALK Rearranged NSCLC

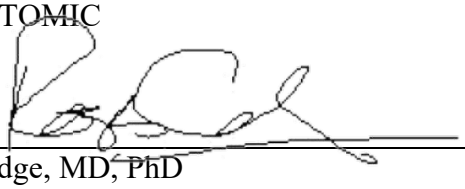
SIGNATURES

Principal Investigator:

Thomas E. Stinchcombe — 7/1/2020

Thomas E. Stinchcombe, MD — Date

Director of ATOMIC



6/23/2020

Ross Camidge, MD, PhD — Date

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1.0 BACKGROUND AND RATIONALE

1.1 Study Synopsis

This multicenter phase II trial will evaluate brigatinib (AP261136) in patients with advanced non-small cell lung cancer (NSCLC) harboring an anaplastic lymphoma kinase (ALK) rearrangement, previously treated with a next generation ALK inhibitor such as ceritinib or alectinib.(Shaw et al. 2014; Soria et al. 2017; Peters et al. 2017; Hida et al. 2017). Ceritinib and alectinib are referred to as 'next generation," and are approved by the Food and Drug Administration (FDA) for patients with a confirmed *ALK* rearrangement (referred to as ALK+) who have progressed on or are intolerant of crizotinib, and alectinib and ceritinib is approved for treatment naïve patients. Alectinib, ceritinib, and crizotinib currently are recommended by the National Comprehensive Cancer Network (NCCN) as first- line therapy with category 1 recommendations; alectinib is the preferred therapy.( ) In addition, multiple other next generation inhibitors are in development. Brigatinib has also demonstrated significant activity in patients who have progressed on crizotinib, with responses reported for both intracranial and extracranial disease.(Kim et al. 2017) The activity of brigatinib in patients who have disease progression after ceritinib or alectinib has not been prospectively investigated. Brigatinib was compared to crizotinib in phase 3 trial of treatment naïve patients, and was found a statistically significant improvement in progression-free survival.

There is increasing concern that patients who have been exposed to multiple therapies may have multiple mechanisms of resistance, including ALK dependent and ALK independent mechanisms of resistance. Therefore, patients will be divided into cohorts (A) patients who have progressed on multiple lines (>1) of ALK directed therapy, including at least one licensed or experimental next generation therapy (B) patients who have progressed on only alectinib.[8] In an exploratory cohort (C) patients who tolerate but progress on 180mg brigatinib (as a part of the trial or as part of routine clinical care) will be treated with 240 mg brigatinib daily to determine if intra-patient dose escalation is safe and tolerable and is associated with greater activity at the higher doses.

Rationale for post alectinib cohort

Brigatinib is predicted to maintain activity against all *ALK* resistance mutations, and such resistance mutations are associated with progression in approximately 50% of patients treated with alectinib.(Gainor et al. 2016; Shaw et al. 2019; Lin, Riely, and Shaw 2017) Brigatinib inhibits ALK with approximately 2-fold greater potency than alectinib in vitro. Steady-state levels of exposure of brigatinib in patients treated with 90 mg daily for 7 days followed by 180 mg daily regimen of brigatinib are at least 2-fold higher than those achieved in patients treated with alectinib (600 mg twice daily), suggesting that brigatinib may also be less susceptible to pharmacologic resistance than alectinib.(Zhang et al. 2016) The mechanisms of resistance and resistance mutations may be unique for alectinib. Investigating brigatinib in patients who have progressed on only alectinib will create a more homogenous cohort, and there is a clinical need to assess the activity of other ALK inhibitors as alectinib is adopted as a first-line therapy.

Rationale for dose escalation cohort.

The rationale for escalation to 240 mg daily at disease progression is to attempt to overcome potential pharmacologic resistance at 180 mg daily brigatinib (i.e. to increase brigatinib exposure in order to have better activity against a given *ALK* resistance mutation may be dose dependent or for increased exposure in the CNS to treat CNS disease progression). A higher dose of brigatinib may have inhibitory activity against resistance mutations, and better CNS penetration which is clinically relevant since many patients experience progressive CNS disease. In the phase 1/2 dose-limiting toxicities (DLT) were grade 3 alanine aminotransferase (ALT) in one patient at 240 mg daily and grade 4 dyspnea in one patient at 300 mg daily.(Gettinger et al. 2016) The maximum tolerated dose was not established. In patients who were treated with 240 mg daily, 300 mg daily or 120 mg twice daily (n=15) the grade 3 or 4 adverse events observed at (>5%) were fatigue (13%), diarrhea (13%), headache (7%), vomiting (14%), increased lipase (13%), hypertension (7%), and pyrexia (7%). Since exposure to lower starting doses of brigatinib has now been associated with an abrogation of early onset pulmonary symptoms at escalation to a higher dose (e.g. 90 mg for 7 days before increasing to 180mg as in ALTA), re-exploration of the tolerability and efficacy of 240 mg QD after tolerable exposure to 180 mg is appropriate clinical question for further study.

Study design

The study will enroll up to 40 patients in each of the cohorts, using a Simon two-stage design, with a primary endpoint of objective response (complete response (CR) + partial response (PR)) as assessed by the investigator. Each cohort is evaluated independently. Secondary objectives include estimating duration of response, progression free survival (PFS), intracranial and extracranial PFS, and overall survival (OS). Exploratory objectives include intracranial ORR among patients with measurable CNS disease. If the trial meets the primary efficacy end-point an exploratory evaluation of molecular predictors of response and resistance, using both tumor tissue samples and circulating tumor DNA (ctDNA) from peripheral blood samples will be conducted.

1.2 Non-small Cell Lung Cancer (NSCLC)

Factors that determine treatment for non-small cell lung cancer (NSCLC) include histology, age, comorbidities, and presence or absence of driver mutations or rearrangements. One such oncogenic driver that influences treatment is the novel fusion oncogene resulting from an inversion in chromosome 2 of two genes: the echinoderm microtubule-associated protein-like 4 (EML4) and the anaplastic lymphoma kinase (ALK) gene. ALK rearrangements are more commonly (but not exclusively) detected in NSCLC patients with adenocarcinoma, patients with a history of light or never smoking, and younger patients. The prevalence among patients with adenocarcinoma is estimated to be 8% (95% confidence interval (CI), 6 to 10%).(Kris et al. 2014; Barlesi et al. 2016). Given that ALK rearrangements are not exclusively found in these groups, current practice guidelines recommend reflexive testing in all patients with non-squamous NSCLC. Current FDA approved methods of detecting ALK rearrangements are the fluorescence in situ hybridization (FISH), and more recently immunohistochemistry (IHC) testing. (Lindeman et al. 2018) Additional

methods that can detect ALK fusions include PCR-based methods and more recently DNA- and RNA-based next generation sequencing (NGS) assays from tumor and/or ctDNA. The Canadian health system has adopted an IHC testing method nationally, and there is increasing adoption of tumor and ctDNA NGS testing methods. (Lindeman et al. 2018; Cutz et al. 2014; Wynes et al. 2014)

Crizotinib, an ALK inhibitor, is a standard first-line treatment for NSCLC patients with this genetic rearrangement, so called ALK+ disease. This is based on superior objective response rates (ORR) and progression free survival (PFS) in phase 3 trials of crizotinib compared to chemotherapy in the first and second line treatment of advanced ALK+ NSCLC patients. A phase 3 trial compared ceritinib to platinum-pemetrexed and demonstrated a statistically significant improvement in PFS as assessed by the independent review committee (IRC) (HR of 0.55, 95% CI, 0.42-0.73, p<0.00001; median PFS 16.6 and 8.1 months, respectively) and superior ORR (72.5% vs 26.7%) with ceritinib.(Soria et al. 2017) The most common grade 3 or 4 AE's were ALT (31%), and AST (17%). The median relative dose intensity was 78.4%.

Two phase 3 trials have compared alectinib to crizotinib in ALK therapy naïve patients, and have demonstrated a superior ORR and PFS with alectinib. A phase 3 trial in Japan compared alectinib to crizotinib in patients with ALK + NSCLC who had not previously been treated with an ALK inhibitor. (Hida et al. 2017; Peters et al. 2017) The independent data monitoring committee stopped enrollment to the trial early since alectinib had demonstrated a statistically significant improvement in PFS.[4] Patients assigned to alectinib compared to crizotinib had a statistically higher ORR (92% vs 79%), a lower rate of grade 3 or 4 AE's (26% vs 52%), treatment discontinuations due to AE's (9% vs 20%), and a longer PFS (hazard ratio (HR) of 0.34; 95% CI, 0.17 to 0.71; p<0.0001; median not reached and 10.2 months, respectively). An international trial compared alectinib to crizotinib and revealed a superior ORR by investigator (82.9% vs 75.5%, p=0.09), and PFS by IRC (HR of 0.50, 95% CI, 0.36 to 0.70; p<0.001; median PFS of 25.7 and 10.4 months, respectively). The grade 3 to 5 AE's were lower in the alectinib than the crizotinib arms (41% vs 51%). The time to CNS disease progression was significantly longer in the alectinib arm compared to the crizotinib arm (HR of 0.16, 95% CI, 0.10-0.28, p<0.001), and the 12-month rate of CNS progression was 9.4% and 41.4%, respectively

The current NCCN recommend crizotinib, ceritinib, and alectinib as first-line therapies (category 1) with alectinib being the preferred therapy.[6] These phase 3 trials and the NCCN guidelines have led to the adoption of second-generation ALK TKI's as first-line therapy.

Recently lorlatinib was approved by the FDA for patients with disease progression after alectinib, after ceritinib, or crizotinib and one other ALK TKI.(Solomon et al. 2018)

Brigatinib, a next generation ALK inhibitor with broad activity against crizotinib resistance mutations and promising CNS activity. It was approved by the FDA for patients who have progressed on or were intolerant of crizotinib. Brigatinib was investigated in a two-arm randomized phase 2 trial of 90 mg daily and 90 mg

daily for 7 days followed by 180 mg daily.(Kim et al. 2017) The primary end-point was ORR, and secondary end-points were PFS and CNS response. In the 90 mg daily arm the ORR by IRC was 48% (95% CI, 39-58%), and the median PFS was 9.2 months (95% CI, 7.4 to not reached). In the 90 mg daily followed by 180 mg daily the ORR by IRC was 53% (95% CI, 43-62%), and the median PFS was 15.6 months (95% CI, 11.0 to not reached). The intracranial response rate in patients with measurable CNS disease by independent radiological review on the 90 mg daily arm (n=26) was 42% (95% CI, 23-635), and in the 90 mg daily followed by 180 mg daily arm (n=18) was 67% (95% CI, 41%-87%). In the 90 mg daily followed by 180 mg daily the grade ≥3 AE's observed at a rate of ≥ 2% of patients were: dyspnea (2%), back pain (2%), increase phosphokinase (9%), rash (3%), and hypertension (6%). Episodes of QT prolongation were not observed.

At this time the activity of brigatinib after ceritinib, or alectinib has not been prospectively studied.

1.3 Brigatinib (AP26113)

Brigatinib (AP26113) is a novel, orally-active tyrosine kinase inhibitor (TKI) discovered and developed by ARIAD Pharmaceuticals, a subsidiary of Takeda Oncology. Primary targets are activated, mutant forms of anaplastic lymphoma kinase (ALK) and c-ros oncogene 1 (ROS1), which play important roles in non-small cell lung cancer (NSCLC) and other cancers.

1.3.1 Pharmacology Summary

A series of in vitro and in vivo studies have been performed to characterize the pharmacodynamic profile of brigatinib. These studies have demonstrated that brigatinib potently inhibits activated variants of ALK, such as echinoderm microtubule-associated protein like (EML4)-ALK, and variants of ALK, including the L1196M gatekeeper mutation, that confers resistance to crizotinib. No ALK mutations have been identified in in vitro mutagenesis assays that confer resistance to brigatinib at clinically achievable concentrations. Overall, the data established that brigatinib has a promising profile as an antitumor agent, and they provided a strong rationale for conducting a clinical development program in cancer patients.

1.3.2 Absorption, Distribution, Metabolism, and Excretion (ADME) Summary

Brigatinib is bioavailable after oral administration in multiple animal species, and in rats and monkeys has been shown to be a low clearance compound that is extensively distributed in extravascular compartments. In vitro, brigatinib was moderately bound to plasma proteins in mouse, rat, monkey and human and also did not show preferential partitioning into red blood cells (RBCs). Brigatinib is a Permeability-glycoprotein (P-gp) substrate.

Overall, the metabolism of brigatinib in rats, monkeys, and humans (both in vitro and in vivo) was qualitatively similar with no unique human metabolites observed. N-demethylation leading to AP26123 was identified as the main biotransformation pathway in liver microsomes and hepatocytes. Other minor

metabolites were present in insignificant amounts in hepatocyte incubations and did not contribute substantially to brigatinib metabolism. Analysis of rat, monkey, and human urine, and feces of rats by liquid chromatography/tandem mass spectrometry (LC/MS/MS) showed that AP26123 also was the principal metabolite in these matrices. In [^{14}C]-brigatinib ADME studies in rats, monkeys, and humans, the majority of the circulating radioactivity was attributed to the parent drug brigatinib (>60%). The metabolite AP26123 accounted for <10% of circulating radioactivity.

In vitro studies suggest that brigatinib and its metabolite, AP26123, do not inhibit CYPs 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4/5 at therapeutically relevant drug concentrations. Thus, clinical DDIs due to inhibition of CYPs by brigatinib and AP26123 are highly unlikely.

1.3.3 Toxicology Summary

The nonclinical safety and toxicity profile of brigatinib was characterized in acute toxicity studies in mice and rats, range-finding and 28-day Good Laboratory Practice (GLP) toxicology studies in rats and cynomolgus monkeys, in vitro genotoxicity studies, and a phototoxicity study in rats. A summary of toxicology observations is summarized in the investigator brochure.

A single oral dose of brigatinib was tolerated in mice at doses up to 75 mg/kg and in rats at doses up to 125 mg/kg. Dose-dependent increases in mortality occurred at dose levels ≥125 mg/kg in mice and ≥250 mg/kg in rats.

In the 28-day GLP oral toxicology/toxicokinetics study in rats, oral administration of brigatinib at doses of 30 or 60 mg/kg/day resulted in a dose-dependent increase in mortality, which led to the cessation of dosing in the 60 mg/kg/day dose group toward the end of Week 1. A clear spectrum of clinical signs of toxicity preceded the deaths of the animals. The key histopathological findings in rats at the 30 and 60 mg/kg/day dose levels that died prematurely and in some 30 mg/kg/day rats that survived the 28-day treatment period were minimal to marked hematopoietic hypocellularity in the bone marrow in conjunction with lymphoid depletion in the spleen, thymus and other lymphoid tissues, which raise the potential for immunosuppressive effects of brigatinib. Other notable brigatinib-related gross anatomic or microscopic findings, including bone and gastrointestinal pathologies, were seen primarily in rats that died prematurely. Brigatinib was physically well tolerated by rats in the 15 mg/kg/day dose group, and by most rats in the 30 mg/kg/day dose group. Reversible, dose-related reductions in group mean body weight, body weight gain, and food consumption were noted at these dose levels from Day 7 until the end of the dosing period. Based on the incidence and severity of gross anatomic and microscopic lesions and mortality observed at the 30 mg/kg/day brigatinib dose level, the no-observed adverse effect level (NOAEL) of brigatinib was considered to be 15 mg/kg/day, which corresponded to a Cmax of 1437 ng/mL and 1527 ng/mL, and AUC0-24 of 21716 h•ng/mL and 23550 h•ng/mL on Day 28 for males and females, respectively.

In the 28-day GLP monkey oral toxicology/toxicokinetic study, clinical signs of toxicity, moribundity, and mortality were evident beginning on Day 3 after daily oral administration of 45 mg/kg/day brigatinib. Consequently, dosing of all animals in the 45 mg/kg/day dose group was stopped on Day 7 or 8. The cause of premature death was attributed to brigatinib-related gastrointestinal toxicity, which involved all segments of the gastrointestinal tract, but was most severe in the stomach and small intestines. Other prominent histopathological findings in monkeys that died prematurely and in animals treated with 15 and 45 mg/kg/day brigatinib that survived to the terminal sacrifice on Day 30 were generally similar to those seen in rats, including lymphoid atrophy/necrosis and bone marrow hypocellularity. No brigatinib-related changes were seen at terminal sacrifice in the 7.5 mg/kg/day treatment group, or in any dose group at the end of the 28-day recovery period. Based on these results, the NOAEL was considered to be 7.5 mg/kg/day brigatinib, corresponding to a Cmax of 526 ng/mL and 560 ng/mL, and AUC0-24 of 3408 h•ng/mL and 3358 h•ng/mL on Day 28 for males and females, respectively.

No evidence of cutaneous phototoxicity or ocular phototoxicity was observed in rats after a single oral administration of brigatinib at doses as high as 60 mg/kg. A bacterial reverse mutation assay and a chromosomal aberration test in human peripheral blood lymphocytes revealed no evidence of brigatinib genotoxic activity.

In summary, the nonclinical safety and toxicity profile of brigatinib was adequately characterized in appropriate animal and in vitro models to inform the design of clinical studies of brigatinib, determine potential risks associated with its administration to patients, and provide recommendations for clinical monitoring.

1.3.4 Preclinical data

The activity of brigatinib against 293 recombinant human protein kinases was analyzed in an in vitro kinase assay. At a concentration of 1 μM, brigatinib was found to inhibit the activity of 36 kinases (12%) by at least 90%. More detailed analysis of the kinases with greatest sensitivity showed that 1 kinase, ALK, was inhibited with a 50% inhibitory concentration (IC_{50}) <1 nM. Eleven kinases, including ROS1, FAK, FLT3, CHK2, and EGFR-L858R were inhibited with IC_{50} values between 1 nM and 10 nM. Nineteen kinases, including EGFR-L858R/T790M, ERBB2, and CHK1, were inhibited with IC_{50} values between 10 nM and 50 nM. Twelve kinases, including IGF-1R and native EGFR, were inhibited with IC_{50} values between 50 nM and 100 nM

These studies demonstrated that brigatinib potently inhibited the kinase activity of ALK, and inhibited the activity of ROS1, mutant EGFR, and to a lesser extent IGF-1R, prompting further analysis of these kinases in non-clinical experiments.

1.3.5 Anaplastic Lymphoma Kinase Inhibitory Activity of Brigatinib

In nonclinical studies, brigatinib has been shown to:

- Inhibit growth of ALK+ human tumor-derived cell lines with potency and selectivity approximately 10-fold greater than that of crizotinib
- Potently inhibit ALK variants with secondary mutations that confer resistance to crizotinib, ceritinib, or alectinib
- Suppress the emergence of any resistant ALK mutant in an in vitro mutagenesis assay, at concentrations that can be achieved clinically
- Induce regressions or inhibit growth of tumor xenografts driven by native ALK or mutant variants that confer clinical resistance
- Prolong survival of mice in an ALK-dependent orthotopic brain tumormodel

1.3.6 In Vitro Activity in Human Tumor-derived Cell Lines

In a panel of 7 anaplastic large cell lymphoma (ALCL) and NSCLC cell lines that express nucleophosmin-ALK (NPM-ALK) or EML4-ALK fusions, the concentration of brigatinib that inhibited growth by 50% (GI_{50}) ranged from 4 nM to 31 nM, and the concentration that inhibited ALK phosphorylation by 50% (IC_{50}) ranged from 1.5 nM to 12 nM. Across 3 ALK-negative ALCL and NSCLC cell lines, the GI_{50} values for brigatinib ranged from 503 nM to 2387 nM. Overall, brigatinib potently inhibited ALK activity and proliferation in all ALK+ cell lines tested, and exhibited >100-fold selectivity over ALK-negative lines. In contrast, crizotinib exhibited 10-fold lower potency compared to brigatinib in ALK+ cell lines, and only approximately 10-fold selectivity over ALK-negative lines. AP26123, the principal metabolite of brigatinib in vivo, was included in a subset of these studies and found to have slightly reduced anti-ALK activity compared to brigatinib.

