Clinical Trial Protocol

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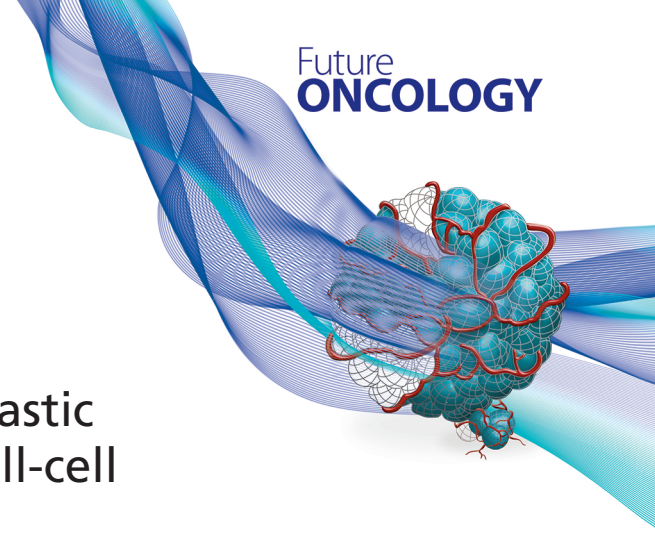

Brigatinib versus alectinib in crizotinib-resistant advanced anaplastic lymphoma kinase-positive non-small-cell lung cancer (ALTA-3)

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Crizotinib is highly efficacious and more tolerable than chemotherapy for ALK$^+$ non-small-cell lung cancer (NSCLC), but its progression-free survival benefit and intracranial efficacy have limitations. Head-to-head comparisons of next-generation ALK inhibitors in patients with ALK$^+$ NSCLC progressing on crizotinib will contribute toward optimizing survival. This international, Phase III, randomized, open-label study (ALTA-3) will therefore assign patients with locally advanced or metastatic ALK$^+$ NSCLC progressing on crizotinib to receive either brigatinib 180 mg qd (7-day lead-in at 90 mg qd) or alectinib 600 mg twice daily. The primary end point is progression-free survival as assessed by a blinded Independent Review Committee; the key secondary end point is overall survival.

Clinical trial registration number: NCT03596866 (ClinicalTrials.gov)

Lay abstract: Tyrosine kinase inhibitor medications like crizotinib may work as a first treatment for people with non-small-cell lung cancer (NSCLC) that has spread to other parts of the body and has the ALK$^+$ mutation (ALK$^+$ NSCLC) in tumor testing. However, many people stop responding to treatment with crizotinib. Brigatinib and alectinib are tyrosine kinase inhibitor medications that may be effective in people with ALK$^+$ NSCLC who have stopped responding to crizotinib treatment. We describe the need for and design of a study comparing brigatinib with alectinib in people with ALK$^+$ NSCLC whose disease worsened on crizotinib.

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Keywords: alectinib • anaplastic lymphoma kinase • brigatinib • disease progression • drug resistance • non-small-cell lung cancer • non-small-cell lung carcinoma • randomized controlled trial • tyrosine kinase inhibitor

Non-small-cell lung cancer (NSCLC) is the most prevalent histologic subtype of lung cancer, accounting for an estimated 84% of lung cancer cases [1]. Approximately 3–5% [2–4] of NSCLC cases are caused by rearrangements in the *ALK* gene. Inhibition of ALK is the preferred treatment approach for ALK-rearranged (ALK$^+$) NSCLC [5]. Crizotinib was the first ALK–tyrosine kinase inhibitor (TKI) approved by the US FDA. The CNS is often the first site of disease progression in patients treated with crizotinib [6,7], suggesting that inadequate drug penetration into the brain is a primary cause of crizotinib resistance [6–8]. Other mechanisms of resistance can be classified as either ALK directed or non-ALK directed, with the latter including upregulation of bypass signaling pathways [9]. ALK-directed mechanisms include the acquisition of ALK secondary mutations that interfere with crizotinib binding, amplification of the *ALK* fusion gene and loss of the ALK fusion gene target [4,9,10]. Secondary resis-