The cellular activity of brigatinib was also compared to that of crizotinib, ceritinib, and alectinib in Ba/F3 cells whose viability was dependent on activity of a native EML4-ALK fusion, or fusions containing mutations in the ALK kinase domain that have been previously been associated with resistance in clinical or nonclinical studies.[10,12,13] Brigatinib inhibited the viability of cells expressing native EML4-ALK with potency 8-fold greater than that of crizotinib (IC_{50} of 14 nM versus 107 nM). Brigatinib also inhibited the viability of cells expressing all 17 ALK mutants (IC_{50} values of 9 to 184 nM), with potency substantially greater than that of crizotinib (IC_{50} values of 170 to 1109 nM) for all 17 mutants except L1198F, which has been associated with resistance to ceritinib but not crizotinib.

The relationship between TKI potency in these cellular assays and levels of TKI exposure in patients (mean steady state plasma concentrations), corrected for the functional effects of protein binding, was analyzed (Figure 1). For crizotinib, drug levels in patients exceed the IC_{50} for native EML4-ALK, but did not exceed, by at least 2-fold, the IC_{50} for variants that have been associated with crizotinib resistance. In contrast, based on PK data from the ongoing phase 1/2 trial, brigatinib plasma concentrations in patients dosed at 90 or 180 mg daily were found to exceed the IC_{50} values for native EML4-ALK and all 17 resistance mutants by at least 2-fold, with the exception of the G1202R mutant, whose IC_{50} was substantially exceeded by brigatinib levels achieved at 180 mg but not 90 mg daily dosing.

A similar analysis of ceritinib and alectinib revealed that certain mutations increased the inhibitory concentrations to levels that were not exceeded, by at least 2-fold, by steady state plasma concentrations at the recommended phase 2 doses (Figure 1). These include T1151Tins, L1152R, L1152P, L1198F, and G1202R for ceritinib, and T1151Tins, I1171N, V1080L, and G1202R for alectinib.

Finally, a cell-based accelerated mutagenesis assay was performed to more broadly assess the mutational liabilities of brigatinib and crizotinib. While this assay successfully identified mutations that cause clinical resistance to crizotinib, no mutations in ALK were identified that had an IC_{50} that exceeded the concentrations of brigatinib achieved in patients dosed with 90 or 180 mg. Taken together, these results demonstrate that brigatinib has pan-ALK inhibitory activity in vitro and is the only ALK TKI predicted to retain potent activity against all secondary ALK mutants described to date. (Figure 1).

Figure 1

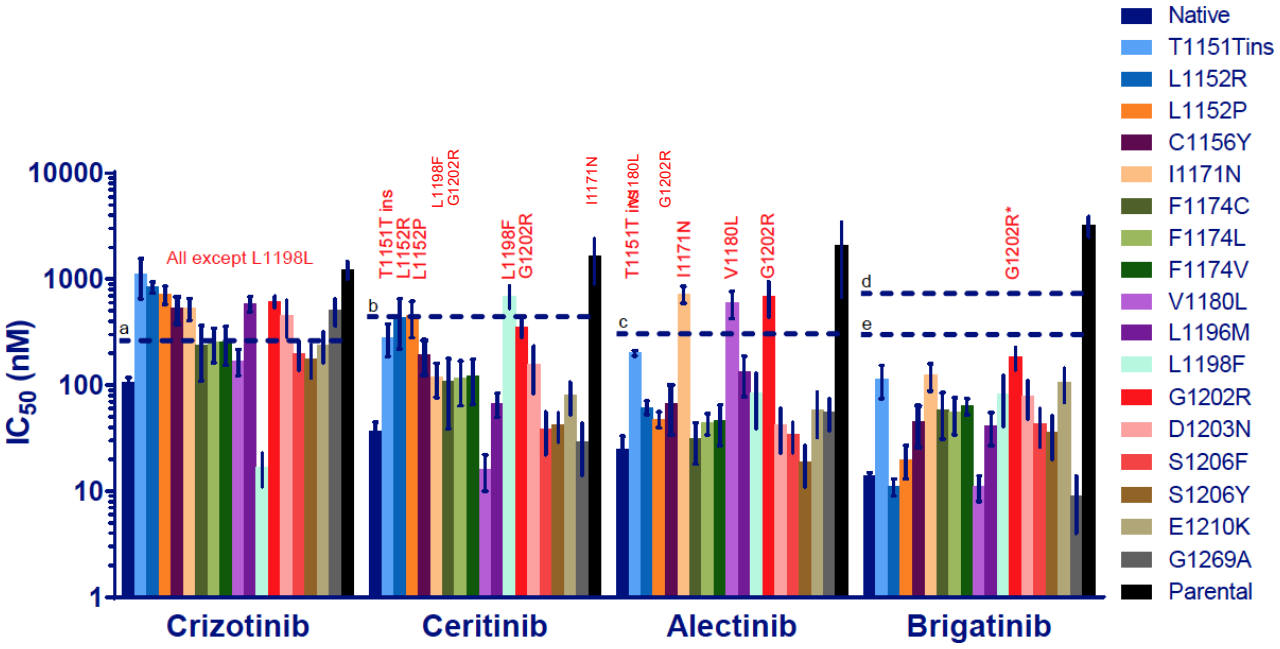


Figure source.(Zhang et al. 2016)

50% maximal inhibitory concentration (IC_{50}) values of Ba/F3 cells dependent on expression of EML4 ALK (native) or kinase domain mutated EML4 ALK variants (n=17). Data for each cell line are derived from at least 3 independent experiments (error bars=standard deviation).

Dashed horizontal lines indicate the mean steady state (SS) concentrations of each drug (expressed as the average plasma drug concentration over the dosing interval determined by dividing: $AUC_{0\text{-}24,\ ss}$ by 24 h, or Cave,ss) corrected for the functional

effects of protein binding (2.7, 2.7, 4.1, and 2.0-fold for crizotinib, ceritinib, alectinib, and brigatinib, respectively;[10, 14,15] at the recommended phase 2 doses:

a: Crizotinib: 250 mg BID, 266 nM ($C_{ave,ss}$ [719 nM]/2.7)
b: Ceritinib: 750 mg QD, 456 nM ($C_{ave,ss}$ [1232 nM]/2.7)[1]
c: Alectinib: 600 mg BID, 302 nM ($C_{ave,ss}$ [1120]/3.7)
d: Brigatinib 180 mg QD, 724 nM ($C_{ave,ss}$ [1477 nM]/2.0) and 90 mg QD, 291 nM (Cave,ss [582 nM]/2.0) (Data on file,Takeda Pharmaceuticals, Inc.)

For each TKI, mutants for which the clinically effective concentration did not exceed the IC_{50} by at least 2-fold are indicated in red text. *For brigatinib, G1202R met this criterion based on exposure in patients dosed with 90 mg daily, but no mutants met this criterion based on exposure in patients dosed with 180 mg daily.

1.3.7 In Vivo Activity in ALK-dependent Subcutaneous Xenografts

The in vivo activity of brigatinib was examined in ALK+ KARPAS-299 (ALCL) and H3122 (NSCLC) xenograft models. Daily oral administration of brigatinib (10, 25, and 50 mg/kg) led to a dose-dependent inhibition of tumor growth in both models, with a dose level of 25 mg/kg inhibiting tumor growth by 89% in the KARPAS-299 model and inducing tumor regression by >90% in the H3122 model. In both models, a prolonged inhibition of ALK signaling was observed after administration of 25 mg/kg brigatinib, with >90% and >60% reductions in levels of phosphorylated ALK observed 10 and 24 hours after dosing, respectively.

Additional in vivo tumor studies were conducted using Ba/F3 cell lines engineered to express native EML4-ALK, a crizotinib-resistant variant (L1196M), and the most recalcitrant mutant identified in in vitro assays (G1202R). Mice bearing subcutaneous tumors expressing native EML4-ALK or EML4- ALK/L1196M were administered vehicle, brigatinib, or crizotinib orally once daily. Crizotinib induced the regression of tumors expressing native EML4- ALK at the highest dose tested (200 mg/kg), but did not show antitumor activity in the EML4-ALK/L1196M model at this same dose. In contrast, brigatinib (50 mg/kg) induced tumor regression in both models. In mice bearing tumors expressing EML4-ALK/G1202R, brigatinib (50 mg/kg) inhibited tumor growth by 88%, while crizotinib (200 mg/kg) inhibited tumor growth by 46%. Doses of ceritinib (50 mg/kg) and alectinib (60 mg/kg) that strongly inhibited growth of native EML4-ALK tumors (by >95%) had little to no impact on growth of EML4- ALK/G1202R tumors (≤15% inhibition of tumor growth).

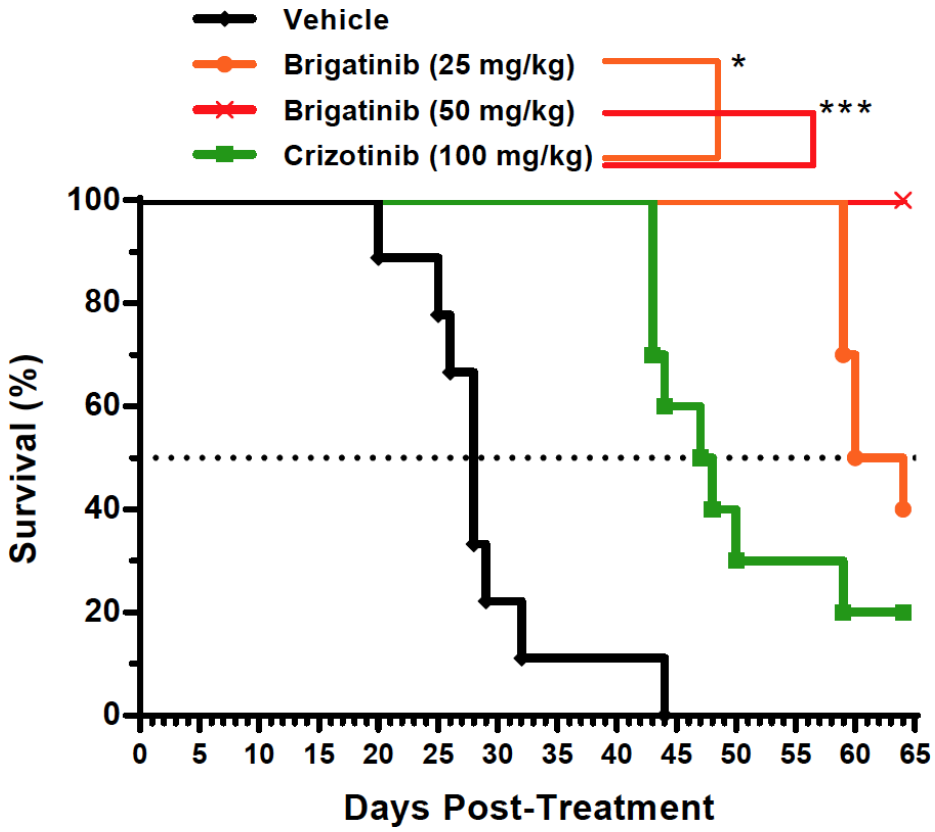
1.3.8 In Vivo Activity in ALK-dependent Orthotopic Brain Tumor Model

Activity of brigatinib in the CNS was assessed in vivo using an orthotopic brain tumor model. ALK+ H2228 (NSCLC) cells were injected intracranially to form tumors in the brain and tumor-bearing mice were treated with vehicle, crizotinib or brigatinib. Daily oral administration of crizotinib at 100 mg/kg extended median survival to 48 days compared to 28 days in vehicle-treated mice (Figure 2).

Compared to crizotinib-treated mice, daily oral dosing with 25 and 50 mg/kg brigatinib significantly prolonged median survival to 62 days and >65 days, respectively (Figure 2). Histological findings demonstrated a significant reduction in tumor burden in the brains of mice treated with 50 mg/kg brigatinib compared with crizotinib-treated mice.[10]

Figure 2:

Brigatinib Enhances Survival of Mice Bearing H2228 Brain Tumors Compared with Crizotinib



1.3.9 Clinical Data

As of 01 August 2017, 634 patients have been enrolled in Takeda-sponsored clinical trials of brigatinib in cancer patients (phases 1, 2, and 3), and 263 subjects have been enrolled in clinical pharmacology studies.

Three company-sponsored clinical studies with brigatinib are being conducted in adult cancer patients as of August 2017:

- A phase 1/2 study of the safety, tolerability, PK and preliminary antitumor activity of brigatinib in advanced malignancies, including ALK+ NSCLC (Study AP26113-11-101).
- A pivotal phase 2 study in patients with locally advanced or metastatic ALK+ NSCLC whose disease has progressed on therapy with crizotinib (Study AP26113- 13-201; ALTA).

- A pivotal randomized phase 3 study of brigatinib versus crizotinib in patients with locally advanced or metastatic ALK+ NSCLC and no previous treatment with an ALK inhibitor (Study AP26113-13-301; ALTA 1L).

An EAP (Study AP26113-16-901) to provide brigatinib to patients with ALK+ NSCLC who are resistant or intolerant to at least 1 prior ALK TKI and for whom brigatinib therapy is requested by the investigator was initiated in 2016 and was closed after brigatinib was granted accelerated approval in the US in April 2017. A similar EAP is ongoing in Europe. As of 25 July 2017, approximately 139 patients have been exposed to brigatinib in the Post-Marketing setting in the US and as of 14 July 2017, 265 patients have been exposed to brigatinib through EAP in the US and Europe.

The following clinical pharmacology studies have been completed or are ongoing:

- An ethnobridging study to determine the PK of orally administered brigatinib in healthy Japanese and Caucasian subjects (Study AP26113-13-102).
- A study to provide a preliminary assessment of the effect of a high-fat meal on the relative bioavailability and PK of a single dose of brigatinib administered orally to healthy subjects (Study AP26113-13-103).
- An ADME study with [14C]brigatinib (Study AP26113-13-104).
- A DDI study evaluating the effects of rifampin, itraconazole, and gemfibrozil on the PK of brigatinib in healthy subjects (Study AP26113-15-105).
- A BE study between 30 mg brigatinib tablets and 90 mg brigatinib tablets in healthy subjects (Study AP26113-15-106).
- A study evaluating the PK of brigatinib in subjects with chronic hepatic impairment and matched healthy subjects (Study AP26113-15-107). This study
- is ongoing.
- A study evaluating the PK of brigatinib in subjects with chronic renal impairment and matched healthy subjects (Study AP26113-15-108). This study is ongoing.
- A study to provide a definitive assessment of the effect of a high-fat meal on the relative bioavailability and PK of a single dose of brigatinib administered orally to healthy subjects (Study AP26113-16-109).
- A BE study between 30 mg brigatinib tablets and 180 mg brigatinib tablets in healthy subjects (Study AP26113-16-110).

Detailed information about these studies is provided in Section 5.2.

Clinical Pharmacology Studies

An overview is presented of the final PK and safety results for the 7 completed clinical pharmacology studies performed in healthy subjects: Study AP26113-13-102 (Ethnobridging), Study AP26113-13-103 (Preliminary Food-Effect), Study AP26113-13-104 (ADME), Study AP26113-15-105 (DDI), Study AP26113-15-106 (30 mg vs 90 mg tablet BE), Study AP26113-16-109 (Pivotal Food-Effect) and Study AP26113-16-110 (30 mg vs 180 mg tablet BE) Study descriptions for the 2 ongoing clinical pharmacology studies in subjects with impaired end-organ function are also described although results are not available: Study AP26113-15-107 (Hepatic Impairment) and Study AP26113-15-108 (Renal Impairment).

Ethnobridging Study (Study AP26113-13-102)

This was a double-blind, randomized, placebo-controlled, single ascending dose study of PO- administered brigatinib in healthy subjects (24 Japanese and 24 Caucasian subjects). Three of the 6 cohorts consisted of 8 Japanese (6 active:2 placebo) subjects each and the other 3 cohorts consisted of 8 Caucasian (6 active:2 placebo) subjects each. The single doses of brigatinib tested were 90 mg, 120 mg, and 180 mg administered under fasting conditions. Each dose was tested in 2 cohorts, 1 of Caucasian subjects and 1 of Japanese subjects.

Following single PO doses, plasma brigatinib concentrations reached a maximum at approximately 2.0 to 3.5 hours and then declined in a multi-exponential manner with all subjects showing quantifiable concentrations up to 72 hours postdose. The arithmetic mean Cmax increased with an increase in dose from 401.8 ng/mL and 451.3 ng/mL for Japanese and Caucasian subjects at 90 mg, respectively, to 640.3 ng/mL and 712.3 ng/mL for Japanese and Caucasian subjects at 180 mg, respectively. Although the mean peak concentration generally appeared higher for the Caucasian population, there was also higher intersubject variability with this population when compared with the Japanese population. The GeoMean coefficient of variation (CV%) Cmax with Caucasian subjects ranged from 41.2% to 65.2% across treatments when compared with the GeoMean CV% Cmax for Japanese subjects, which ranged from 26.6% to 37.0% across treatments. The mean AUC0-∞ increased from 6064 h•ng/mL and 6783 h•ng/mL for Japanese and Caucasian subjects at 90 mg, respectively, to 9910 h•ng/mL and 12149 h•ng/mL for Japanese and Caucasian subjects at 180 mg, respectively. Similar to the observation with Cmax, AUC0-∞ estimated for Caucasian subjects generally appeared higher with higher variability when compared with Japanese subjects. Given the variability, assessment of race on single dose PK parameters of brigatinib indicated that Caucasian and Japanese subjects had comparable systemic exposure at the studied dose levels. A could not be ruled out due to variability. Mean t½ was comparable across populations and dose levels and ranged from approximately 20 to 26 hours following single dose administration. Brigatinib was safe and well tolerated in healthy male and female Caucasian and Japanese subjects in this study after single PO dose administration of 90, 120, and 180 mg.

Based on these single-dose PK findings, the PK of brigatinib appears to be similar between Japanese and Caucasian subjects.

Preliminary Food-Effect Study (Study AP26113-13-103)

The objective of this randomized, open-label study was to rule out a clinically significant food effect by assessing the effect of high-fat conditions on the PK and relative bioavailability of brigatinib as compared to fasting conditions. This study was designed to be a preliminary food-effect assessment intended to guide further development of brigatinib. Healthy male or female (of non-childbearing potential) adult subjects were eligible for study participation. Doses were administered in the fasting state or after the completion of a standard high-fat meal. Ten healthy subjects were enrolled (evaluable for safety) and 8 subjects were considered evaluable for all PK comparisons. Single PO doses of brigatinib 180 mg (6 x 30 mg tablets) were

administered on Day 1 and subjects remained at the research site until at least 96 hours postdose (Day 4).

When administered under fasting conditions, the median (range) time to reach first Cmax (Tmax) for brigatinib was 2.5 hours (range: 1 to 6 hours) after intake of the 180 mg brigatinib dose. After administration following a high-fat meal, median (range) Tmax was 6 hours (range: 1 to 8 hours). GeoMean Cmax for the fasted and high-fat regimens were 804.5 ng/mL and 612 ng/mL, respectively, representing a 24% decrease under fed conditions. Importantly, GeoMean AUC0-∞ values for the fasted and high-fat regimens were similar at 15607 h•ng/mL and 15488 h•ng/mL, respectively.The limits of the 90% CIs of the estimated GeoMean ratios of Cmax (67.766, 85.401) did not fall within the 80% to 125% margin, suggesting the presence of an effect of food on brigatinib absorption. However, the limits of the 90% CIs of the estimated GeoMean ratios for both AUC0-∞ (88.163, 113.479) and AUC0-t (88.086, 107.147) fell within the 80% to 125% margins required to support the absence of a clinically relevant effect of food intake on brigatinib PK.

Brigatinib was well tolerated in healthy subjects under both fasted and fed conditions.