tance mutations have been detected in approximately 20% of patients with ALK$^+$ NSCLC who progressed on crizotinib [4,9]. The most common secondary mutations in ALK that have been linked to crizotinib resistance in patients are L1196M and G1269A [4,9,10]. Four next-generation ALK inhibitors have now demonstrated marked first-line superiority over crizotinib, fundamentally driven by better intracranial control [11–15]. Nevertheless, in patients without CNS metastases at baseline, crizotinib may represent a viable first-line treatment option, allowing sequencing of ALK inhibitors, particularly in healthcare economies where access to first-line next-generation ALK inhibitors is challenging. Moreover, many patients continue on first-line crizotinib having commenced it prior to first-line next-generation ALK inhibitor availability. The optimal ALK inhibitor to use on crizotinib progression is therefore still a valid question.

Introduction to the ALTA-3 trial

Here, we describe the rationale and design for the ALK in Lung Cancer Trial of AP26113 (ALTA)-3 study (NCT03596866; EudraCT 2018-001957-29), a Phase III, randomized, open-label, comparative, multicenter, international study designed to compare brigatinib versus alectinib treatment in patients with ALK$^+$ locally advanced or metastatic NSCLC whose disease has progressed on therapy with crizotinib. The study is sponsored by ARIAD Pharmaceuticals, Inc., Cambridge, MA, USA, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited.

Background & rationale

Since the approval of crizotinib, several ALK TKIs (i.e., alectinib, ceritinib, brigatinib, lorlatinib and ensartinib) have been developed that have better brain penetration and/or more potent inhibition of ALK with on-target acquired resistance mutations [16–21]. Alectinib was one of the first ALK TKIs to demonstrate efficacy and acceptable safety in patients with ALK$^+$ NSCLC progressing on crizotinib [22,23]. However, given a median progression-free survival (PFS) of 8–9 months with alectinib [22,23], by the time of alectinib-acquired resistance, secondary ALK kinase domain resistance mutations are detected in approximately 50% of patients, most commonly I1171N and G1202R [9,24].

Brigatinib was designed to have potent activity against a broad array of *ALK* mutants [19,25]. The inhibitory profile of brigatinib was superior to that observed with crizotinib, ceritinib and alectinib when *in vitro* potencies were related to steady-state plasma levels achieved in patients for each drug at its approved dose (Figure 1) [19,26]. Based on the results of a Phase II trial (ALTA; NCT02094573) randomizing between 2 dosing schedules [27], brigatinib was granted accelerated approval in the United States in 2017 and approval in Canada and the EU in 2018 for the treatment of patients with ALK$^+$ NSCLC who have progressed on or are intolerant to crizotinib. In the ALTA trial, brigatinib demonstrated high systemic and CNS objective response rates (ORRs) with an acceptable safety profile in patients progressing on crizotinib [12,27,28]. A median independent review committee (IRC) assessed PFS with the subsequently approved brigatinib dosing regimen of 180 mg qd (with 7-day lead-in at 90 mg) was 16.7 months [28], which is the longest observed with any ALK inhibitor in the post-crizotinib setting (alectinib median PFS, 8–9 months [22,23], ceritinib median PFS, 5–7 months [17,29–31] and lorlatinib median PFS, 11.1 months) [32]. A subsequent Phase III trial (ALTA-1L; NCT02737501) in patients with ALK TKI-naive ALK$^+$ NSCLC identified marked improvement in efficacy with brigatinib over crizotinib (median PFS, 24.0 vs 11.0 months; hazard ratio [HR], 0.49; $p < 0.0001$) [13].

There remain a significant number of patients globally who cannot access next-generation ALK inhibitors as first-line therapy [33,34]. For these patients, commencing crizotinib is a viable alternative, particularly for those without CNS metastases at baseline, where immediate intracranial control is less concerning. Moreover, there are significant numbers of long-term survivors globally who continue to derive benefit from first-line crizotinib, or who commenced crizotinib prior to availability of next-generation ALK inhibitors, who have yet to progress. There is, however, a need for a head-to-head comparison of the newer ALK inhibitors in patients with crizotinib-refractory ALK$^+$ NSCLC. In ALTA-3, alectinib was chosen as the comparator because at the time ALTA-3 was initiated it was more widely used than ceritinib for crizotinib-refractory ALK$^+$ NSCLC and data on lorlatinib efficacy post crizotinib were sparse.

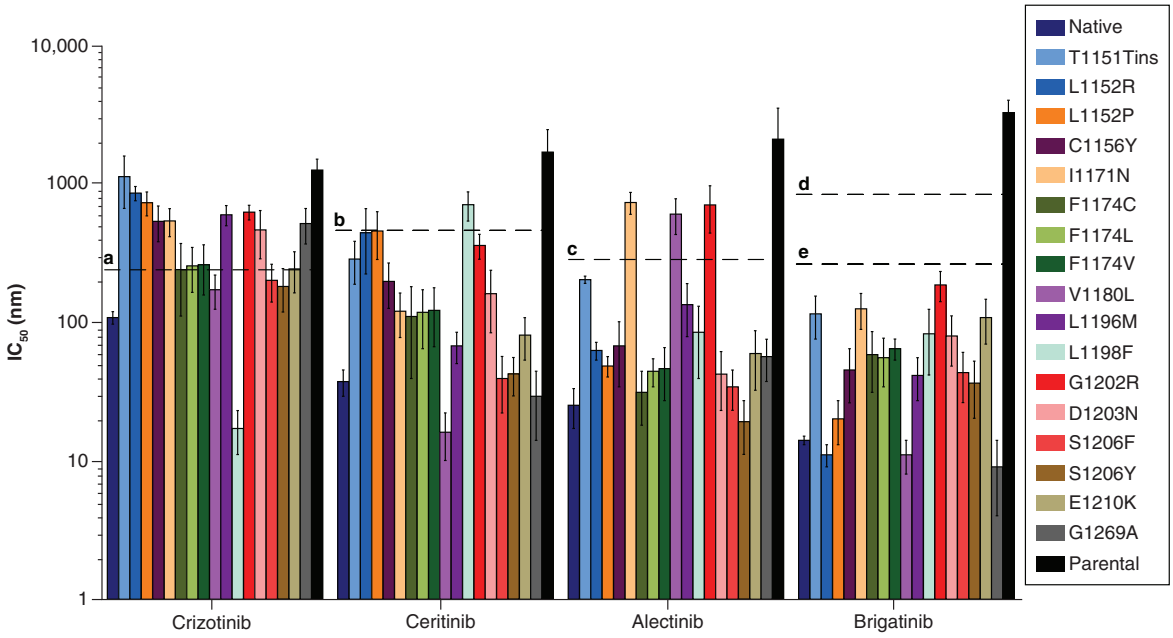

Figure 1. ALK inhibitory profile of brigatinib, alectinib, ceritinib and crizotinib in cellular models [19,26]. IC_{50} values of Ba/F3 cells harboring native EML4-ALK or 17 mutant variants, and in ALK- (parental) cells. Data for each cell line are derived from at least four independent experiments (error bars = standard deviation). Dashed horizontal lines indicate 'clinically effective' plasma concentration, defined as the mean steady-state exposure concentrations of each drug corrected for the functional effects of protein binding at the recommended Phase II doses (see footnotes a–e).
[a]Crizotinib: 250 mg twice daily, 266 nM.
[b]Ceritinib: 750 mg qd, 456 nM.
[c]Alectinib: 600 mg twice daily, 277 nM.
[d]Brigatinib: 180 mg qd, 899 nM.
[e]Brigatinib: 90 mg qd, 264 nM.

Design

Study design

ALTA-3 is a Phase III, randomized, open-label, comparative, multicenter, international study. Eligible patients will be randomized in a 1:1 ratio to receive brigatinib or alectinib.