[14C]ADME Study (Study AP26113-13-104)

This was an open-label, non-randomized, mass balance study performed in 6 healthy male subjects to investigate the absorption, metabolism, and excretion of brigatinib. On Day 1, each subject received a single 180 mg PO dose of [14C]brigatinib (approximately 100 µCi). Serial PK sampling (blood, urine, feces) and safety assessments were conducted up to 216 hours postdose (morning of Day 10) or until the release criterion was met.[14C]radioactivity concentrations in plasma above the detectable level were observed up to 96 hours postdose in all 6 subjects, and in 4 of 6 subjects at 120 hours postdose. Brigatinib plasma concentrations were observed up to 240 hours postdose in all 6 subjects and in 5 of the 6 subjects who were still in the study at 264 hours postdose. Plasma brigatinib concentrations closely followed the plasma radioactivity concentrations. GeoMean plasma Cmax for both total radioactivity and brigatinib was approximately 1,000 ng/mL (Cmax for [14C]brigatinib equivalents was 7.6% higher than Cmax for brigatinib), and the median Tmax was 2 hours. The GeoMean exposure to total radioactivity in terms of AUC0-t and AUC0-∞ was close to approximately 20,000 h•ng/mL and only marginally higher (3.5% and 6.4% higher, respectively), than the values for brigatinib. The respective exposure PK parameter values (Cmax, Tmax, AUC) in plasma were very similar for brigatinib and TRA, indicating that concentrations of metabolites, if any, were negligible compared to those of brigatinib. The mean (±SD) total recovery of the administered radioactivity was 89.75±1.44%, of which 24.99±1.89% and 64.76±2.36% were recovered in urine and feces, respectively, indicating that feces was the major route of excretion of dosed [14C]brigatinib, although urinary excretion also contributed to drug elimination. Most of the radioactivity (approximately 80% of the dose) had been recovered by 120 hours postdose.

Following PO administration of [14C]brigatinib, parent brigatinib was the major circulating radioactive component accounting for 91.5% of the plasma radioactivity.

AP26123 was the principal metabolite observed and was present at 3.5% in the plasma. No other metabolites greater than 2% of the total plasma radioactivity were observed. Similarly in 0 to 240 hours pooled urine, parent brigatinib was the major species observed (85.57%) with AP26123 being the sole metabolite detected (6.17%). The major radioactive component in 0 to 240 hours pooled feces was brigatinib, accounting for 40.91% of the fecal TRA. Metabolites identified in feces were M36 (N-desmethyl brigatinib; AP26123), M28 (brigatinib cysteine conjugate), M25 (brigatinib N-oxide; AP32830), and M27 (monooxy-brigatinib), accounting for 39.13%, 14.03%, 1.04%, and 0.59% of the fecal TRA, respectively.

Overall, the metabolism of brigatinib in humans was qualitatively similar to nonclinical toxicology species (rat and monkey) with no unique human metabolites observed.

A single 180 mg PO dose of [14C]brigatinib was safe and well tolerated in the healthy male subjects in this study.

DDI Study of Brigatinib with Gemfibrozil, Rifampin, and Itraconazole (Study AP26113-15-105)

In vitro studies demonstrated that brigatinib is primarily metabolized by CYP2C8 and CYP3A4, and is a substrate of the efflux transporter P-gp. This study was conducted to determine whether strong inhibitors of CYP2C8 or CYP3A4 (gemfibrozil and itraconazole, respectively) and a strong inducer of both enzymes, as well as P-gp, (rifampin) alter the single dose PK of brigatinib in healthy subjects.

This was a single-center, 3-part, open-label, single-dose, 1-sequence, crossover study evaluating the effects of gemfibrozil (Part 1), rifampin (Part 2), and itraconazole (Part 3) on brigatinib PK in healthy subjects. In each part of the study, subjects received a single PO dose of brigatinib indose-proportional relationship treatment period 1. In treatment period 2, subjects were pretreated with the CYP inhibitor or inducer for either 4 or 6 days prior to co-administration with brigatinib.

Subjects received the following treatments:

- Part 1: Gemfibrozil DDI Study Treatment period 1: 90 mg brigatinib. Treatment period 2: 600 mg gemfibrozil twice daily (BID) + 90 mg brigatinib.
- Part 2: Rifampin DDI Study Treatment period 1: 180 mg brigatinib. Treatment period 2: 600 mg rifampin QD + 180 mg brigatinib.
- Part 3: Itraconazole DDI Study Treatment period 1: 90 mg brigatinib. Treatment period 2: 200 mg itraconazole BID + 90 mg brigatinib.

Subjects received the single doses of brigatinib following an overnight fast of at least 10 hours at approximately the same time on each dosing day. During treatment period 2, the CYP inducer or inhibitor was administered first for either 4 or 6 days, followed by co-administration with brigatinib. A washout period of at least 16 days between brigatinib doses was implemented and blood samples for brigatinib plasma PK characterization were collected for at least 120 hours following each brigatinib dose for all 3 study parts.

Part 1 Gemfibrozil DDI Study

Twenty healthy subjects were enrolled in Part 1 of the study and received at least 1 dose of the study drug in the treatment phase, and were included in the PK and safety populations. One subject was discontinued from the study due to vomiting within 4 hours of dosing in treatment period 2 and therefore, 19 subjects were evaluable for statistical PK comparisons.

Median Tmax of brigatinib was similar for the 2 treatment periods. Compared with brigatinib administered alone, co-administration with gemfibrozil reduced the Cmax of brigatinib by 41% and the AUC0-∞ and AUC0-120 of brigatinib were decreased by 11.5% and 14.7%, respectively. The percent GeoMean ratio for Cmax was 59.086% with a 90% CI of 53.847 to 64.835. The percent GeoMean ratios and 90% CI for AUC0-∞ and AUC0-120 were 88.469% (83.186, 94.088) and 85.339% (80.036, 90.993), respectively.

Although exposure to brigatinib was reduced following gemfibrozil administration, the degree of decrease for each parameter is well within the typical observed interpatient PK variability for brigatinib in patients under SS conditions. *Therefore, CYP2C8 does not appear to contribute meaningfully to the clearance of brigatinib in vivo. No dose modification is required for brigatinib during co-administration with strong CYP2C8 inhibitors***.** Single PO doses of 90 mg brigatinib alone and when co-administered with gemfibrozil were well tolerated. No deaths or serious adverse events (SAEs) occurred during the study.

Part 2 Rifampin DDI Study

Twenty healthy subjects were enrolled in Part 2 of the study and all subjects received at least 1 dose of the study drug in the treatment phase, and were included in the PK and safety populations. One subject was discontinued from the study due to elevated liver enzymes approximately 21 days after dosing in treatment period 2 and therefore, 19 subjects were evaluable for statistical PK comparisons.
Median Tmax of brigatinib was similar for both treatment periods. Compared with brigatinib administered alone, co-administration with rifampin reduced the Cmax of brigatinib by 59.5%; AUC0-∞ and AUC0-120 were decreased by 80.4% and 80.0%, respectively. The percent GeoMean ratio for Cmax was 40.478% with 90% CI (36.833, 44.484). The GeoMean ratios and 90% CI for AUC0-∞ and AUC0-120 were 19.582% (18.151, 21.127) and 20.021% (18.562, 21.594), respectively.

Co-administration of multiple 600 mg daily doses of rifampin with a single 180 mg brigatinib dose resulted in a statistically significant decrease in brigatinib Cmax by 59.5%. A 5-fold higher apparent oral clearance after extravascular administration, calculated using the observed value of the last quantifiable concentration (CL/F) of brigatinib was observed, and brigatinib AUC0-∞ and AUC0-120 were decreased by 80.4% and 80.0%, respectively, relative to a single 180 mg brigatinib dose given alone. *Therefore, the concomitant use of strong and moderate CYP3A inducers with brigatinib should be avoided*. Single PO doses of 180 mg brigatinib alone and when co-administered with rifampin were well tolerated. No deaths or serious AEs occurred during Part 2 of the study.

Part 3 Itraconazole DDI Study

Twenty healthy subjects were enrolled in Part 3 of the study and all subjects received at least 2 doses of study drug and completed the treatment phase, and were included in the PK and safety populations.

The median Tmax of brigatinib was similar for the 2 treatments. Compared with brigatinib administered alone, co-administration with itraconazole resulted in an increase in brigatinib Cmax. The GeoMean ratio for brigatinib Cmax was 121.165% with an associated 90% CI of 113.318 to 129.554. AUC0-∞ and AUC0-120 GeoMean ratios (90% CI) were 201.165% (183.917, 220.030) and 182.069% (171.579, 193.201), demonstrating increases by 101.2% and 82.1 respectively, in the presence of itraconazole. The t½ of brigatinib was prolonged from 30 to 45 hours in the presence of itraconazole.

Itraconazole, a strong CYP3A4 and a P-gp inhibitor, had a moderate effect on the PK of brigatinib. Co-administration of multiple 200 mg BID doses of itraconazole with a single 90 mg brigatinib dose resulted in a statistically significant increase in brigatinib Cmax by 21.2%. A 2-fold decrease in CL/F of brigatinib was observed and brigatinib AUC0-∞ and AUC0-120 were increased by brigatinib dose given alone. *Accordingly, the concomitant use of strong CYP3A inhibitors with brigatinib should be avoided***.** If concomitant use of strong CYP3A inhibitors cannot be avoided, the dose of brigatinib should be reduced by approximately 50% (ie, from 180 mg to 90 mg or from 90 mg to 60 mg considering the available tablet strengths). After discontinuation of a strong CYP3A inhibitor, the brigatinib dose that was tolerated prior to the initiation of the strong CYP3A inhibitor should be resumed.Single PO doses of 90 mg brigatinib alone and when co-administered with itraconazole were well tolerated. No deaths or SAEs occurred during Part 3 of the study, and no subject was discontinued from the study due to an AE.101.2% (2-fold) and 82.1% (<2-fold), respectively, relative to a single 90 mg

Hepatic Impairment Study (Study AP26113-15-107)

This study is an open-label, single-dose, parallel-group, inpatient, non-randomized study conducted in patients with chronic hepatic impairment and matched healthy subjects. A total of approximately 27 participants will be enrolled into the study, including 18 patients with hepatic impairment (6 each with Child-Pugh classes A, B, and C) and approximately 9 matched healthy controls. Patients with hepatic impairment will be matched with healthy subjects by age, sex, body mass index (BMI), and, if possible, smoking habits. Each participant will receive a single 90 mg PO dose of brigatinib in the morning of study Day 1 under fasting conditions and will remain in the clinic to complete PK sampling through 192 hours. This study is ongoing.

Renal Impairment Study (Study AP26113-15-108)

This study is an open-label, parallel-group, inpatient, non-randomized, single-dose study conducted in patients with severe renal impairment and matched healthy subjects with normal renal function Approximately 8 subjects with severe renal

impairment are planned to be enrolled along with 8 matched healthy subjects with normal renal function. Patients with renal impairment will be matched to the greatest extent possible with healthy subjects by age, sex, BMI and, if possible, smoking habits. Each participant will receive a single 90 mg PO dose of brigatinib in the morning of study Day 1 under fasting conditions and will remain in the clinic to complete blood and urine PK sampling through 168 hours. This study is ongoing.

Pivotal Food-Effect Study (Study AP26113-16-109)

Study AP26113-16-109 was conducted to provide a definitive assessment of the effect of a high-fat meal on the PK of a single PO dose of brigatinib, administered using the commercial 90 mg tablet formulation, in healthy subjects. This was a single-dose, randomized, open-label, 2-period, 2-sequence crossover study in healthy subjects. Single PO doses of brigatinib 180 mg (2 x 90 mg tablets) were administered after consumption of a high-fat meal or under fasting conditions. Each study drug administration was separated by a washout interval of at least 16 days. PK blood samples were collected and safety assessments were conducted at designated time points from predose until 168 hours postdose.

A total of 24 subjects were randomized and were administered at least 1 dose of study drug and were included in the safety and PK populations. Three subjects were discontinued from the study prior to treatment period 2; therefore, 21 subjects completed the study and are included in the final statistical analyses. Two subjects were withdrawn early due to positive breath carbon monoxide test results; and 1 subject was withdrawn early due to noncompliance with clinic rules.

Median brigatinib Tmax was 2 hours after dosing brigatinib 180 mg in the fasted state and 5.0 hours after dosing brigatinib in the fed state. The observed GeoMean Cmax was approximately 13% lower after dosing in the fed state (604.6 ng/mL) than after dosing in the fasted state (701.3 ng/mL). GeoMean values for AUC0-t were similar for both fasted and fed treatments (13054 h•ng/mL and 12742 h•ng/mL after dosing in the fasted and fed states, respectively). GeoMean values for AUC0-∞ were similar after dosing in the fasted state and fed state (13261 h•ng/mL and 12944 h•ng/mL, respectively).The results of the analyses conducted to evaluate the effect of a high-fat meal on brigatinib Cmax, AUC0-t, and AUC0-∞, demonstrated that the limits of the 90% CI of the estimated mean ratio of AUC0-t (89.396, 107.399) and AUC0-∞ (89.430, 107.386) fell within the 80% to 125% margins, but the lower bound of the 90% CI for Cmax (78.261, 96.752) fell below the 80% lower margin required to conclude BE between the fasted and fed treatments, with food intake reducing the GeoMean Cmax (estimated mean ratio was 87.016%) by approximately 13%. Brigatinib median Tmax was delayed by 3 hours after dosing in the fed state compared to the fasted state. Overall, the observed 13% decrease in plasma Cmax following a high-fat meal was small relative to typical variability in Cmax observed for brigatinib in patients under SS conditions (approximately 60% CV). Without a corresponding decrease in AUC when brigatinib is administered with a high-fat meal, these changes in Cmax are not considered to be clinically important for the safety and efficacy of brigatinib.

Therefore, brigatinib may be administered without regard to food intake.

Concentration-QTc Analysis

Electrocardiogram (ECG) and time-matched PK data were available from a subset of the 137 patients enrolled in Study AP26113-11-101. Specifically, a total of 110 patients administered brigatinib doses ranging from 30 mg to 240 mg QD contributed PK time -matched ECG data to this concentration-QTc analysis, with 29 patients receiving the recommended 90 mg to 180 mg QD dose regimen. Therefore, data over a wide concentration range, including concentrations higher than those observed with the recommended dose regimen, contributed to the analysis, and brigatinib had no clinically significant effect on cardiac repolarization as assessed by concentration-QTc analysis. The one-sided upper 95% confidence bound of the predicted change from baseline in QTc corrected by Fridericia's formula (QTcF) was -4.7 milliseconds

Phase 2 Study AP26113-13-201 (ALTA)

This is a pivotal phase 2, randomized, multicenter, international study of brigatinib in patients with ALK+ NSCLC who previously progressed on crizotinib. A total of 222 patients were randomized 1:1 to receive brigatinib in 1 of 2 different dosing regimens: (A) 90 mg QD, continuously, or (B) 90 mg QD for 7 days, then 180 mg QD, continuously (90 mg to180 mg QD). For both treatment regimens, dose modifications (dose interruptions, dose reductions) were allowed. Eligible patients had histologically or cytologically confirmed locally advanced or metastatic NSCLC with documented ALK rearrangement by a positive result from the Vysis® ALK. Break-Apart fluorescence in situ hybridization (FISH) Probe Kit; or documented ALK positivity by a different test and tissue available for the Vysis® FISH test to be performed centrally. Patients were required to have progressive disease (PD) while on crizotinib. The first patient was randomized in June 2014 and the last patient was randomized in September 2015. Treatment and follow up are ongoing. The primary endpoint of this study was confirmed ORR as assessed by the investigator, per RECIST, Version 1.1. Secondary endpoints include confirmed ORR as assessed by a central IRC; CNS response assessed by an IRC (ORR and PFS in patients who had active brain metastases); time to response; DOR; time on treatment; disease control rate (DCR); PFS; OS; safety and tolerability; SS plasma level of brigatinib for use in population PK modeling; and patient-reported symptoms of lung cancer and health-related quality of life scores, assessed with the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30, Version 3.0). The study is being conducted at approximately 100 study centers in 18 countries in North America, Europe, Asia, and Australia. Overall, 222 patients were enrolled into the study in 18 countries; 105 patients at 38 sites in 12 countries in Europe (Austria, Belgium, Denmark, France, Germany, Italy, Netherlands, Norway, Spain, Sweden, Switzerland, and the United Kingdom); 68 patients at 17 sites in 4 countries in the Asian Pacific region (Australia, Hong Kong, Republic of South Korea, and Singapore); and 49 patients at 16 sites in North America (Canada and US).

Overall, the median age was 54.0 years (range: 18 to 82); over half the patients were female (56.8%, 126/222), while 23.5% were ≥65 years. At baseline, the ECOG performance status was 2 for 7.2% (16/222) of all patients (6.3% [7/112] in Arm A and 8.2% [9/110] in Arm B). The NSCLC histopathological classification

was adenocarcinoma for the majority (96.8% [215/222]) of all patients (95.5% [107/112] in Arm A and 98.2% [108/112] in Arm B). The majority of patients had a local or centrally confirmed ALK Vysis FISH test result (89.2% [198/222] of all patients; 89.3% [100/112] in Arm A and 89.1% [98/110] in Arm B). Crizotinib was the most recent prior systemic therapy at baseline for 95.9% (213/222) of all patients (95.5% [107/112] in Arm A and 96.4% [106/110] in Arm B).

The best response to the prior crizotinib therapy was a partial response (PR) for 60.8% (135/222) of all patients (58.0% [65/112] in Arm A and 63.6% [70/110] in Arm B), and 3.2% (7/222) of all patients had achieved a complete response (CR) with crizotinib (4.5% [5/112] in Arm A and 1.8% [2/110] in Arm B). The majority of patients had received prior chemotherapy (73.9% [164/222] of all patients; 74.1% [83/112] in Arm A and 73.6% [81/110] in Arm B) and prior platinum-based chemotherapy (73.4% [163/222] of all patients; 74.1% [83/112] in Arm A and 72.7% [80/110] in Arm B). Brain metastases at baseline, as assessed by the investigator, were present in 69.4% (154/222) of all patients (71.4% [80/112] in Arm A and 67.3% [74/110] in Arm B)

Objective response rate

The investigator-assessed confirmed ORR was 45.5% (51/112) of patients in Arm A and 55.5% (61/110) of patients in Arm B. The best overall response was a confirmed PR for 43.8% (49/112) of patients in Arm A and 50.9% (56/110) of patients in Arm B, and a confirmed CR for 1.8% (2/112) of patients in Arm A and 4.5% (5/110) of patients in Arm B.

Prospectively defined criteria for efficacy stated that a treatment regimen will be considered to have achieved the primary objective when the investigator-assessed ORR is shown to be significantly higher than 20% at a two-sided alpha level of 0.025 at the primary analysis for that regimen; the lower limit of the 97.5% CI rules out an alternate rate of 20% when the true rate is 35% or higher. Therefore, these prospectively defined criteria for efficacy were met (the lower limit of the 97.5% CI exceeds 20%) with statistical significance for investigator-assessed ORR in both arms: 45.5% for Arm A (97.5% CI: 34.8, 56.5) and 55.5% for Arm B (97.5% CI: 44.3, 66.2). The IRC-assessed confirmed ORR was 50.9% (57/112) of patients in Arm A and 54.5% (60/110) of patients in Arm B. IRC-assessed confirmed CR was observed in 5.4% (6/112) of patients in Arm A and 5.5% (6/110) of patients in Arm B

Progression-free survival

Investigator-assessed PFS in the ITT population is presented in Figure XX. Median (KM estimate) for investigator-assessed PFS was 9.2 months (95% CI: 7.4, 11.1) in Arm A and 15.6 months (95% CI: 11.1, 19.4) in Arm B. In Arms A and B, 73/112 (65%) and 55/110 (50%) events have been observed, respectively. The hazard ratio observed between the two arms is 0.64 (95% CI: 0.45, 0.91). Median (KM estimate) for IRC-assessed PFS was 9.2 months (95% CI: 7.4, 12.8) in Arm A and 16.7 months (95% CI: 11.6, NE) in Arm B. In Arms A and B, 60/112 (53.6%) and 45/110 (40.9%) events have been observed, respectively. The hazard rat in between the two arms is 0.69 (95% CI: 0.47, 1.02).

Overall survival

OS by arm is shown in Figure 5.n. Median OS has not been reached in Arm A (95% CI: 20.2, NE) and is 27.6 months (95% CI 27.6, NE) in Arm B, with 42/112 (37.5%) and 32/110 (29.1%) events observed in Arm A and Arm B, respectively. The hazard ratio observed between the 2 arms is 0.67 (95% CI: 0.42, 1.06).