Objectives

The primary objective of the ALTA-3 trial is to compare the efficacy of brigatinib with that of alectinib in patients with locally advanced or metastatic ALK^+ NSCLC that has progressed on crizotinib on the basis of PFS assessment using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 by blinded independent review. Secondary objectives are: to compare the efficacy of brigatinib with that of alectinib as evidenced by overall survival (OS), PFS as assessed by the investigator, ORR, duration of response (DoR), and time to response (all as assessed by RECIST v1.1); to compare the efficacy of brigatinib in the CNS with that of alectinib, as evidenced by intracranial ORR, intracranial DoR, and time to intracranial progressive disease (PD) as assessed by modified RECIST criteria; to assess the safety and tolerability of brigatinib in comparison with alectinib; to collect plasma concentration-time data for brigatinib to contribute to population pharmacokinetic (PK) analyses; and to assess patient-reported symptoms and health-related quality of life (HRQoL) with the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) (v3.0) and its Quality of Life Lung Cancer Module (QLQ-LC13) in patients treated with brigatinib compared with those treated with alectinib. Exploratory objectives include comparing the efficacy in the CNS of brigatinib with that of alectinib as evidenced by intracranial ORR, intracranial DoR, and time to intracranial PD (iPD), per the Response Assessment in Neuro-Oncology Brain Metastases criteria; exploring the molecular determinants of efficacy and safety with brigatinib and alectinib; evaluating health resource utilization; and using patient-reported outcome measures to assess morbidity related to CNS symptoms.

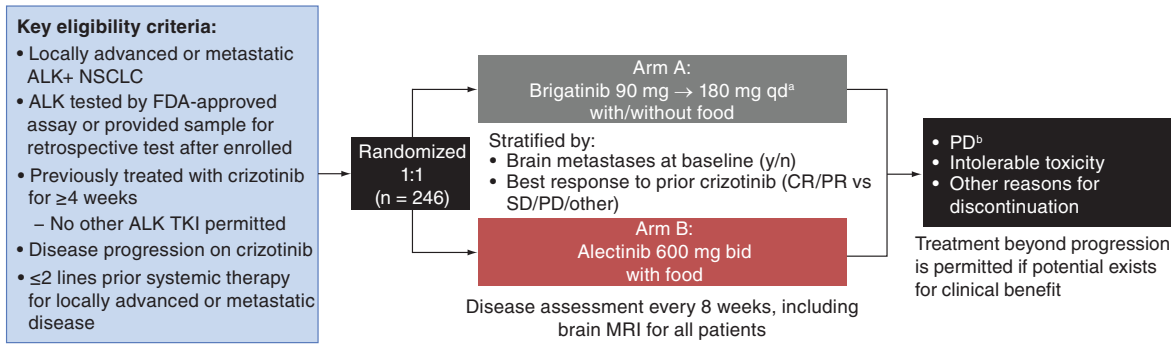

Figure 2. ALTA-3 trial design. Phase III trial comparing brigatinib and alectinib in patients with advanced ALK$^+$ NSCLC that progressed on crizotinib. An ALK$^+$ test result by central laboratory is not required before enrollment. Re-biopsy is strongly encouraged (but not mandated) at screening and progression. Plasma samples for exploratory biomarker analyses will be collected at screening, on Day 1 of Cycle 3 (28 days per cycle), and at progression. [a]180 mg qd with 7-day lead-in at 90 mg. [b]Based on investigator assessment.
CR: Complete response; NSCLC: Non-small-cell lung cancer; PD: Progressive disease; PR: Partial response; qd: Once daily; SD: Stable disease; TKI: Tyrosine kinase inhibitor.

Dosing

Brigatinib will be given at 180 mg qd with a 7-day lead-in at 90 mg qd (arm A) or alectinib 600 mg twice daily (arm B) at their approved dose schedules (Figure 2). Brigatinib is taken as a single tablet with or without food. Alectinib is taken as four tablets twice daily with food. Randomization will be stratified by the presence of intracranial brain metastases at baseline (yes vs no) and best prior response to crizotinib therapy as assessed by the investigator (complete response [CR] or partial response [PR] vs other response status or unknown).

Patients will receive study treatment until they experience PD as assessed by local investigator or intolerable toxicity or when another discontinuation criterion (e.g., significant protocol deviation, study termination by sponsor, patient withdrawal, patient lost to follow-up, pregnancy) is met. Study treatment may be continued after disease progression if there is ongoing clinical benefit.