CNS Efficacy

To evaluate the potential for brigatinib anti-tumor activity in the CNS, an additional IRC assessment was performed to assess efficacy endpoints in the intracranial CNS in randomized patients with active brain metastases assessed by MRI at enrollment. Contrast -enhanced brain MRI scans were analyzed by neuroradiologists in an independent central review. The reviewers were blinded to investigator assessment and treatment assignment. Up to 5 measurable brain metastases could be chosen as target lesions by the independent reviewers. Response in patients with at least 1 measurable brain lesion (≥10 mm) was defined as a ≥30% decrease in the sum of the longest diameters of target lesions and nonprogression in non-target lesions. Response in patients with only nonmeasureable brain metastases was defined as disappearance of all lesions (CR).

Of the 222 patients in the ITT population, 217 patients had baseline MRI scans of the brain read by IRC, and 153 patients had brain metastases identified by IRC at baseline.

- 44 patients with measurable lesions; of which, 34 patients had at least 1 active brain metastasis at baseline identified by the investigator (with 'active' defined as no prior history of radiation to the brain or clear progression after local radiotherapy).
- 109 patients had only nonmeasureable lesions at baseline; of which, 67 patients who had a least 1 active brain metastasis at baseline identified by the investigator.

The IRC database extraction included a last scan date of 28 February 2017 for all patients with brain metastases at baseline and 24 January 2017 for patients with measurable brain metastases at baseline.

Intracranial ORR

Patients with Measureable Brain Metastases at Baseline

At this database extraction, the IRC-assessed confirmed intracranial ORR was 50.0% (13/26) for patients in Arm A and 66.7% (12/18) for patients in Arm B for patients with measurable brain metastases at baseline. Confirmed intracranial CR was the best response for 7.7% (2/26) of patients in Arm A and for no patients (0/18) in Arm B. Confirmed intracranial PR was the best response for 42.3% (11/26) of patients in Arm A and 66.7% (12/18) of patients in Arm B.

The intracranial DCR for patients with measureable brain metastases at baseline was 84.6% (22/26) of patients in Arm A and 83.3% (15/18) of patients in Arm B.

Patients with Only Nonmeasurable Brain Metastases at Baseline

For patients with only non-measureable brain metastases at baseline, intracranial

ORR was observed in 7.4% (4/54) of patients in Arm A and 18.2% (10/55) of patients in Arm B. Intracranial response for patients with only non-measureable brain metastases is defined for purposes of this study as complete radiographic disappearance of lesions and is the only response possible for patients with only non-measureable lesions.

The intracranial DCR for patients with non-measureable brain metastases at baseline was 74.1% (40/54) of patients in Arm A and 87.3% (48/55) of patients in Arm B.

Phase 2 Study AP26113-13-201 (ALTA) Safety

TEAEs that occurred in >20% of patients overall were nausea (42.5%), diarrhea (35.6%), cough (34.2%), headache (32.9%), vomiting (32.9%), fatigue (27.9%), dyspnea (25.6%), blood creatine phosphokinase (CPK) increased (25.6%), decreased appetite (24.7%), hypertension (22.4%), and constipation (21.0%). The most common TEAE in both Arm A and Arm B was nausea (occurring in 37.6% and 47.3% of patients, respectively).

Grade ≥3 TEAEs and Treatment-Related Grade ≥3 TEAEs

Treatment-emergent AEs Grade ≥3 occurred in 62.1% (136/219) of patients overall and in similar proportions in Arm A and in Arm B (58.7% [64/109] and 65.5% [72/110], respectively). Treatment-emergent AEs Grade ≥3 by PT (occurring in ≥2% of all patients) that occurred in a greater proportion (≥50% relative increase) of patients in Arm A than in Arm B were neoplasm progression (15.6% [17/109] vs 7.3% [8/110], respectively), lipase increased (4.6% [5/109] vs 3.6% [4/110], respectively), and neutrophil count decreased (3.7% [4/109] vs 1.8% [2/110], respectively); and a greater proportion (≥50% relative increase) of patients in Arm B than in Arm A were blood CPK increased (12.7% [14/110] vs 4.6% [5/109], respectively).

The most common treatment-related TEAE Grade ≥3 in Arm A was lipase increased and hypertension (3.7% [4/109] for each) and in Arm B was blood CPK increased (10.9% [12/110]). A greater proportion (≥50% relative increase) of patients in Arm B than in Arm A had blood CPK increased (10.9% [12/110] vs 2.8% [3/109], respectively), pneumonitis (3.6% [4/110] vs 1.8% [2/109], respectively), and rash (3.6% [4/110] vs 0.9% [1/109], respectively). No treatment-related TEAEs Grade ≥3 occurring in ≥2% of all patients occurred in a greater proportion (≥50% relative increase) of patients in Arm A than in Arm B.

Overall, 49.8% (109/219) of patients experienced a treatment-emergent AEs (TEAE) that led to dose interruption of any duration. A greater proportion of patients in Arm B than in Arm A had a TEAE that led to dose interruption (59.1% [65/110] vs 40.4% [44/109], respectively). The TEAEs occurring in ≥3% of patients overall by PT that led to dose interruption were blood CPK increased (5.5% [12/219]), pneumonitis (4.6% [10/219]), neoplasm progression (4.1% [9/219]), lipase increased (3.2% [7/219]) and vomiting (3.2% [7/219]). The most common TEAEs that led to dose interruption in Arm A were neoplasm progression, vomiting, and pyrexia; in Arm B, the most comment TEAEs that led to dose interruption were blood CPK increased, pneumonitis, rash, and lipase increased.

TEAEs that led to dose reduction occurred in 9.2% (10/109) of patients in Arm A and 30.0% (33/110) of patients in Arm B. The only TEAE leading to dose reduction that occurred in ≥2% of patients overall by PT was blood CPK increased (4.1% [9/219]), which occurred in 1.8% (2/109) of patients in Arm A and 6.4% (7/110) of patients in Arm B.

TEAEs that led to discontinuation of brigatinib occurred in 7.3% (16/219) of patients overall, 3.7% (4/109) of patients in Arm A and 10.9% (12/110) of patients in Arm B. A greater proportion (≥50% relative increase) of patients in Arm B than in Arm A had a TEAE that led to brigatinib discontinuation (10.9% [12/110] vs 3.7% [4/109], respectively). The most common TEAE (occurring in ≥2 patients overall) that led to brigatinib discontinuation by PT were pneumonitis (1.8% [4/219]), neoplasm progression (0.9% [2/219]), and pneumonia (0.9% [2/219]).

Specific adverse events of clinical importance

Early Onset Pulmonary Event (EOPE)

As of a database extraction date of 21 February 2017, out of 219 treated patients, 4 patient cases were determined to meet the criteria for definite EOPE, and 10 cases met the criteria for possible EOPE. In total, 14 of 219 (6.4%) patients overall had an event that was at least possibly an EOPE. All EOPEs occurred at a dose of 90 mg QD, regardless of arm (ie, within the first 7 days of treatment in Arm B). No EOPEs were identified after escalation to 180 mg QD in Arm B. Median time of onset of EOPE was Day 2 (range: 1 to 9). Of the 14 patients who had an EOPE (Arm A: 5/109 [4.6%] and Arm B: 9/110 [8.2%]), all occurred while patients were receiving brigatinib 90 mg QD.

Eleven EOPE patient cases included SAEs, and 3 EOPE patient cases included only nonserious events. Seven (3.2%) patients had events that were Grade 1 or 2 only. Seven (3.2%) patients had events that were Grade ≥3, all of whom permanently discontinued brigatinib after the EOPE. There were 6 patients who had an EOPE with highest Grade of 3 or 4 (pneumonitis [n=4], radiation pneumonitis [n=1], pneumonia [n=1]). One patient (Patient 615-002) had a possible EOPE that was Grade 5. This patient developed pneumonia Grade 5 after taking brigatinib for 7 days (90 mg QD at event onset). At autopsy, microscopic examination revealed widespread dissemination of lung cancer, with spread to the paratracheal lymph nodes and left half of the chest, and lymphangitis carcinomatosis in the right lung. Additionally, histological changes in the right lung were compatible with diffuse alveolar damage, which indicated acute respiratory distress syndrome. Although the patient's lung cancer and infection were considered to be underlying causes of death, a contribution of brigatinib could not be ruled out, and this case was considered a possible EOPE given the association of events within 7 days of the start of brigatinib, as well as evidence for a pneumonitis-like process.

In 7 of 14 (50.0%) patients experiencing EOPE, brigatinib was permanently discontinued after the EOPE (including the fatal case). All 7 patients who permanently discontinued had Grade ≥3 events. In 6 of 14 cases, brigatinib was interrupted and successfully resumed after resolution of the pulmonary event. In 1

of these 6 cases (Patient 588-001), brigatinib was continued during the event, with interruption for 1 day prior to escalating to 180 mg QD, and the events resolved. In 1 of 14 patient cases (Patient 590-003), the brigatinib dose was reduced to 60 mg QD without an interruption and the event resolved. Events resolved with dose interruption or brigatinib discontinuation (drug withdrawn). Steroids and antibiotics were administered in 11 of 14 (78.6%) and 4 of 14 (28.6%) patient cases, respectively. There were 7 patients who successfully resumed brigatinib or continued administration through the pulmonary event; 2 of the patients had a confirmed PR and 5 of the patients had stable disease as best response.

Later-Onset Pneumonitis Events

Five patients each experienced a single later-onset pneumonitis event. Four of these occurred with the most recent dose being 180 mg QD, and 1 occurred at a dose of 90 mg QD. In 3 cases, brigatinib was successfully restarted without recurrence of pneumonitis. In 1 case, the patient had already permanently discontinued due to progression of disease. In the last case, the patient permanently discontinued brigatinib due to the event

Bradycardia

Bradycardia TEAEs of any grade occurred in 5.5% (12/219) of patients overall (Arm A: 6.4% [7/109] and Arm B: 4.5% [5/110]). Sinus bradycardia and bradycardia TEAEs occurred in 3.7% (8/219) and 1.8% (4/219) of patients overall, respectively. None of the bradycardia events were Grade ≥3. There were no dose reductions or treatment discontinuations due to bradycardia.

Hypertension

Hypertension TEAEs of any grade occurred in 22.4% (49/219) of patients overall (CSR AP26113-13-201 Table 14.3.3.4). Hypertension TEAEs were reported in a greater proportion of patients in Arm B than in Arm A (27.3% [30/110] vs 17.4% [19/109], respectively). Grade 3 hypertension TEAEs occurred in 6.8% (15/219) of patients overall; 5.5% (6/109) and 8.2% (9/110) of patients in Arm A and Arm B, respectively (CSR AP26113-13-201 Table 14.7.2.2). No Grade 4 hypertension has been reported. One patient in Arm A had retinopathy hypertensive. One patient in each arm (0.9%) had a dose reduction due to hypertension. No patient discontinued brigatinib due to hypertension.

Elevated Insulin/Hyperglycemia Events

Elevated insulin/hyperglycemia TEAEs of any grade occurred in 5.5% (6/109) in Arm A and 11.8% (13/110) in Arm B. The elevated insulin/hyperglycemia events that occurred in >2 patients in either treatment arm by PT were hyperglycemia (3.7% [4/109] of patients in Arm A and 5.5% [6/110] of patients in Arm B) and diabetes mellitus (0.9% [1/109] of patients in Arm A and 4.5% [5/110] of patients in Arm B). Elevated insulin/hyperglycemia events Grade ≥3 occurred in only 1 patient; this patient had a Grade 3 event of diabetes mellitus (which was also present in the previous 31 May 2016 data extraction) (Study AP26113-13-201 Table 14.3.7.2.7). No patients have had dose reduction or treatment discontinuation due to increased insulin/hyperglycemia TEAEs.

Pancreatic Events

Pancreatic TEAEs based on laboratory elevations (pancreatic enzyme elevations) of any grade occurred in 20.5% (45/219) of patients overall. No patients experienced clinical pancreatitis. A greater proportion of patients in Arm B than in Arm A had pancreatic events of any grade (24.5% [27/110] vs 16.5% [18/109], respectively). Pancreatic events Grade ≥3 occurred in 5.9% of patients overall (Arm A: 5.5% [6/109] and Arm B: 6.4% [7/110]) (Study AP26113-13-201 Table 14.3.7.5.6). Amylase increased led to dose reduction in 0.9% of patients overall (1 patient in each arm). Lipase increased led to dose reduction in 0.9% of patients (1/109) in Arm A and 1.8% of patients (2/110) in Arm B. No patients discontinued treatment due to TEAEs of lipase increased or amylase increased.

Hepatic Events

Hepatic TEAEs of any grade occurred in 21.9% (48/219) of patients overall, and occurred in 19.3% (21/109) of patients in Arm A and in 24.5% (27/110) of patients in Arm B. The most common hepatic events that occurred in >2 patients overall by PT were AST increased (15.1% [33/219] of patients overall; 10.1% [11/109] in Arm A and 20.0% [22/110] in Arm B) and ALT increased (12.8% [28/219] of patients overall; 10.1% [11/109] in Arm A and 15.5% [17/110] in Arm B). Grade 3 to 4 ALT increased TEAEs occurred in 3 patients (all in Arm B; 2.7%) and Grade 3 to 4 AST increased TEAEs occurred in 2 patients (both in Arm; 1.8%) (Study AP26113-13-201 Table 14.3.7.3.8). One patient had a dose reduction due to a hepatic event. No patient discontinued treatment due to a hepatic event. There were no TEAEs of clinical hepatic failure, and no patients satisfied the laboratory criteria threshold for a possible Hy's Law case.

Vision Impairment Events

Vision impairment events of any grade occurred in 15.1% (33/219) of patients overall (Arm A: 11.0% [12/109] and Arm B: 19.1% [21/110]). The most common vision impairment event by PT in patients overall was vision blurred (5.0% [11/219]), which occurred in in a higher number of patient in Arm B compared with Arm A (7.3% [8/110] and 2.8% [3/109], respectively). Two patients had Grade 3 vision impairment events (macular oedema and cataract). Two patients have had a dose reduction due to vision impairment TEAEs (macular oedema, retinal oedema). No patients have discontinued treatment due to vision impairment TEAEs.

1.4 Rationale

A significant population of ALK+ NSCLC patients exist that have progressed on or who were intolerant of next generation ALK inhibitor (e.g. ceritinib or alectinib). Brigatinib has demonstrated activity in patients who have progressed on crizotinib, but the activity of brigatinib in patients who have progressed on ceritinib, alectinib, or other next generation ALK inhibitors is unknown. Based on the preclinical data summarized in section 1.3, brigatinib has potent activity against known secondary ALK mutations suggesting it may retain activity as third-line treatment of ALK+ disease.

Patients enrolled must have previously received a next generation ALK inhibitor other than brigatinib. Given that third-line treatment of ALK+ disease is analogous to a phase I population, we have chosen 20% as a clinically meaningful response

rate that would justify further study of brigatinib in previously treated ALK+ disease. The recent data on brigatinib's activity in the central nervous system (CNS) provides additional rationale for study of this drug in refractory disease. We have elected to use the dose regimen (90mg PO QD for 7 days followed by 180mg PO QD continuously) from the above ongoing randomized Phase II trial of brigatinib as second-line treatment for cohorts A and B. For cohort C we have chosen the dose of 240 mg daily based on the phase I/II trial, and the fact all patients will have tolerated brigatinib at 180 mg daily.

1.5 Correlative Studies to Explore Mechanisms of Resistance

The mechanisms of resistance to *ALK* inhibitors is an active area of investigation, and multiple mechanisms have been identified including *ALK* kinase domain mutations, *ALK* copy number gain, acquisition of oncogenic driver mutations and activation of the EGFR pathway. A substantial proportion of patients do not have an identifiable molecular mechanism of resistance. In a case series of 18 patients who underwent biopsy after experiencing disease progression on crizotinib, four patients had a mutation within the *ALK* tyrosine kinase domain and an additional patient had amplification of the *ALK* fusion gene.(Katayama et al. 2012) Other mechanisms of resistance identified include amplification of KIT and increased auto-phosphorylation of EGFR suggesting activation of the EGFR pathway as a mechanism of resistance.

A similar case series of 11 patients identified secondary mutations in the tyrosine kinase domain (n=4), *ALK* copy number gain (n=2; one patient also demonstrated an *ALK* resistance mutation), *KRAS* mutation (n=2; one without the evidence of the original *ALK* rearrangement), EGFR mutation without evidence of a persistent *ALK* rearrangement (n=1), and *ALK* rearrangement negative (n=1).(Doebele et al. 2012) *ALK* secondary resistance mutations are identified in approximately 30% of patients after crizotinib, and include 1151Tins, C1156Y, L1196M, S 1206Y and G1269A.(Gainor et al. 2016) Tumor specimens from patients who received crizotinib or next generation *ALK* inhibitors were analyzed. In patients who received crizotinib *ALK* resistance mutations were identified in 20% of specimens, and *ALK* amplification (defined as ALK/centromere 2 ratio of > 2.0) was observed in 8% (none of which had an ALK resistance mutation). In contrast an *ALK* resistance mutation was observed in 54% of the specimens of patients with disease progression on ceritinib, and 53% of specimens of patients with disease progression on alectinib. Collectively, these data suggest the rate of *ALK* resistance mutations is higher after next-generation ALK inhibitors and the most common resistance mutation is the G1202R.

No association between ALK resistance mechanism and ceritinib response was observed in the initial trial but the number of patients with a known mutation was small (n=19).(Shaw et al. 2014) Preclinical models suggest that different ALK inhibitors have differing degrees of activity depending on the resistance mutation. Ceritinib has activity against the L1196M, G1296A, I1171T and S1206Y, but not against the ALK secondary mutations C1156Y, 1151Tins, G1202R and F1174C.(Friboulet et al. 2014) Patients treated with ceritinib have developed resistance mutations in G1202R or F1174. Patients previously treated with alectinib have been shown to develop V1180L and I1171T resistance mutations.[22] Ceritinib

demonstrated activity against the V1180L and I1171T mutations, brigatinib demonstrated activity against the V1180L mutation but less activity against the I1171T, and ASP3026 was active against V1180L and inactive against the I1171T mutation.(Katayama et al. 2014) Thus, ALK tyrosine kinase inhibitors may have differing level of clinical activity depending on the resistance mutation. None of the previous studies are definitive, but they suggest that an understanding of the molecular mechanisms of resistance at the time of initiating a new ALK inhibitor will be important in assessing the clinical activity of an ALK inhibitor.

In this study, pre-treatment tumor samples will undergo next generation sequencing to explore for an association between mutation presence or absence and type of mutation as well as other mechanisms of resistance and response to brigatinib. Tumor samples at progression will be used to identify resistance mutations after brigatinib. Participation in the biopsy at the time of progression on brigatinib is optional since biopsies may not be feasible, patients may not be candidates for further therapy, or patients may need to proceed to the next line of therapy in an expedited time frame.

There is increasing interest in detecting oncogenic mutations in ctDNA obtained from peripheral blood samples.(Oxnard et al. 2014; Cui et al. 2017; Newman et al. 2014; Wang et al. 2016) This will also be explored in the present study. The overall sensitivity, specificity, and accuracy of capture-based NGS of ctDNA was 54%, 100%, and 72%, respectively. Of 13 ALK positive samples were identified by capture-based NGS among 24 samples with positive tumor samples for *ALK*. An additional study revealed a sensitivity and specificity was 79% and 100%, respectively. *ALK* rearrangements were successfully detected in 19 of 24 patients. Crizotinib resistance mutations were detected from a single patient. While the focus has been on the detection of *ALK* resistance mutations it is important to note the *ALK* resistance mutations are detected in approximately 50% of patients with progressive disease on next-generation ALK inhibitors and there is a need to identify other mechanisms of resistance.

2.0 STUDY OBJECTIVES

2.1 Primary Objective

Estimate ORR (rate of CR+PR) of brigatinib in patients with ALK+ NSCLC who have progressed on next generation ALK inhibitors

2.2 Secondary Objectives

2.2.1 Further characterize treatment-related adverse events associated with brigatinib including at different doses in patients with ALK+ NSCLC

2.2.2 Estimate duration of response in patients with ALK+ NSCLC treated with brigatinib who have progressed after prior ALK inhibition

2.2.3 Estimate PFS in patients with ALK+ NSCLC treated with brigatinib who have progressed after prior ALK inhibition

2.2.4 Estimate intracranial and extra-cranial PFS in patients with ALK+ NSCLC treated with brigatinib who have progressed after prior ALK inhibition

2.2.5 Estimate OS in patients with ALK+ NSCLC treated with brigatinib who have progressed after prior ALK inhibition

2.3 Exploratory Objectives

2.3.1 Explore association between presence and/or type of mutation or mechanism of resistance at baseline and efficacy outcomes (ORR and PFS)

2.3.2 Identify resistance mutations or other mechanisms of resistance after brigatinib by evaluating tumor samples at time of progression

2.3.3 Explore whether ctDNA from peripheral blood samples can identify development of resistance mutations

2.3.4 Estimate intracranial ORR in patients with ALK+ NSCLC treated with brigatinib who have progressed after prior ALK inhibition who have measurable CNS disease at baseline

2.4 Primary Endpoint

ORR as determined by RECIST 1.1 as assessed by the investigator

2.5 Secondary Endpoints

2.5.1 The treatment-related adverse events will be assessed using the NCICTCAE version 4.0 as assessed by the investigator.

2.5.2 Duration of response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date of progression

2.5.3 PFS with progression events as per RECIST 1.1 and as assessed by the investigator; PFS is defined from day 1 of treatment until progression of disease (either intracranial or extracranial) or death as a result of any cause

2.5.4 Intracranial PFS is defined from day 1 of treatment until intracranial progression of disease or death as a result of any cause; extracranial PFS is defined from day 1 of treatment until extracranial progression of disease or death as a result of any cause. Only patients with brain metastases at baseline will be included in this analysis

2.5.5 OS is defined from day 1 of treatment until death as a result of any cause

2.5.6 Intracranial ORR as determined by RECIST 1.1 as assessed by the investigator

3.0 PATIENT ELIGIBILITY

Patients must meet all of the following inclusion criteria to participate in this study:

3.1 Inclusion Criteria for all cohorts

3.1.1 Locally advanced or metastatic NSCLC that has been cytologically or histologically confirmed

3.1.2 ALK positive status based on Clinical Laboratory Improvement Amendments (CLIA) or test approved for use in Canada. Diagnostic test may be based on ctDNA testing or based in tumor testing

3.1.3 ECOG PS ≤2

3.1.4 Age of ≥ 18 years

3.1.5 Brain lesions may be used as target lesions if progressing, ≥10mm in longest diameter and if they were not previously treated with any of the following:

- Whole brain radiation therapy (WBRT) within 3 months
- Stereotactic radiosurgery (SRS)
- Surgical resection

3.1.6 Availability of core biopsy of progressive lesion taken within 60 days prior to D1 of treatment under study therapy or willing to undergo tumor biopsy: NOTE: All subjects must consent to provide tumor blocks or slides.

- If archival tissue is not available and biopsies to obtain fresh tumor tissue cannot be performed with minimal risk to the subject, subjects may be permitted to enroll on the study with prior approval of the Study PI.
- In the situation the patient undergoes biopsy within 60 days prior to D1 and there is insufficient tumor tissue for the correlative science part of the protocol, the patient will be permitted to enroll on the study with prior approval of the study PI
- In the situation the patient undergoes molecular testing or next-generation sequencing as part of standard care there must be sufficient tumor sample available for participation in the study (i.e. a next generation sequencing report is not sufficient for enrollment)

3.1.7 Recovered from toxicities related to prior anticancer treatment to ≤Grade 2 or baseline with the exception of alopecia

3.1.8 Have normal QT interval on ECG evaluation QT corrected Fridericia (QTcF) of ≤ 450 ms in males or ≤ 470 ms in females

3.1.9 Adequate organ function defined as:

Absolute neutrophil count (ANC)	≥1500/μL
Platelets	≥75,000/μL
Hemoglobin	≥ 10g/dL
AST /ALT	≤ 2.5 x upper limit of normal (ULN); ≤ 5 x ULN if liver metastasis
Total serum bilirubin	≤ 1.5 x ULN
Serum creatinine	≤ 1.5 x UNL
Serum amylase	≤ 1.5 x UNL

3.1.10 At least 1 measurable lesion per RECIST version 1.1

3.1.11 Female patients who:

- Are postmenopausal for at least 1 year before the screening visit, OR
- Are surgically sterile, OR
- If they are of childbearing potential, agree to practice 2 effective methods of contraception, at the same time, from the time of signing the informed consent through *4 months* after the last dose of study drug, or agree to completely abstain from heterosexual intercourse. (Oral and implantable contraceptives are not considered effective forms of contraception for study purposes. See Appendix C (auxiliary patient document)).
- Women of child-bearing potential (WOCBP) must have a negative serum pregnancy test within 7 days of D1 of treatment.

3.1.12 Male patients, even if surgically sterilized (i.e., status post-vasectomy), who:

- Agree to practice effective barrier contraception during the entire study treatment period and through 4 *months* after the last dose of study drug, or
- Agree to completely abstain from heterosexual intercourse

3.1.13 Ability to provide signed informed consent and willing and able to comply with all study requirements.

3.2 Inclusion criteria for cohort assignment

3.2.1 **Cohort A**: Progressive disease on any next generation ALK inhibitor except first line alectinib alone (eligible for study but assigned to cohort B) or brigatinib (any line). Patients who received previous therapy with lorlatinib will be assigned to cohort A.

3.2.2 **Cohort B:** Progressive disease on first-line therapy with alectinib, and no other ALK inhibitors

3.2.3 **Cohort C:** Previous treatment brigatinib at 180 mg daily for ≥4 weeks without > grade 2 drug-related toxicities and with radiographic evidence of

progressive disease and no intervening systemic therapies such as chemotherapy, immunotherapy or another ALK inhibitor (radiation therapy allowed as intervening therapy).

3.2.4 Patients who are treated on cohorts A and B will be allowed to enroll in cohort C if they meet the inclusion and exclusion criteria. Patients are required to undergo a biopsy before enrollment in cohort C. Patients who change cohorts from A or B to cohort C should not have EOT assessments completed and do not discontinue brigatinib, and should complete a new registration form and will be given a new subject number

3.3 Exclusion Criteria for cohorts A, B, and C

Patients meeting any of the following exclusion criteria will not be able to participate in this study:

3.3.1 History or the presence of pulmonary interstitial disease, drug-related or immune-related pneumonitis, or radiation pneumonitis requiring medical management within 6 months of trial enrollment

3.3.2 Prior treatment with brigatinib for cohorts A and B

3.3.3 History of or active significant gastrointestinal (GI) bleeding within 3 months

3.3.4 Malabsorption syndrome or other GI illness that could affect oral absorption of the study drug

3.3.5 Received cytotoxic chemotherapy, investigational agents or radiation within 7 days prior to D1 of study treatment

3.3.6 Received prior ALK TKI therapy within 7 days prior to D1 of treatment under study drug. 7 day wash out period is required after prior ALK inhibitor treatment for cohorts A and B. Patients enrolling in cohort C should continue brigatinib and 7 day wash out is not required).

3.3.7 Have significant, uncontrolled, or active cardiovascular disease, specifically including, but not restricted to:

- Myocardial infarction (MI) within 6 months of trial enrollment
- Unstable angina within 6 months of trial enrollment
- Congestive heart failure (CHF) with 6 months prior to trial enrollment
- Any history of ventricular arrhythmia
- Cerebrovascular accident or transient ischemic attack within 6 months of D1 of study treatment
- Clinically significant atrial arrhythmia (as determined by the investigator) or severe baseline bradycardia defined as resting heart rate < 60 beat per minute
- Uncontrolled hypertension defined as baseline SBP> 160 and DBP > 100 on 3 separate clinic visits or past history of hypertensive urgency, emergency, or encephalopathy

3.3.8 Another primary malignancy for which the patient is currently receiving therapy

3.3.9 Have been diagnosed with another primary malignancy within the past 3 years (except for adequately treated non-melanoma skin cancer, cervical cancer in situ, or prostate cancer, which are allowed within 3 years)

3.3.10 Have symptomatic CNS metastases which require an increasing dose of corticosteroids within the last 2 weeks to remain asymptomatic.

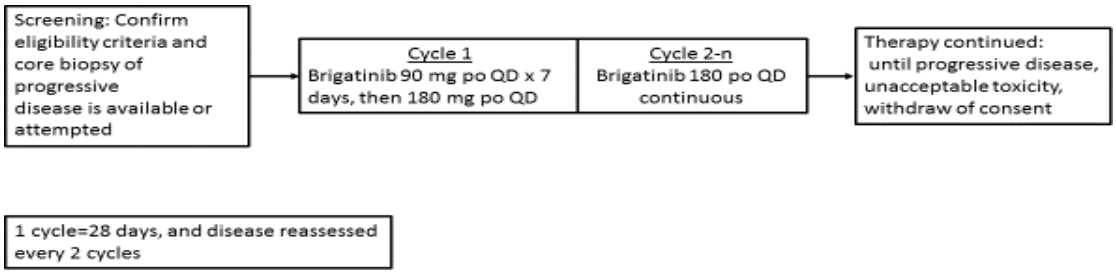
3.3.11 Have active infection requiring intravenous antibiotics

3.3.12 Pregnant or breastfeeding

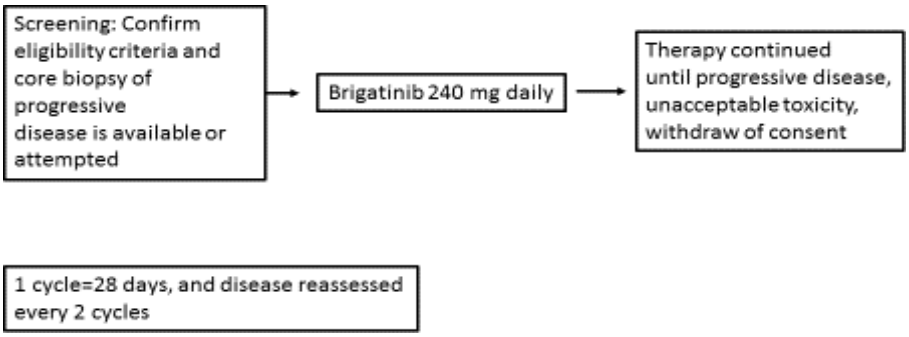
3.3.13 Have any condition or illness that, in the opinion of the investigator, would compromise patient safety or interfere with evaluation of the study drug.

4.0 TREATMENT PLAN

4.1 Schema for cohorts A and B



4.2 Schema for cohort C



4.3 Treatment Dosage and Administration

4.3.1 Cohorts A and B

Brigatinib will be administered at a dose of 90 mg (3 by 30 mg tablets) orally once a day (QD) for the first 7 days of cycle 1 followed by 180 mg (6 by 30 mg tablets) orally once a day continuously thereafter. NOTE: during cycle 1, patients will be seen on D8 to determine if dose escalation to 180mg is appropriate (see section 4.3.1 and 4.3.2. Should drug formulation change, equivalent doses in smaller numbers of capsules may be substituted to reduce patient pill burden in any cohort.

A cycle of therapy will comprise 28 days of treatment, regardless of dose. Patients will be instructed to take the prescribed dose with water (recommended 240 mL(8 oz)) at the same time each day, and *without regard to food intake*. Patients who forget to take their scheduled dose of study drug should be instructed not to make up the missed dose. Patients who vomit immediately after taking a dose should be instructed NOT to retake the dose. All doses should be recorded in the patient diary, with a notation made by the patient if any dose is missed, or if a dose is vomited.

4.3.2 Cohort C

Brigatinib will be administered at 240 mg daily (8 by 30 mg tablets). A cycle of therapy will comprise 28 days of treatment, regardless of dose. Patients will be instructed to take the prescribed dose with water [recommended 240 mL (8 oz)] at the same time each day, and without regard to food intake. Patients who forget to take their scheduled dose of study drug should be instructed not to make up the missed dose. Patients who vomit immediately after taking a dose should be instructed NOT to retake the dose. All doses should be recorded in the patient diary, with a notation made by the patient if any dose is missed, or if a dose is vomited.

4.4 Toxicities and Dosing Delays/Dose Modifications for cohorts A and B

Any patient who receives treatment on this protocol will be evaluable for toxicity. Each patient will be assessed periodically for the development of any AE according to the Time and Events table (Section 6.0). AE will be assessed according to the NCI CTCAE v4 for 30 days after dosing is completed. Of note, monitoring for signs of liver or vision dysfunction, monitoring serum levels of testosterone is recommended due to the safety profile of the ALK inhibitor crizotinib.

Missed doses of brigatinib will be omitted and not made up. Unless otherwise noted in the tables below, treatment may be interrupted ≤ 2 weeks for any reason. If treatment is interrupted ≤ 2 weeks, subjects will proceed with treatment at the dose level recommended according to the tables below. In the event that brigatinib dosing is interrupted, the duration of cycle/treatment will not be extended. Therefore, if treatment is delayed on D1 of a cycle due to toxicity, and the patient does not begin therapy until D5 (for example), the start date of drug for that cycle remains D5, not D1 If treatment is delayed >2 weeks, then the patient should be discontinued from protocol mandated therapy and followed-up per protocol.

4.4.1 Non-Hematologic Treatment-Related AEs during Brigatinib 90mg Daily 7 day lead-in other than Pneumonitis

Grade[1]	Dose Modification	Criteria for Dose Escalation
1	Continue 90mg daily	Escalate to 180 mg daily D8 as scheduled
2 (≤ 3 days)	Continue 90mg daily	If AE returns to ≤ Grade 1 or baseline at D8, escalate to 180mg daily on D8
2 (≥ 3 days despite optimal supportive care)	Hold until event is ≤ Grade 1 or returned to baseline, then resume 90mg daily	If no recurrence of Grade 2 AE after 90 mg daily for 7 days, escalate to 120 mg daily. Do **NOT** escalate to 180 mg daily. If recurrence of Grade 2 after 90mg daily, do **NOT** escalate dose.
3	Hold until event is Grade ≤ 1 or has returned to baseline, then resume at 90mg daily	Do **NOT** escalate dose
4	Hold until event is Grade ≤ 1 or has returned to baseline, then resume at 60 mg daily.	Do **NOT** escalate dose
[1]Per NCI CTCAE v4.0		

4.4.2 Hematologic Treatment-Related AEs during Brigatinib 90mg Daily 7 day lead-in

Grade[1]	Dose Modification	Criteria for Dose Escalation
1 or 2	Continue 90mg daily	Escalate to 180 mg daily D8 as scheduled
3 or 4	Hold until event is ≤ Grade 2 or returned to baseline, then resume 90mg daily	Do **NOT** escalate dose
[1]Per NCI CTCAE v4.0		

4.4.3 Non-Hematologic Treatment-Related AEs during Brigatinib 180mg Daily other than Pneumonitis

Grade[1]	Dose Modification
1 or 2	Continue current dose

3	• When the current dose is 180 mg QD: Hold until event is grade ≤ 1, or has returned to baseline. Resume at 180 mg QD or 120 mg QD at the discretion of the investigator • Upon recurrence at 180 mg QD: Hold until event is grade ≤ 1, or has returned to baseline and resume at 120 mg QD • When the current dose is 120 mg QD: Hold until event is ≤Grade 1, or has returned to baseline. Resume at 90 mg QD after recovery • When the current dose is 90 mg QD: Hold until event is ≤Grade 1, or has returned to baseline. Resume at 60 mg QD after recovery, or discontinue at the discretion of the Investigator. • When the current dose is 60 mg QD: Consider discontinuing treatment at the discretion of investigator
4	• When the current dose is 180 mg QD: Hold until event is grade ≤1, or has returned to baseline. Resume at 120 mg QD, or discontinue, at the discretion of the investigator • When the current dose is 120 mg QD, hold until event is grade ≤ 2, or has returned to baseline. Resume at 90 mg QD after recovery • When the current dose is 90 mg QD: Hold until event is grade ≤ 1, or has returned to baseline. Resume at 60 mg QD after recovery, or discontinue at the discretion of the Investigator
	• When the current dose is 60 mg QD: Consider discontinuing treatment at the discretion of investigator
[1]Per NCI CTCAE v4.0	

4.4.4 Hematologic Treatment-Related AEs during Brigatinib 180mg Daily

Grade[1]	Dose Modification
1 or 2	Continue at same dose

3	• When the current dose is 180 mg QD: hold until event is grade ≤ 2, or has returned to baseline. Resume at 180 mg or 120 mg QD at the discretion of the investigator • Upon recurrence at 180 mg QD: Hold until event is grade ≤ 2, or has returned to baseline. Resume at 120 mg QD • When the current dose is 120 mg QD: Hold until event is grade ≤ 2, or has returned to baseline. Resume at 90 mg QD • When the current dose is 90 mg QD: Hold until event is grade ≤1, or has returned to baseline. Resume at 60 mg QD after recovery, or discontinue at the discretion of the investigator • When the current dose is 60 mg QD: Consider discontinuing treatment
4	• When the current dose is 180 mg QD: Hold until event is grade ≤ 2, or has returned to baseline. Resume at 120 mg QD after recovery • When the current dose is 120 mg QD, hold until event is grade ≤ 2, or has returned to baseline. Resume at 90 mg QD after recovery • When the current dose is 90 mg QD: Hold until event is ≤Grade 1, or has returned to baseline. Resume at 60 mg QD after recovery, or discontinue at the discretion of the Investigator • When the current dose is 60 mg QD Consider discontinuing treatment
[1]Per NCI CTCAE v4.0	

4.4.5 Treatment-Related Pneumonitis during Brigatinib 90mg Daily 7 day lead-in

Grade[1]	Recommended Action
1	• Withhold the dose until pneumonitis returns to grade 0 (baseline), then resume at 90 mg and do not escalate. • If pneumonitis recurs, permanently discontinue treatment.
2	• Withhold dose until pneumonitis returns to grade 0, then resume at 60 mg and do not escalate. • If pneumonitis recurs, permanently discontinue treatment.
3 or 4	**Permanently discontinue treatment**
[1]Per NCI CTCAE v4.0	

4.4.6 Treatment-Related Pneumonitis during Brigatinib 180mg Daily

Grade[1]	Recommended Action
1	• Withhold the dose until pneumonitis returns to grade 0 (baseline), then resume at same dose. • If pneumonitis recurs, permanently discontinue treatment.
2	• Withhold dose until pneumonitis returns to grade 0, then resume at 120 mg QD. • If pneumonitis recurs, permanently discontinue treatment.
3 or 4	**Permanently discontinue treatment**
[1]Per NCI CTCAE v4.0	

4.5 Toxicities and dose modifications for cohort C

Patients on cohort C will have tolerated brigatinib 180 mg daily and experienced disease progression. Patients will receive 240 mg daily. Since the purpose of this cohort is to investigate doses of brigatinib at dose greater than 180 mg daily and patients have experienced disease progression on that dose, dose reduction to 180 mg daily will not be permitted. One cycle is 28 days.