Eligibility criteria

Complete eligibility criteria are listed in Table 1. Adult patients (aged 18 years or older) with locally advanced or metastatic ALK$^+$ NSCLC are eligible for enrollment if they had disease progression while on crizotinib and had received crizotinib treatment for at least 4 weeks before disease progression. Patients must have documentation of *ALK* rearrangement by positive result from the Vysis ALK Break Apart FISH Probe Kit, the Ventana ALK (D5F3) CDx Assay or Foundation Medicine's FoundationOne CDx. Patients who have documented *ALK* rearrangement by a different test must be able to provide a tumor sample to the central laboratory. Central laboratory *ALK* rearrangement testing results are not required to be obtained before randomization. Patients must have at least 1 measurable lesion per RECIST v1.1.

Patients previously treated with any ALK inhibitor other than crizotinib or with more than 2 lines of prior systemic therapy (other than crizotinib) for advanced/metastatic disease are not eligible for enrollment. Patients with symptomatic CNS metastases (parenchymal or leptomeningeal) at screening are also excluded; however, patients with asymptomatic brain metastases or those who have stable symptoms and did not require an increased dose of corticosteroids to control symptoms within 7 days before randomization will be enrolled. If a patient has worsening neurological symptoms or signs due to CNS metastasis, the patient must complete local therapy and be neurologically stable (with no requirement for an increasing dose of corticosteroids or use of anticonvulsants) for at least 7 days before randomization. Patients who have current spinal cord compression (symptomatic or asymptomatic and detected by radiographic imaging) are not eligible, but patients with leptomeningeal disease and without cord compression are allowed to participate.

Planned sample size

Approximately 246 patients will be enrolled at 100 to 120 sites globally (Figure 3).

Table 1. Eligibility criteria for ALTA-3.