Dose level	Brigatinib dose	Schedule
1	240 mg	Daily

Brigatinib Dose Modification Recommendations for patients with for pneumonitis for cohort C

Toxicity Grade per CTCAE v4.0	Recommended Action
Grade 1	Withhold the dose until pneumonitis returns to grade 0 (baseline), then resume at the same dose. If pneumonitis recurs, permanently discontinue treatment.
Grade 2	Withhold the dose until pneumonitis returns to Grade 0. Resume at 240 mg daily If pneumonitis recurs or remains grade ≥ 1, permanently discontinue treatment.
Grade 3	Permanently discontinue treatment.
Grade 4	Permanently discontinue treatment.
Abbreviations: CTCAE=Common Terminology Criteria for Adverse Events; QD=once daily	

Brigatinib Dose Modification Recommendations for TRAEs (Excluding Pneumonitis) for cohort C

Toxicity Grade per CTCAE v4.0	Recommended Action*
Hematologic Toxicity	
Grade 1 or Grade 2	Continue at current dose
Grade 3	First grade AE: Hold until event is ≤ grade 1, or has returned to baseline If grade 3 AE for < 7 days then resume therapy at 240 mg daily. If second grade 3 hematologic toxicity occurs then discontinue brigatinib If grade 3 AE for ≥ 7 days then discontinue study therapy
Grade 4	Discontinue study therapy
Nonhematologic Toxicity	
Grade 1 or Grade 2	Manage the toxicity with supportive care while continuing at the same dose
Grade 3	First grade AE: Hold until event is ≤ grade 1, or has returned to baseline If grade 3 AE for < 7 days then resume therapy at 240 mg daily. If second grade 3 non-hematologic toxicity occurs then discontinue brigatinib If grade 3 AE for ≥ 7 days then discontinue study therapy
Grade 4	Discontinue study therapy
Bradycardia (heart rate less than 60 bpm)	
Grade 1	Continue at current dose
Grade 2 or Grade 3	Withhold until recovery to ≤ grade 1 or to heart rate 60 bpm or above Evaluate concomitant medications known to cause bradycardia, as well as antihypertensive medications If contributing concomitant medication is identified and discontinued, or its dose is adjusted, resume at previous dose upon recover to ≤ grade 1 or to heart rate 60 bpm or above If no contributing concomitant medication is identified, or if contributing concomitant medications are not discontinued then discontinue study therapy
Grade 4	Discontinue treatment if no contributing concomitant medication is identified

Toxicity Grade per CTCAE v4.0	Recommended Action*
* Apply these recommendations after either dose escalation was accomplished, or after dose reduction for grade 3 or grade 4 toxicity was implemented resulting in no dose escalation. Abbreviations: bpm=beats/minute; CTCAE=Common Terminology Criteria for Adverse Events; QD=once daily	

4.6 Concomitant Medications/Juices/Herbal Supplements

Patients may receive standard supportive care at the discretion of investigator (i.e. anti-emetics, bisphosphonates, narcotics for pain control, etc.).

In vitro studies suggest that brigatinib, at the doses being evaluated clinically, is unlikely to inhibit CYPs 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4/5. Thus, drug interactions (DDIs) due to inhibition of CYPs by brigatinib are highly unlikely. However, other medications that inhibit CYPs may cause DDIs because of their impact on brigatinib's metabolism as outlined in section 1.3.9 and management is outlined in section 4.6.3.

4.7 Prohibited Palliative Radiotherapy

Patients who require palliative radiotherapy for symptomatic or asymptomatic metastases will be considered as experiencing disease progression as per Section 4.5 and will be followed up per protocol.

Patients on cohort A or B who receive local ablative therapies such as radiation to sites of oligo-and/or isolated CNS progression should be considered for cohort C.

4.8 Prohibited Systemic Therapy

Patients cannot receive systemic therapy (i.e. chemotherapy or targeted therapy) while on protocol therapy.

4.9 Prohibited Medications/Juices/Herbal Supplements

See section 1.3.9 for rationale of why use of concomitant medications that fall into the following categories are prohibited: medications/juices/herbal supplements that are strong or moderate inducers or strong inhibitors of CYP3A4. Please refer to Appendix C (see as auxiliary patient document).

4.10 Duration of Therapy

Patients should continue on protocol therapy until one of the following events:

- Disease progression
- Inter-current illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Pregnancy
- Patient decides to withdraw from study treatment, **OR**
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

4.11 Duration of Follow Up

Long-term follow up will occur every 3 months from the last administration of protocol-directed therapy for up to 2 years or until death, whichever occurs first. Subsequent therapy and survival status will be documented. NOTE: follow-up may occur via review of medical records, on-site visits are not required.

4.12 Removal of Patients from Protocol Therapy

Patients will be removed from protocol therapy and the PI notified when any of the criteria listed in section 4.5 apply. The reason for discontinuation of protocol therapy will be documented on the eCRF.

In case a patient decides to prematurely discontinue protocol therapy ("refuses Treatment or withdraws consent") the patient should be asked if she or he may still be contacted for further scheduled study assessments. The outcome of that discussion should be documented in both the medical records and in the eCRF. Excessive patient withdrawals from protocol therapy or from the study can render the study un-interpretable; therefore, unnecessary withdrawal of patients should be avoided.

4.13 Study Withdrawal

If a patient decides to withdraw from the study (and not just from protocol therapy) all efforts should be made to complete and report study assessments as thoroughly as possible. The investigator should contact the patient or a responsible relative by telephone or through a personal visit to establish as completely as possible the reason for the study withdrawal. A complete final evaluation at the time of the patient's study withdrawal should be made with an explanation of why the patient is withdrawing from the study. If the reason for removal of a patient from the study is an adverse event, the principal specific event will be recorded on the eCRF.

5.0 DRUG INFORMATION

5.1 Investigational Agent Description and Management

5.1.1 Description and Characteristics of Drug

Brigatinib is a novel, orally active, small molecule tyrosine kinase inhibitor (TKI). Brigatinib drug substance is isolated in crystalline form as a free base. Brigatinib has a melting point of 214°C (determined by differential scanning calorimetry [DSC]). The aqueous solubility of brigatinib is pH-dependent (e.g., at a pH of approximately 2.4, aqueous solubility is > 300 mg/mL, and at a pH of approximately 7.2, aqueous solubility is 11 mg/mL). Brigatinib does not contain any chiral centers.

5.1.2 Formulation

Brigatinib drug product is supplied as film-coated tablets, which contain brigatinib active pharmaceutical ingredient (please refer to pharmacy manual). All strengths are dose-weight proportional and manufactured with a common-blend including typical pharmaceutical excipients (lactose monohydrate,

microcrystalline cellulose, sodium starch glycolate, hydrophobic colloidal silica, magnesium stearate); tablet film-coating is comprised of typical pharmaceutical grade coating components (talc, polyethylene glycol, polyvinyl alcohol, titanium dioxide).

The drug product is manufactured under Current Good Manufacturing Practice (cGMP) in accordance with approved procedures.

5.1.3 Supplier, Storage and Stability

Brigatinib will be provided at no cost to the study patient by Takeda Pharmaceuticals Inc., the manufacturer of the drug. Takeda will ship the drug to the main study center. Brigatinib will be supplied in white high density polyethylene (HDPE) bottles with induction sealed caps. Bottle labels will bear the appropriate label text as required by governing regulatory agencies. At a minimum, such text will include product name, product strength, number of tablets, lot number, and use by dating. The recommended storage condition for brigatinib is under 30°C. It should not be refrigerated or frozen.

5.1.4 Handling and Disposal

Brigatinib should be handled using standard precautions for the safe handling of antineoplastic agents. Latex gloves are recommended. It must be dispensed only from official study sites by authorized personnel according to local regulations, and stored in a secure area according to local regulations. It is the responsibility of the investigator to ensure that study drug is only dispensed to eligible study patients.

The study pharmacist or designee at the site will be responsible for handling and dispensing study drug, and completing associated documentary paperwork. The site must use an appropriate dispensing log/accountability form.

5.1.5 Return and Retention of Study Drug

All used bottles or blister packs of study drug must be returned to Takeda or destroyed in an appropriate manner according to the standard practice at each study center. Destruction of such supplies will be documented. During the study and at termination, patients must return all unused study drug supplies to their study site and the return of these unused study drug supplies must be recorded. Returned supplies must not be re-dispensed.

5.1.6 Management of Adverse Events of Note

See section 6.1.2.1 of the Investigator's Brochure for additional information on the safety of brigatinib. The study sponsor will be responsible for distributing the IB to all sites when a new version is released from Takeda.

Pulmonary Symptoms

Pulmonary events occurring within the first week of brigatinib treatment, including, but not limited to, dyspnea, hypoxia, dry cough, chest tightness, and presumptive lung infection (pneumonia) that may be accompanied by chest x-ray or CT findings of linear or ground-glass opacities should be monitored and

reported. In some patients, the symptoms resolved without drug interruption, dose modification, or specific intervention. This suggests that the pathogenesis and natural history of this condition may differ from later-onset pneumonitis, rarely observed with brigatinib, but described with other TKIs. Pulmonary events have been observed after a single dose of brigatinib in patients. It is possible that patients with pre-existing pulmonary interstitial disease, including lymphangitic involvement by tumor, may be at increased risk. Nonetheless, investigators must be aware that these pneumonitis-like symptoms may present within 24 hours of initial dosing.

The management of these pulmonary events should include drug interruption, monitoring of oxygen saturation, and radiographic evaluation, and treatment with high-dose corticosteroids, supplemental oxygen therapy, and empiric antibiotics, as indicated.

The diagnosis of pneumonitis and determination of causal relationship to the drug is often confounded by the underlying disease (especially lymphangitic carcinomatosis) and other factors such as lung infection and radiation effect due to non-specific signs and symptoms as well as similar radiological appearance.

Pneumonitis should be suspected when such signs and symptoms develop or in asymptomatic patients when a new ground glass opacity or interstitial infiltration is noted in imaging studies. If a patient is considered to have the potential diagnosis of drug-related pneumonitis, physical examination, assessment of O_2 saturation, and evaluation for infectious etiologies, and thoracentesis, bronchoscopy, or open lung biopsy should be considered to reach a diagnosis

After dose interruption and symptom work-up, dose modification should be accomplished according to the recommendations in section 4.3.4 and 4.3.5 (treatment-related pneumonitis). If the symptoms include documented hypoxia and/or radiologic evidence of interstitial or ground glass changes, or result in an SAE, the early onset condition should be treated according to section 4.3.4 and 4.3.5 (treatment-related pneumonitis)

Hypertension

Brigatinib may result in elevations in BP (blood pressure, systolic or diastolic). During brigatinib treatment, BP should be regularly monitored and hypertension should be clinically managed. Brigatinib treatment might need to be temporarily interrupted if hypertension is not medically controlled.

Bradycardia

Treatment with brigatinib may result in bradycardia. An analysis of intensive ECG and PK data indicates a decrease in heart rate is associated with the timing of brigatinib maximum plasma concentrations (C_{max}). During brigatinib treatment, heart rate should be monitored at each physician visit; especially in patients who have a medical history of bradycardia.

6.0 EVALUATIONS AND ASSESSMENTS

6.1 Time and Events Table

Assessment	Screening 1	C1 D1[1,2]	C1 D8 [2]	C2 D1[1,2, 14]	C3 D1[1,2]	C4 D1[1,2, 14]	C5 D1 [1,2]	C6 D1[1,2]	C7 D1[1,2]	C8 D1[1,2, 14]	C9 D1[1,2]	C10 D1[1,2, 14]	C11 D1[1,2]	C12 D1[1,2]	EOT[3]	FU[4]
Informed consent[12]	X															
Medical History[5]	X														X	
Prior cancer therapy[13]	X															
Physical exam & vital signs[5, 14]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	
ECOG Performance Status	X	X		X	X	X	X	X	X	X	X	X	X	X	X	
CBC with differential[6]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Serum Chemistries[7]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Testosterone (males)	X				X		X		X		X		X			
ECG	X															
Serum pregnancy Test[8]	X															
CT scan chest/abdomen[2]	X				X[2]		X[2]		X[2]		X[2]		X[2]			
Brain MRI[2]	X				X[2]			X[2]			X[2]			X[2]		
Peripheral blood sample[9]		X[9]			X[9]		X[9]		X[9]		X[9]		X[9]		X[9]	
Tumor sample	X[10]														X[10]	
Adverse event assessment[5, 14]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Patient Diary		Provide[11]	Review	Review	Review	Review	Review	Review	Review	Review	Review	Review	Review	Review	Review	
Concomitant Meds	Review	Review	Review	Review	Review	Review	Review	Review	Review	Review	Review	Review	Review	Review	Review	
Subsequent Therapy and Survival Status																X
Brigatinib			See section 4.2 for brigatinib schedule and dose													

Key to Footnotes

[1] Within 28 days prior to Day 1 of brigatinib unless otherwise noted. If screening (baseline) hematology and serum chemistries were performed within 7 days of D1 of cycle 1, these do not need to be repeated.

[2] Unless otherwise noted, a window of 2 days will be applied to all study visits; for every other cycle tumor imaging starting with D1 of cycle 3, imaging may take place within 7 days prior to the study visit to accommodate holiday, weekends, and transportation issues. CT scan should be of the chest and abdomen. The pelvis should only be performed if there is evidence on metastatic disease in the pelvis.

Brain imaging MRI of the brain should be performed at baseline. In patients with known brain metastases MRI is performed every 3 cycles to assess for intracranial disease progression. Patients without brain metastases on screening MRI will undergo repeat brain imaging as clinically indicated or institutional standard (i.e. a specific interval is not mandated by the protocol). If patient cannot tolerate or has contraindication to brain MRI, a CT scan with and without contrast can be used.

[3] This visit should occur 30 days (+/- 3 days) after brigatinib treatment stops for whatever reason (adverse event, progression, or at discretion of the investigator). Patients who have an ongoing grade 4 AE or SAE at the time of discontinuation from treatment will be contacted every 2 weeks until the event is resolved, determined to be irreversible by the investigator, or until the patient begins an alternate form of treatment. For patients participating on cohorts A or B who are enrolled in cohort C this visit is omitted.

[4] Long-term follow up will occur every 3 months from the last administration of protocol-directed therapy for up to 2 years or until death, whichever occurs first. Subsequent therapy and survival status will be documented. NOTE: follow-up may occur via review of medical records, on-site visits are notrequired.

[5] Complete history at baseline only, thereafter focused history on symptoms/adverse event. Blood pressure and heart rate should be checked at each physician visit

[6] This includes CBC with differential and platelet count

[7] Serum chemistries include blood urea nitrogen (BUN), creatinine, bilirubin, ALT (SGPT), AST (SGOT), alkaline phosphatase, amylase, creatinine phosphokinase (CPK). Additional can be ordered if clinically indicated or at the discretion of the investigator but are not required by the protocol

[8] Within 7 days of D1 of treatment with brigatinib in women of child-bearing potential

[9] This blood sample will be used to explore whether resistance mutations can be detected in ctDNA; see laboratory manual for additional details. Sample is to be drawn on C1D1 and Day 1 of every odd cycle (3, 5, etc.) while patient is receiving treatment with brigatinib.

[10] **Biopsy after progression on previous ALK inhibitor and within 60 days prior to D1 of treatment is mandatory (i.e., if tissue available from pre-study biopsy, this**

tissue will be accessed for correlative studies, otherwise, patients must consent to tumor biopsy to meet eligibility criteria). All subjects must consent to provide tumor blocks or slides. Patients treated on cohorts A or B and enrolling in cohort C are required to undergo biopsy.

Biopsy specimens and peripheral blood samples will be destroyed as per standard institutional procedures at the time study termination or may be stored for future research. **Patients will be provided both options on the informed consent document.**

[11] On C1D1 provide the patient diary for use. D1 of all subsequent cycles patient diary is to be collected from previous cycle, reviewed with the patient, and a new diary provided.

[12] Patients in cohort A and B are brigatinib treatment naïve and receiving brigatinib at a standard dose. Patients in cohort C will have progressed on brigatinib and will be receiving a higher than the standard dose brigatinib. Depending on the institutional practice and policies this may require patients on cohort C to sign a "post-progression" treatment informed consent document.

[13] Prior systemic therapy will be collected including number of prior ALK TKI's and names, prior chemotherapy treatment. The sites of disease progression (CNS, extra-CNS or both) and if the patient received local therapy (e.g. radiation therapy, SBRT, etc.) to site of disease progression between disease progression and enrollment in study (i.e. disease progression in brain and lungs, brain metastases treated with SBRT and lungs metastases or primary not)

[14] Even day cycle visits not including Brain MRI imaging and are conducted (at treating physician's discretion) as telemedicine visits will not include standard clinic assessments (i.e., symptoms/adverse event, blood pressure and heart rate). To maintain data integrity, these missed assessments are to be noted in the EDC as deviations (planned) and indicate that visit was conducted remotely.

6.2 Pre-Study Assessments

The assessments required as part of screening can be completed in one or more visits, as long as the assessments are completed within the time frames listed in the Key to the Time and Events table.

Clinical evaluation: complete history, comprehensive physical examination (to include height and weight), vital signs, ECOG performance status

Laboratory studies:

- **Pregnancy Test**: Serum pregnancy test is required for all women of childbearing potential within 7 days prior to D1
- **Hematology**: CBC with differential
- **Serum Chemistries**: blood urea nitrogen (BUN), creatinine, bilirubin, ALT (SGPT), AST (SGOT), alkaline phosphatase, amylase, creatinine phosphokinase (CPK)
- **Serum Testosterone**: Limited to male patients

Cardiac studies: ECG

Tumor measurement: Tumor imaging should remain consistent throughout study, and should always include CT scans of chest and abdomen. CT scan of the pelvis should only be done if there is known metastatic disease to the pelvis. Brain MRI should be done, and if the patient cannot tolerate or has contraindication to MRI a CT scan with and without contrast should be done.

Concomitant medications: Documentation of all concomitant medications, and in particular any drugs that moderately or strongly inhibit or induce CYP3A4 and/or CYP2C8. **NOTE**: Patients will be instructed to bring their list of medications (all, including over the counter medications) to each study visit for review by their study team and for all visits to healthcare professionals (e.g., primary care physicians, consultants) while on study.

Patient diary: Patients will be provided a diary at baseline and instructed to document all doses of study medication (referenced herein as Appendix B, see as independent IRB/REB approved (patient) document).

Tissue acquisition: Tumor biopsy after progression on previous ALK inhibitor and within 60 days prior to study entry is mandatory i.e., if tissue available from pre-study biopsy, this tissue will be accessed for correlative studies, otherwise, patients must consent to tumor biopsy to meet eligibility criteria; see section 6.6 and laboratory manual for additional details. If patients have undergone NGS testing, as part of standard of care, on tumor sample after experiencing disease progression on prior therapy and prior to starting study therapy we will collect redacted report. If not performed/unavailable, sites will note not performed/not available in the database.

Prior cancer therapy: Prior systemic therapy will be collected including number of prior ALK TKI's and names, prior chemotherapy treatment. The sites of disease progression (CNS, extra-CNS or both) and if the patient received local therapy (e.g. radiation therapy, SBRT, etc.) to site of disease progression between disease progression and enrollment in study (i.e. disease progression in brain and lungs, brain metastases treated with SBRT and lungs metastases or primary not)

6.3 Treatment Assessments

6.3.1 D1 each Cycle

Tests and procedures in this Section 6.3.1 are to be conducted during each Day 1 cycle visit. Sections 6.3.3 and 6.3.4 include additional assessments to be conducted during each Day 1 at specific numbered cycle visit (e.g., odd cycles, each third cycle visit).

Clinical evaluation: focused medical history on symptoms/adverse events, comprehensive physical examination (to include weight), vital signs, ECOG performance status

Laboratory studies:

- **Hematology**: CBC with differential
- **Serum Chemistries**: blood urea nitrogen (BUN), creatinine, bilirubin, ALT (SGPT), AST (SGOT), alkaline phosphatase, amylase, creatinine phosphokinase (CPK).
- **Blood sample:** A blood sample for ctDNA will be requested (mandatory); see section 6.6 and the laboratory study for additional details. (Cycle 1 Day 1 & Day 1 of every odd cycle- 3, 5, etc.).

Patient diary: Collect, review with patient, and provide patient with new diary. (C1D1- provide patient with initial diary)

Concomitant medications: Review any additions or deletions.

AE: Adverse events will be assessed according to the NCI CTCAE v. 4.0.

6.3.2 D8 Cycle 1

Clinical evaluation: focused medical history on symptoms/adverse events,

Laboratory studies:

- **Hematology**: CBC with differential
- **Serum Chemistries**: blood urea nitrogen (BUN), creatinine, bilirubin, ALT (SGPT), AST (SGOT), alkaline phosphatase, amylase, creatinine phosphokinase (CPK)

Patient diary: Review

Concomitant medications: Review any additions or deletions.

AE: Adverse events will be assessed according to the NCI CTCAE v. 4.0.

6.3.3 D1 Cycle 3 and every odd numbered cycle thereafter (Cycle 3, 5, 7, etc.)

Tumor measurement: Tumor imaging should remain consistent throughout study, and should include CT scans of chest and abdomen. Pelvis should only be done if there is known metastatic disease in the pelvis.

Laboratory studies:

- **Serum Testosterone**: Male patients only

Blood sample: A blood sample for ctDNA will be requested (mandatory); see section 6.6 and the laboratory study for additional details.

6.3.4 D1 Cycle 3 and every third cycle thereafter (Cycle 3, 6, 9, etc.)

Brain metastases: Brain MRI or CT scan with or without contrast should be done every 3 cycles (3 months) for patients with known brain metastases to evaluated for CNS disease progression.

6.3.5 D1 Cycle 2 and each non-imaging even numbered cycle thereafter (Cycle 2, 4 or 8, etc.)

The safety profile of the Study Drug is well-known at this point of this research

study and many patients may be demonstrating stable tolerance of the Study Drug. For these patients, at the treating physician's discretion, even numbered cycle visits that do not include imaging procedures (i.e., CT scan, Brain MRI) may be conducted as telemedicine visits. When standard clinic assessments (i.e., symptoms/adverse event, blood pressure and heart rate) are not conducted, to maintain data integrity, these missed assessments are to be noted in the EDC as deviations (planned) and indicate that visit was conducted remotely.

6.4 EOT Visit

This visit should occur 30 days (+/- 3 days) after brigatinib treatment stops for whatever reason (adverse event, progression, or at discretion of the investigator). Patients who have an ongoing grade 4 AE or SAE at the time of discontinuation from treatment will be contacted every 2 weeks until the event is resolved, determined to be irreversible by the investigator, or until the patient begins an alternate form of treatment.

NOTE: The first EOT follow up visit is to be performed 30 days (+/- 3 days) after the date a participant receives the last dose of study drug. The date of the EOT visit will not match the date the last dose of study drug was administered and should be entered accordingly on the eCRF/EDC system.

Clinical evaluation: focused medical history on symptoms/adverse events, comprehensive physical examination (to include weight), vital signs, ECOG performance status.

Laboratory studies:

- **Hematology**: CBC with differential
- **Serum Chemistries**: blood urea nitrogen (BUN), creatinine, bilirubin, ALT (SGPT), AST (SGOT), alkaline phosphatase, amylase, creatinine phosphokinase (CPK)

AE: Adverse events will be assessed according to the NCI CTCAE v. 4.0. All SAEs (see section 7.0) ongoing 30 days or more after last dose of study drug is administered should be followed at least every 4 weeks until they resolve to baseline (or CTCAE grade $\leq$1), stabilize, or are considered to be chronic/irreversible regardless of causality. See also section 7 for documentation of AEs/SARs, when applicable, for patients remaining in the study after transition from cohort A or B to cohort C.

Concomitant medications: Review for any changes since previous visit.

Tissue acquisition: At time of progression on study therapy, biopsy will be repeated in patients who consent to this optional biopsy; see section 6.6 and laboratory manual for additional details.

Blood sample: A blood sample for ctDNA will be requested at time of progression on current therapy. Time of progression for cohort C means patient's further progression (as indicated by CT scan) from their entry into cohort C); see section 6.6 and the laboratory study for additional details.

Cohort C: For patients enrolling in cohort C from cohorts A or B end of treatment is not required; however:

- The EOT section of the eCRF form must still be completed;
- To avoid repeating assessments, EOT (cohort A or B) and screening (cohort C) assessments (including CT scans, brain MRIs, etc.), reasonable efforts should be taken to perform these assessments as standard of care at EOT to be used for cohort C screening assessments;
- Data relevant to each cohort's participation in the study will be independent according to their cohort assignment and recorded on each applicable eCRF for (i.e., EOT for cohort A or B, screening for cohort C).
- In the event of active AE's which continue past the subjects transition to cohort C, and continuing past the transition date, they are to be recorded under the new Subject number within the Medical History Log, to be updated upon change in AE. severity or status.

6.5 Post-Treatment/Follow-up Assessments

Long-term follow up will occur every 3 months from the last administration of protocol-directed therapy for up to 2 years or until death, whichever occurs first. Subsequent therapy and survival status will be documented.

Each cohort A, cohort B and cohort C participant's follow-up data will be captured from their time of enrollment in the cohort (for up to 2 years, or until death, whichever occurs first).

NOTE:

- The first post-treatment follow-up is to be performed 30 days (+/- 3 days) after the date a participant receives the last dose of study drug.
- The date of the EOT visit will not match the date the last dose of study drug was administered and should be entered accordingly on the eCRF/EDC system.
- Follow-up may occur via review of medical records, and on-site visits are not required. To maintain the every 3 month follow-up schedule, these methods should be used for long-term follow up of cohort A or B participants, when their participation and treatment in the study continues as a cohort C participant.

6.6 Correlative Studies Procedures

6.6.1 Tumor Biopsies

Tumor biopsy (core biopsy) after progression on previous ALK inhibitor and within 60 days prior to D1 of study treatment is mandatory i.e., if tissue available from pre-study biopsy, this tissue will be accessed for correlative studies, otherwise, patients must consent to tumor biopsy to meet eligibility criteria. All subjects must consent to provide tumor blocks or slides. If archival tissue is not available and biopsies to obtain fresh tumor tissue cannot be performed with minimal risk to the subject,

subjects may be permitted to enroll on the study with prior approval of the Study PI. Patients who undergo biopsies and subsequently found to have insufficient will be permitted to enroll on the study with prior approval of the study PI. Patients who have standard of care next-generation sequencing performed are able to enroll on the study, but must have sufficient tumor tissue to participate in the study (i.e. next generation sequencing cannot be substituted for providing tumor sample).

Core biopsies may be performed by clinical personnel trained in this procedure for standard of care collections. The number of passes made through the tumor per biopsy will be determined by the treating physician and the physician performing the biopsy procedure with primary consideration being safety. The tissue collected will be divided into aliquots (depending on size of collection, up to 4 aliquots per collection) to enable enough tissue for planned correlative studies. Additional details regarding processing, storing and handling tissue will be provided in a separate laboratory manual.

Biological samples collected for the study will be shipped to and stored in the research laboratories at the University of Colorado until the completion of the study. With patient consent, any remaining tumor tissue after protocol specific studies are complete will be stored for future research concerning lung cancer.

6.6.2 Blood Sample for ctDNA

Blood samples from enrolled patients will be evaluated via next generation sequencing for circulating tumor DNA (no germline studies will be performed). If possible, blood sample at progression should be performed while patient is still taking brigatinib; if drug is discontinued, the blood sample should be performed within 2 days of discontinuation.

6.6.3 Risks of Correlative Study Procedures-Biopsy

Liver (core needle biopsy):
Likely: local discomfort and minor bleeding
Less likely: moderate or major bleeding, need for blood transfusion, hospitalization due to bleeding or other complications, infection, bowel perforation or damage to adjacent organs

Lung (core needle biopsy in all patients):
Likely: local discomfort and minor bleeding
Less likely: pneumothorax, hemothorax, intraparenchymal hemorrhage, hemoptysis, bronchopleural fistula, air embolism, and vascular injury

In order to minimize the risk of a biopsy, only qualified personnel will perform these procedures. Prior to the procedure, the physician performing the procedure will discuss the risks with each study participant, answer any questions, and obtain separate procedure consent. For biopsies of lesions that are not superficial and clearly palpable, imaging studies such as CT scan will be used to guide the biopsy in order to minimize the risk of damage to adjacent structures. After liver biopsies, patients will be observed for approximately 4 hours (range 4-6 hours) after the procedure, or per institutional standard guidelines. Less than the goal quantity of tissue is acceptable for each type of biopsy, and will be left to the clinical judgment of the physician performing the procedure.

6.6.4 Risks of Correlative Study Procedures-Anesthesia

Local Anesthesia

All biopsy procedures require local anesthesia using lidocaine, xylocaine, or related compounds. There is a small risk of an allergic reaction associated with these drugs. In order to minimize the risk of local anesthesia, only qualified personnel will perform the biopsy procedure. Patients will be queried if they have had previous allergic reactions to local anesthetics.

Intravenous Conscious Sedation

Certain biopsy procedures may require IVCS. IVCS is a minimally depressed level of consciousness that retains the patient's ability to maintain a patent airway independently and continuously and respond appropriately to physical stimulation and verbal commands. The medications used to induce conscious sedation include the benzodiazepine midazolam and the opioid agonist fentanyl, as per standard of care. IVCS is performed once over a 30-60 minute period, and may require administration of multiple doses of each agent over this time-frame.

Rarely, IVCS will last longer than 60 minutes.

Midazolam:

See http://www.drugs.com/pro/midazolam-injection.html for complete prescribing information on midazolam, including complete information on risks associated with its use.

The risks of midazolam include respiratory depression and respiratory arrest, especially when used for sedation in non-critical settings. Respiratory arrest could require intubation. In very rare cases, when this was not recognized promptly and treated effectively, death or hypoxic encephalopathy has resulted. Other serious cardiorespiratory adverse events have occurred after administration of midazolam, including airway obstruction, oxygen desaturation, apnea, and cardiac arrest, rarely resulting in death or permanent neurologic injury. There have also been rare reports of hypotensive episodes requiring treatment, particularly in patients with hemodynamic instability. Agitation, involuntary movements, hyperactivity and combativeness have been reported in adults patients treated with midazolam.

Concomitant use of midazolam with other respiratory depressants like fentanyl may increase the risk of hypoventilation, airway obstruction, desaturation or apnea, and may contribute to profound and/or prolonged drug effect. Prolonged sedation may also be seen midazolam is administered concomitantly with drugs known to inhibit the P450 3A4 enzyme system such as cimetidine, erythromycin, diltiazem, verapamil, ketoconazole and itraconazole.

Adverse effects reported after intravenous administration of a single dose when used as a sedative include the following (percentage is percentage of adult patients with adverse events): hiccoughs (3.9%), nausea (2.8%), vomiting (2.6%), coughing (1.3%), "oversedation" (1.6%), headache (1.5%), and drowsiness (1.2%). In addition, the following local effects at the site of the injection have been reported: tenderness (5.6%), pain during injection (5.0%), redness (2.6%), induration (1.7%), and phlebitis (0.4%).

Additional rare (<1.0%) adverse events occurring when midazolam is used as a sedative include:

- Respiratory (laryngospasm, bronchospasm, dyspnea, hyperventilation, wheezing, shallow respirations, airway obstruction, tachypnea);
- Cardiovascular (bigeminy, premature ventricular contractions, vasovagal episode, bradycardia, tachycardia, nodal rhythm);
- Gastrointestinal (acid taste, excessive salivation, retching);
- CNS/Neuromuscular (retrograde amnesia, euphoria, hallucination, confusion, argumentativeness, nervousness, anxiety, grogginess, restlessness, emergence delirium or agitation, prolonged emergence from anesthesia, dreaming during emergence, sleep disturbance, insomnia, nightmares, athetoid movements, seizure-like activity, ataxia, dizziness, dysphoria, slurred speech, dysphonia, paresthesia);
- Special Senses (blurred vision, diplopia, nystagmus, pinpoint pupils, cyclic movements of eyelids, visual disturbance, difficulty focusing eyes, ears blocked, loss of balance, light-headedness);
- Integumentary (hive-like elevation at injection site, swelling or feeling of burning, warmth or coldness at injection site);
- Hypersensitivity (allergic reactions including anaphylactoid reactions, hives, rash, pruritus);
- Miscellaneous (yawning, lethargy, chills, weakness, toothache, faint feeling, hematoma).

Fentanyl

See http://www.drugs.com/pro/fentanyl-injection.html for complete prescribing information on fentanyl (Duragesic®), including complete information on risks associated with its use.

Fentanyl may cause muscle rigidity, particularly involving the muscles of respiration. Skeletal muscle movements in the extremities, neck and external eye have also been reported with fentanyl; rarely, these have been strong enough to pose patient management problems. Fentanyl may also produce euphoria, miosis, bradycardia and bronchoconstriction, as seen with other narcotic analgesics. The most common serious adverse reactions reported with fentanyl include respiratory depression, apnea, rigidity, and bradycardia. If these remain untreated, respiratory arrest, circulatory depression or cardiac arrest could occur. Other adverse reactions that have been reported are hypertension, hypotension, dizziness, blurred vision, nausea, emesis, laryngospasm and diaphoresis.

The risks of IVCS also include inhibition of the gag reflex and concomitant risk of aspiration and allergic reactions to the sedative or analgesic medications. The chances of serious risks from IVCS are small but real; for example, in a prospective study of 14,149 patients undergoing IVCS during upper gastrointestinal endoscopies, the rate of immediate cardiopulmonary events was 2 in 1000. The 30-day mortality was 1 per 2,000 cases. In this study, there was a strong association between lack of monitoring and use of high-dose benzodiazepines with adverse outcomes. There was also an association between the use of local anesthetic sprays to the oropharynx and the development of

pneumonia (Waring JP, B.T., Hirota WK, et al Gastrointestinal Endoscopy).

In order to minimize the risk of IVCS, only qualified personnel (M.D. and R.N) will be responsible for conscious sedation. A minimum of two individuals will be involved in the care of patients undergoing conscious sedation—the physician performing the biopsy procedure, and the individual (R.N.) who monitors the patients and his/her response to both the sedation and the procedure, and who is capable of assisting with any supportive or resuscitative measures. The room where the procedure utilizing IVCS takes place in the interventional radiology suite will have adequate equipment to provide supplemental oxygen, monitor vital signs, and maintain an airway should this be necessary. An emergency cart will also be immediately accessible to the room where the procedure is to take place, and emergency support services will be available on page. Patients will be screened and evaluated for their fitness to undergo conscious sedation by a trained physician. Patients with active cardiac disease are excluded from this study. No local anesthetic spray to the oropharynx will be necessary, given that endoscopy is not a planned procedure. Following the procedure, patients will be observed closely in the recovery room according to standard institutional guidelines.

6.6.5 Risks of Correlative Study Procedures-Blood Draws and IV Insertion

Risks of Blood Draws and I.V. Insertion

Blood draws may be associated with slight discomfort from the needle-stick, localized erythema, bleeding/bruising, or soreness around the area where the needle is inserted. Insertion of an intravenous catheter (I.V.) has similar risks, in addition to a small risk of infection at the site where the needle is inserted.

In order to minimize the risk of blood draws and I.V. insertion, only trained personnel will perform these procedures, according to standard institutional guidelines.

6.6.6 Risks of Study Procedures-Imaging Studies

Risks of Imaging Studies

CT scans will expose study participants to controlled amounts of radiation. The total dose of radiation from these tests is not anticipated to cause any adverse effects. There is also a risk of an allergic reaction to the intravenous contrast dye used during CT imaging, as well as a risk of experiencing feelings of anxiety or claustrophobia while undergoing a CT scan. There are no anticipated risks with the use of ultrasound.

In order to minimize these risks, patients will be queried, as per standard institutional practice, regarding their history of reactions to intravenous contrast dye. If a patient has had such a reaction, she/he will be premedicated, or dye will not be used, as per standard institutional practice. If a patient has previously experienced anxiety or claustrophobia while undergoing a CT scan, she/he will be encouraged to discuss this with her primary oncologist. Anxiolytics may be considered by the patient's primary oncologist as indicated.

6.7 Assessment of Safety

Any patient who receives treatment on this protocol should be evaluable for toxicity. The criteria used to assess safety (typically the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Please refer back to the Time and Events table for the schedule of AE assessment.

6.8 Assessment of Efficacy

Patients will be assessed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee, version 1.1for objective response and disease progression.[27] See section 8.3**.**

6.8.1 Assessment of Disease-Tumor Measurement Based on RECIST 1.1

See the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee, version 1.1 (Eur J Cancer 45;2009:228-247) for additional details on RECIST1.1.

Measurable disease will be defined as the presence of at least one measurable lesion that can be accurately measured in at least one dimension with the longest diameter a minimum size of:

- ≥10 mm by CT scan (CT scan slice thickness no greater than 5 mm)
- 10mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non- measurable).
- 20 mm by chest x-ray.
- >10 mm by MRI scan (MRI scan slice thickness no greater than 5 mm)

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

All other lesions, including small lesions (longest diameter <10mm or pathological lymph nodes with ≥10 to <15 mm short axis) as well as truly non- measurable lesions, will be considered non-measurable. Lesions considered truly non-measurable include: leptomeningeal disease; ascites; pleural/pericardial effusion; inflammatory breast disease; lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start 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 should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam. Clinical lesions will only be considered measurable when they are superficial and ≥10 mm diameter as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation

by color photography including a ruler to estimate the size of the lesions is recommended.

6.8.2 Baseline Documentation of Target and Non-Target Lesions

All measurable lesions up to a maximum of 5 lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline.

Target lesions should be selected on the basis of their size (lesions with the longer diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize the objective tumor response of the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as "present" or "absent", or in rare cases "unequivocal progression".

6.8.3 Evaluation of Target Lesions using RECIST 1.1 Criteria

NOTE: In addition to the information below, also see section 4.3.2 in the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee, version 1.1 for special notes on the assessment of target lesions.[25]

Complete response (CR) −Disappearance of all target lesions. Any pathological lymph node (LN) (whether target or non-target) must have decreased in short axis to <10mm.

Partial response (PR) −At least a 30% decrease in the sum of the LD of the target lesions taking as reference the baseline sum LD.

Progressive Disease (PD)−At least a 20% increase in the sum of the LD of the target lesions taking as reference the smallest sum LD recorded since the treatment started including baseline if that is the smallest on study. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5mm. The appearance of one or more new lesions also constitutes PD.

Stable disease (SD) −Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as references the smallest sum LD since the treatment started.

6.8.4 Evaluation of Non-Target Lesions using RECIST 1.1 Criteria

Complete response (CR)−Disappearance of all non-target lesions and normalization of tumor marker levels. All LN must be non-pathological in size (<10mm short axis).

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

Progressive disease (PD) −Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

6.8.5 Evaluation of Best Overall Response using RECIST 1.1 Criteria

The best overall response is the best response recorded from the start of the study treatment until the end of treatment provided the confirmation criteria are met. To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat studies that should be performed ≥ 4 weeks after the criteria for response are first met. If a CR/PR cannot be confirmed the original "response" should be considered stable disease. The best overall response will be defined according to the following table:

Overall Response First Time Point	Overall Response Subsequent Time Point	BEST Overall Response
CR	CR	CR
CR	PR	SD, PD, or PR[1]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE[2]	SD provided minimum criteria for SD duration met, otherwise, NE[2]
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE[2]	SD provided minimum criteria for SD duration met, otherwise, NE[2]
NE	NE[2]	NE[2]

[1] If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

[2] NE=inevaluable

7.0 ADVERSE EVENTS

7.1 *Intentionally blank.*

7.2 Definitions

7.2.1 Adverse Event (AE)

An adverse event (AE) is any untoward medical occurrence (e.g., an abnormal laboratory finding, symptom, or disease temporally associated with the use of a drug) in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including

an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

Hospitalization for elective surgery or routine clinical procedures that are not the result of an AE (e.g., surgical insertion of central line) need not be considered AEs and should not be recorded as an AE. Disease progression should not be recorded as an AE, unless it is attributable by the investigator to the study therapy.

7.2.2 Suspected Adverse Reaction (SAR)

A suspected adverse reaction (SAR) is any AE for which there is a *reasonable possibility* that the drug is the cause. *Reasonable possibility* means that there is evidence to suggest a causal relationship between the drug and the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

Causality assessment to a study drug is a medical judgment made in consideration of the following factors: temporal relationship of the AE to study drug exposure, known mechanism of action or side effect profile of study treatment, other recent or concomitant drug exposures, normal clinical course of the disease under investigation, and any other underlying or concurrent medical conditions. Other factors to consider in considering drug as the cause of the AE:

- Single occurrence of an uncommon event known to be strongly associated
- with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome)
- One or more occurrences of an event not commonly associated with drug exposure, but otherwise uncommon in the population (e.g., tendon
- rupture); often more than once occurrence from one or multiple studies would be needed before the sponsor could determine that there is
- *reasonable possibility* that the drug caused the event.
- An aggregate analysis of specific events observed in a clinical trial that indicates the events occur more frequently in the drug treatment group
- than in the concurrent or historical control group.

7.2.3 Unexpected AE or SAR

An AE or SAR is considered unexpected if the specificity or severity of it is not consistent with the applicable product information (e.g., Investigator's Brochure (IB) for an unapproved investigational product or package insert/summary of product characteristics for an approved product). Unexpected also refers to AEs or SARs that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

7.2.4 Serious AE or SAR

An AE or SAR is considered serious if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death;
- Is life-threatening (places the subject at immediate risk of death from
- the event as it occurred);
- Requires inpatient hospitalization (>24 hours) or prolongation of
- existing hospitalization;*
- Results in congenital anomaly/birth defect;
- Results in a persistent or significant incapacity or substantial
- disruption of the ability to conduct normal life functions;
- Important medical events that may not result in death, be life-
- threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical
- judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definition. For reporting purposes, also consider the occurrences of pregnancy as an event which must be reported as an important medical event.

* Hospitalization for anticipated or protocol specified procedures such as administration of chemotherapy, central line insertion, metastasis interventional therapy, resection of primary tumor, or elective surgery, will not be considered serious adverse events.

Pregnancy that occurs during the study must also be reported as an SAE.

7.3 Documentation of non-serious AEs or SARs

For non-serious AEs or SARs, documentation must begin from day 1 of study treatment and continue through the 30-day follow-up period after treatment is discontinued.

Collected information should be recorded in the Case Report Forms (CRF) for that patient. Please include a description of the event, its severity or adverse event grade, onset and resolved dates (if applicable), and the relationship to the study drug. Documentation should occur at least monthly.

For patients with two Subject Identification Numbers (SI#), resulting as participants in Cohort A or Cohort B, and then Cohort C (upon disease progression), each AE should be recorded as applicable to their cohort participation including the following:

- An original AE under their SI#1 should be completed (followed and recorded to resolution) under that cohort.
- AEs for Cohort C should be applicable to their participation under Cohort C:
    a. AEs from SI#1 should be recorded once resolved under SI# 1.
    b. AE history from the patient's SI#1 to be included as medical history for the patient under their SI# 2.
    c. Original AEs under SI#1 that increase in severity to be recorded as a new AE under the patient's SI#2 (as cohort C).

7.4 SAEs or Serious SARs

7.4.1 Timing

After informed consent but prior to initiation of study medications, only SAEs caused by a protocol-mandated intervention will be collected (e.g. SAEs related to invasive procedures such as biopsies, medication washout).

For any other experience or condition that meets the definition of an SAE or a serious SAR, recording of the event must begin from day 1 of study treatment and continue through the 30-day follow-up period after treatment is discontinued.

7.4.2 Documentation and Notification

All SAEs or Serious SARs must be recorded as an SAE within the study electronic data capture system and the printed SAE eCRF must be submitted to Criterium Project Manager & Duke Principal Investigator via email at ARIAT002SAE@criteriuminc.com within 24 hours of learning of its occurrence.

7.4.3 Reporting

Institutional Review Board (IRB) / Research Ethics Reporting (REB) Reporting Requirements:

Sites using a local IRB/REB of record, are required to submit adverse events per their local IRB/REB policy.

Reporting of Pregnancy

Pregnancy

It is not known what effects *brigatinib* has on human pregnancy or development of the embryo or fetus. Therefore, female patients participating in this study should avoid becoming pregnant, and male patients should avoid impregnating a female partner. Non-sterilized female patients of reproductive age group and male patients should use effective methods of contraception through defined periods during and after study treatment as specified below.

Female patients must meet 1 of the following:

- Postmenopausal for at least 1 year before the screening visit, or
- Surgically sterile, or
- If they are of childbearing potential, agree to practice 2 effective methods of contraception from the time of signing of the informed consent form through 4 months after the last dose of study drug, or agree to completely abstain from heterosexual intercourse.

Male patients, even if surgically sterilized (i.e., status post-vasectomy) must agree to 1 of the following:

- Practice effective barrier contraception during the entire study treatment period and through 4 months after the last dose of study drug, or

- completely abstain from heterosexual intercourse.

If a subject becomes pregnant during the study, or within 30 days of the subject's last dose of study drug, the investigator is to stop dosing with study drug immediately. A pregnancy is not considered to be an AE or SAE; however, it must be reported to Takeda at Toll-Free Fax #: 1-800-963-6290, E-mail: takedaoncocases@cognizant.com using the Pregnancy Report Form within the same timelines as an SAE. This applies to female subjects as well as female partners of male subjects. A pregnancy should be followed through to outcome, whenever possible. Once the outcome of the pregnancy is known, the Pregnancy Outcome Report Form should be completed and reported to the IND Office and Takeda.

It is not known whether brigatinib passes into the breast milk. Mothers should not breastfeed while receiving study drug.

In cases of pregnancy or suspected pregnancy, the patient is to be discontinued immediately (within 24 hours) from the study and the female subject should be referred to an obstetrician- gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.

In addition to reporting to Takeda, pregnancy, suspected pregnancy, positive pregnancy test and pregnancy outcome must be reported to the Criterium Project Manager & Duke Principal Investigator immediately via email:

ARIAT002SAE@criteriuminc.com

If the pregnancy results in spontaneous abortion or stillbirth, the event should be reported as an SAE. If there are any abnormal outcomes that meet the serious criteria, it must be reported as an SAE. Please follow the SAE reporting instructions in Section 7.3.2.

Pregnancy outcomes must be collected for the female partners of any males who took study drug in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the female partner.

Overdose

An overdose is defined as the accidental or intentional ingestion or infusing of any dose of study treatment that exceeds the dose described in the protocol. Overdoses are not considered AEs; however, all overdoses should be recorded on an Overdose Report Form and submitted to Criterium Project Manager and Duke Principal Investigator within 24 hours. An overdose should be reported even if it does not result in an AE. Overdoses do not need to be recorded on the eCRF; dosing information is recorded on the dose administration eCRF.

Email for submitting an Overdose Report Form to Criterium Project Manager and Duke PI: ARIAT002SAE@criteriuminc.com.

Takeda Reporting Requirements:

The sponsor or designee is responsible for emailing pregnancy and overdose reports to Takeda at takedaoncocases@cognizant.com as soon as they are aware.

FDA Expedited Reporting requirements for studies conducted under an IND:

If an investigator deems that an event is a Suspected Unexpected Serious Adverse Reaction (SUSAR), de-identified supporting documentation defining the event and causality within 24 hrs. of knowledge of the event should be emailed to the Criterium Project Manager and Duke Principal Investigator at:

ARIAT002SAE@criteriuminc.com.

Once the Duke Principal Investigator determines an event is a SUSAR, the MedWatch 3500A form will be created by Criterium Project Manager or designee and submitted to the FDA.

The **MedWatch 3500a** form can be accessed at:

http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/default.htm.

(Please be sure and access **form 3500a**, and not form 3500). ATOMIC, as the Sponsor of the study, will make the final determination regarding FDA submission).

Criterium Project Manager or designee is responsible for emailing expedited reports to Takeda Pharmaceuticals, Inc. at takedaoncocases@cognizant.com immediately but no later than 24 hours after the FDA submission.

Criterium Project Manager or designee will also be responsible for informing each site of all serious and unexpected SARs reported to the FDA via email as soon as possible.

Product Complaints or Medication Errors (Including Overdose)

A product complaint is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Individuals who identify a potential product complaint situation should immediately contact Takeda Pharmacovigilance or designee (see below) and report the event. Whenever possible, the associated product should be maintained in accordance with the label instructions pending further guidance from a Takeda Quality representative.

A medication error is a preventable event that involves an identifiable patient and that leadsto inappropriate medication use, which may result in patient harm. While overdoses and underdoses constitute medication errors, doses missed inadvertently by a patient do not. Investigators must record all medication errors (including overdose) on the appropriate CRF form. Individuals who identify a potential medication error situation should immediately contact Takeda (see below) and report the event.

For Product Complaints or Medication Errors (Including Overdose), contact Takeda Pharmacovigilance
Email: GlobalOncologyMedInfo@takeda.com
Fax: 1-800-881-6092, Hours Mon – Fri, 9 a.m. – 7 p.m. ET

Product complaints in and of themselves are not AEs. If a product complaint results in an SAE, an SAE form should be completed and sent to Takeda Pharmacovigilance

7.5 Data and Safety Monitoring Plan

The Principal Investigator will provide continuous monitoring of patient safety in this trial with annual reporting to the ATOMIC Data and Safety Monitoring Committee (DSMC).

Additional safety meetings/teleconferences will be held at a frequency dependent on study accrual, and in consultation with the study biostatistician. These meetings will include the investigators as well as protocol nurses, clinical research associates, regulatory associates, data managers, biostatisticians, and any other relevant personnel the principal investigators may deem appropriate. At these meetings, the research team will discuss all issues relevant to study progress, including enrollment, safety, regulatory, data collection, etc.

The team will produce summaries or minutes of these meetings. These summaries will be available for inspection when requested by any of the regulatory bodies charged with the safety of human subjects and the integrity of data.

The Data and Safety Monitoring Committee (DSMC) will be constituted by ATOMIC and will review the study on an annual basis. The Duke PI, with Criterium Project Manager's support, will be responsible for submitting the following information for review: 1) safety and accrual data including the number of patients treated; 2) significant developments reported in the literature that may affect the safety of participants or the ethics of the study; 3) preliminary response data; and 4) summaries of team meetings that have occurred since the last report. Findings of the DSMC review will be disseminated by memo to the participating sites.

8.0 STATISTICAL CONSIDERATIONS

8.1 Study Design/Study Endpoints

The statistical design for this protocol involves a single arm phase II trial to investigate the clinical activity of brigatinib in three patient populations (Cohorts A, B, and C). Each cohort will be assessed separately. A Simon two-stage design is used to determine the primary endpoint of objective response rate (ORR). (Eisenhauer et al. 2009) Secondary endpoints include duration of response, PFS, intracranial PFS, extracranial PFS, OS and safety. We will also explore for any association between presence and/or type of mutation at baseline and efficacy outcomes (ORR and PFS). Resistance mutations will also be identified using a tumor sample from progression as well as ctDNA from peripheral blood samples.

8.2 Sample Size and Accrual

With the number of sites being increased, the study is expected to complete accrual (40 patients in each of the 3 cohorts) in about 2 years from amendment approval. The primary endpoint is objective tumor response of brigatinib via RECIST1.1. A true response rate of 20% would be considered active and worthy of further investigation, and a response rate of 5% will be considered inactive and not worthy of further investigation.

A two-stage design will be used for this study. (Simon 1989) Twenty patients will be initially entered in Stage I of the study for each cohort, assuming all twenty are eligible. If there are at least 2 responses among the 20 eligible patients, an additional 20 patients will be entered into that cohort. If there are fewer than 2 responses among the first twenty patients in a cohort, then the cohort will be stopped early for futility. If at least 5 responses are observed among the 40 eligible patients in a cohort, then the treatment will be considered promising for that cohort population.

Table below gives the characteristics of this design as a function of the true response rate.

If the true response rate of a cohort is 20%, for example, then the probability of stopping that cohort early for futility is 7% and the overall probability of rejecting the treatment for that cohort after the second stage is 11%. This is comparable to a power of 89%. If the true response rate of a cohort is 10%, the probability of stopping that cohort early is 39% and the overall probability of rejecting the treatment for that cohort after the second stage is 67%.

		PROBABILTY OF RESPONSE				
	0.05	0.10	0.15	0.20	0.25	0.30
Probability of stopping early (<2 responses)	0.74	0.39	0.18	0.07	0.02	0.008
Probability >1 responses during stage 1 (and rejecting the treatment)	0.22	0.28	0.14	0.04	0.01	0.002
Overall probability of rejecting the treatment	0.96	0.67	0.32	0.11	0.03	0.009

8.3 Data Analysis Plans

All analyses for the three cohorts will be separated. A modified intent-to-treat approach will be followed in all data summaries using all available data in the analyses. Consequently, no special adjustments to the data are intended for dealing with missing values or patients who withdraw prior to completing study. Patients who sign informed consent for the study but who voluntarily withdraw prior to treatment or never initiate treatment due to the development of inter-current illness or death will not be included in the analysis. Patients who sign inform consent and

subsequently have a change in their functional status, laboratory values, or other eligibility criteria prior to initiating treatment, which makes them ineligible will not be included in the analysis. All patients who enroll and start study therapy will be included in the analysis.

Patients who are not able to get radiographic assessment due to decline in performance status, symptomatic progression, and any other reason will be considered non-responders and will be considered as having disease progression at the time they discontinue protocol therapy.

The primary endpoint is objective response rate (ORR); the secondary endpoints are duration of response, PFS, intracranial PFS, extra-cranial PFS, OS and the evaluation of the AE using NCI CTCAE version 4.0. For the primary analysis on ORR, the ORR and its 95% CI will be estimated using the statistical method taking into account the 2-stage design.[28] Mean and median of duration of response and their 95% CIs will be estimated. Time to event endpoints, including PFS and OS, will be summarized using the method of Kaplan and Meier. PFS is the time from Day 1 treatment to disease progression or death, whichever comes first. OS is the time from Day 1 treatment to death of all causes. Patients without relevant events at last follow up will be treated as censored. Median PFS and median OS will be provided as well as their 95%CI. The association of survival endpoints with baseline covariates will be evaluated using Cox regression models. Treatment-related adverse events will be summarized by type, grade, and attribution.

The association between presence and/or type of mutation or mechanism of resistance at baseline and efficacy outcomes will be explored using logistic regression (ORR) and Cox regression model (PFS). The frequency/rate of resistance mutations after brigatinib will be estimated using tumor samples collected at time of progression. The association between cfDNA from peripheral blood samples and resistance mutations will be evaluated using Wilcoxon rank sum test.

All demographic and analytic data will be summarized by descriptive statistics. Categorical data will be summarized using frequency tables while summary statistics such as means, medians, standard deviation, range, etc. will be provided for continuous data.

9.0 STUDY MANAGEMENT

9.1 Institutional Review Board (IRB) / Research Ethics Board (REB) Approval and Consent

It is expected that the IRB/REB will have the proper representation and function in accordance with federally mandated regulations. The IRB/REB should approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by applicable regulations (i.e., FDA, Health Canada, and local or state regulations). Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB/REB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

Patients in cohort C will have progressed on brigatinib and will be receiving a higher than the standard dose brigatinib. Depending on the institutional practice and policies this may require patients on cohort C to sign a "post- progression" treatment informed consent document.

9.2 Required Documentation

Before a site can be open to enrollment, the following documentation must be on file with Criterium, Inc.

- A copy of the official IRB/REB approval letter for the protocol and informed consent
- IRB/REB membership list
- IRB FWA documentation and GCP compliance statement, or REB equivalent, as applicable
- CVs and medical licensure for the principal investigator and any sub-investigators who are listed on the 1572.
- Current GCP certificates for site PI and all sub-investigators on the 1572
- Form FDA 1572 appropriately filled out and signed with appropriate Financial Disclosures for PI and all sub-investigators on the1572
- Laboratory certificates (e.g., CLIA (and CAP if applicable)) and associated lab normal values
- Executed clinical research contract
- Protocol signature page of IRB/REB approved protocol
- Investigator Brochure acknowledgement of receipt

9.3 Enrollment Procedures

All patients must be approved by the Duke Principal Investigator or designee before enrollment to study. Site is to email completed eligibility checklist, signed informed consents with all but first initial of first and last name of patient censored and all de-identified source documents used to confirm eligibility to:

ARIAT002PM@criteriuminc.com

Enrollment confirmations will be sent via email. Date of enrollment will be defined as the date of the confirmation e-mail in the EDC.

9.4 Data Management and Monitoring/Auditing

Data for each cohort (A, B and C) participant data will be captured from their time of enrollment in the cohort for up to 2 years, or until death, whichever occurs first.

Data will be collected through a web-based electronic data capture system. All study institutions will be given a password to directly enter their own data into the study electronic case report forms (eCRFs). Criterium, Inc. will coordinate and manage data for quality control assurance and integrity.

All data will be collected and entered by site research coordinators or other designees from participating institutions. The investigators at each site will be required to submit de-identified source documentation to Criterium, Inc for routine data monitoring upon request.

On site monitoring visits will be performed by ATOMIC representative according to the Monitoring Plan. During these visits, information recorded in the eCRFs will be verified against source documents. Data will be reviewed for safety information, legibility, completeness, and accuracy.

9.5 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

9.5.1 Emergency Modifications

Investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior Duke Principal Investigator or their respective institution's IRB/IEC/REB approval/favorable opinion.

For investigators relying on their own institution's IRB/REB, as soon as possible after the modification has been made, the implemented deviation or change and the reasons for it should be submitted to:

- To Duke Principal Investigator for agreement
- The institution's IRB/REB for review and approval. (Once IRB/REB's response is received, this should be forwarded to the Criterium Project Manager).

9.5.2 Other Protocol Deviations/Violations

A protocol deviation is any unplanned variance from an IRB/REB approved protocol that:

- Is generally noted or recognized after it occurs
- Has no substantive effect on the risks to research participants
- Has no substantive effect on the scientific integrity of the research plan or the value of the data collected
- Did not result from willful or knowing misconduct on the part of the investigator(s).

An unplanned protocol variance is considered a violation if the variance meets any of the following criteria:

- Has harmed or increased the risk of harm to one or more research participants.
- Has damaged the scientific integrity of the data collected for the study.
- Results from willful or knowing misconduct on the part of the investigator(s).
- Demonstrates serious or continuing noncompliance with federal regulations, State laws, or University policies.

If a deviation or violation occurs, please follow the guidelines below:

For Institutions Relying on Their Own IRB/REB:
In addition to adhering to the policies regarding protocol compliance set forth by your institution's IRB/REB, the following is also required:

Protocol Deviations: In the event a deviation from protocol procedures is identified, record the deviation in the electronic data capture system.

The protocol was amended in 2020 adding the ability, in limited situations and at treating physician's discretion, for some Day 1 even cycles to be conducted as telemedicine visits. Some standard in clinic assessments (i.e., symptoms/adverse event, blood pressure and heart rate) will not be conducted with these remote visits. To maintain data integrity, these missed assessments are to be noted in the EDC as protocol deviations (planned) and indicate the visit was conducted remotely. For purposes of regulatory reporting, these are not considered Protocol Deviations and will not require reporting to your IRB/REB, or the Duke Principal Investigator or designee to determine safety.

Protocol Violations: Any protocol violation that occurs must be reported to your IRB/REB per institutional policies and reported to the Criterium Project Manager within 5 days.

Duke Principal Investigator or designee will determine if the violation affects the safety of the patient and integrity of the data. Once your institution's IRB/REB response is received, please forward to the Criterium Project Manager within 5 business days of receipt via email.

9.5.3 Termination rules

The Duke principal investigator and the study sponsor have the right to terminate this clinical study at any time. The Duke principal investigator and study sponsor, as appropriate, will be involved in any decisions regarding terminating the study, temporarily suspending enrollment, or stopping ongoing treatment with study treatment.

Reasons for terminating the clinical study or a study site's participation include, but are not limited to, the following:

- The incidence or severity of an adverse reaction related to treatment in this study or other studies indicates a potential health hazard to patients
- Patient enrollment is unsatisfactory
- Data recording is significantly inaccurate or incomplete
- Study site personnel are noncompliant with study procedures
- Pattern of noncompliance is observed

9.6 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator at Duke. It should also be noted that when an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

The written amendment, and if required the amended consent form, must be sent to your site IRB/REB for approval prior to implementation.

All sites must submit their informed consent revisions to the Criterium Project Manager or designee for review and approval prior to submission to their IRB/REB.

9.7 Record Retention

Study documentation includes all eCRFs, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB/REB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that all study documentation pertaining to the conduct of a clinical trial must be retained by the study investigator. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In Canada the Principal Investigator will retain the study records in a secure and confidential location for 25 years as required by Canadian law. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

9.8 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered into the eCRFs. Periodically, data monitoring will be conducted and the Principal Investigator or designee must provide de-identified source upon request to permit remote verification of proper entry of data. At the completion of the study, all eCRFs will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

10.0 APPENDICES

Appendix A: ECOG Performance Status

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

Appendix B: Model Patient Diary for Brigatinib (see as auxiliary patient document)

Appendix C: Prohibited Drugs, Juices and Herbal Supplements, and Medications to be used with Caution (see as auxiliary patient document)

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