Inclusion criteria	Exclusion criteria
• Male or female, aged 18 years or older or of local legal adult age • ECOG performance status of 0 to 2 • Histologically or cytologically confirmed stage IIIB (locally advanced or recurrent) or stage IV NSCLC • Must meet one of the following criteria: – Documentation of *ALK* rearrangement by a positive result from the Vysis ALK Break-Apart FISH Probe Kit or the Ventana ALK (D5F3) CDx Assay or Foundation Medicine's FoundationOne CDx – Documented *ALK* rearrangement by a different test and able to provide a tumor sample to the central laboratory. Note: Central laboratory *ALK* rearrangement testing results are not required to be obtained before randomization • PD while on crizotinib, as assessed by the investigator or treating physician[†] • Treatment with crizotinib for at least 4 weeks before progression • No other ALK inhibitor other than crizotinib • No more than two prior regimens of systemic anticancer therapy (other than crizotinib) in the locally advanced or metastatic setting[‡] • At least one measurable (i.e., target) lesion per RECIST v1.1 • Recovered from toxicities related to prior anticancer therapy to the National Cancer Institute Common Terminology Criteria for Adverse Events v4.03 grade ≤ 1[§] • Adequate organ function, as determined by: – Total bilirubin $\leq$1.5-times ULN – eGFR $\geq$30 ml/minute/1.73 m^2, using the modification of diet in renal disease equation – ALT/AST $\leq 2.5 \times$ ULN; $\leq 5 \times$ ULN is acceptable if liver metastases are present – Serum lipase $\leq 1.5 \times$ ULN – Platelet count $\geq 75 \times 10^9$/l – Hemoglobin $\geq$9 g/dl – Absolute neutrophil count $\geq 1.5 \times 10^9$/l • Suitable venous access for study-required blood sampling (i.e., including PK and laboratory safety tests) • Willingness and ability to comply with scheduled visits and study procedures • Female patients of childbearing potential must have a negative pregnancy test documented before randomization • Female patients of childbearing potential and male patients with partners of childbearing potential must agree to use a highly effective nonhormonal form of contraception with their sexual partners during the dosing period and for a period of at least 120 days after the end of treatment with either brigatinib or alectinib • Male patients, even if surgically sterilized (i.e., status postvasectomy), who: (a) Agree to practice effective barrier contraception during the entire study treatment period and through 120 days (or if the drug has a very long half-life, for 90 days plus 5 half-lives) after the last dose of study drug, or (b) Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject (periodic abstinence [e.g., calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together), (c) Do not donate semen or sperm during treatment and for 90 days after the last dose of study therapy • Voluntary written consent must be given before performance of any study-related procedure not part of standard medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care **Note:** Given that, globally, the patient population that has received crizotinib as the sole ALK inhibitor is decreasing, the sponsor reserves the right to amend the inclusion criteria to include crizotinib-intolerant patients and/or patients who have progressed on or been found intolerant to ALK inhibitors other than crizotinib, brigatinib or alectinib	• Participation in the control (crizotinib) arm of ALTA-1L (NCT02737501) • Received crizotinib within 7 days before randomization • History or presence at baseline of pulmonary interstitial disease, drug-related pneumonitis or radiation pneumonitis • Uncontrolled hypertension. Patients with hypertension should be under treatment for control of blood pressure upon study entry • Systemic treatment with strong cytochrome P-450 (CYP) 3A inhibitors, moderate CYP3A inhibitors, strong CYP3A inducers or moderate CYP3A inducers within 14 days before randomization • Treatment with any investigational systemic anticancer agents within 14 days or 5 half-lives, whichever is longer, before randomization • Have been diagnosed with another primary malignancy other than NSCLC, except for adequately treated nonmelanoma skin cancer or cervical cancer *in situ*; definitively treated nonmetastatic prostate cancer; or patients with another primary malignancy who are definitively relapse-free with at least 3 years elapsed since the diagnosis of the other primary malignancy • Chemotherapy or radiation therapy within 14 days before randomization, except for stereotactic radiosurgery or stereotactic body radiation therapy • Antineoplastic monoclonal antibodies within 30 days of randomization • Major surgery within 30 days of randomization. Minor surgical procedures, such as catheter placement or minimally invasive biopsies, are allowed • Symptomatic brain metastases (parenchymal or leptomeningeal) at screening (patients with asymptomatic brain metastases or who have stable symptoms that did not require an increased dose of corticosteroids to control symptoms in the 7 days before randomization will be enrolled)[¶] • Current spinal cord compression (symptomatic or asymptomatic and detected by radiographic imaging). Patients with leptomeningeal disease and without cord compression are allowed • Significant, uncontrolled or active cardiovascular disease, specifically including, but not restricted to the following: – Myocardial infarction within 6 months before randomization – Unstable angina within 6 months before randomization – New York Heart Association Class III or IV heart failure within 6 months before randomization – History of clinically significant atrial arrhythmia (including clinically significant bradyarrhythmia), as determined by the treating physician – Any history of clinically significant ventricular arrhythmia • Cerebrovascular accident or transient ischemic attack within 6 months before first dose of study drug • Malabsorption syndrome or other gastrointestinal illness or condition that could affect oral absorption of the study drug • Ongoing or active infection, including but not limited to, the requirement for intravenous antibiotics • Known history of HIV infection. Testing is not required in the absence of history • Known hepatitis B surface antigen-positive, or known or suspected active hepatitis C infection; testing is not required in the absence of history • Any serious medical condition or psychiatric illness that could, in the investigator's opinion, potentially compromise patient safety or interfere with the completion of treatment according to the protocol • Known or suspected hypersensitivity to brigatinib or alectinib or their excipients • Life-threatening illness unrelated to cancer • Female patients who are lactating and breastfeeding • Admission or evidence of illicit drug use, drug abuse or alcohol abuse

[†]Crizotinib does not need to be the last therapy a patient received. The patient may have received chemotherapy as his/her last systemic anticancer therapy.
[‡]A systemic anticancer therapy regimen will be counted if it is administered for at least 1 complete cycle. A new anticancer agent used as maintenance therapy will be counted as a new regimen. Neoadjuvant or adjuvant systemic anticancer therapy will be counted as a prior regimen if disease progression/recurrence occurred within 12 months upon completion of this neoadjuvant or adjuvant therapy. Systemic therapy followed by maintenance therapy will be considered as 1 regimen if the maintenance therapy consists of a drug or drugs that was/were used in the regimen that immediately preceded maintenance.
[§]Treatment-related alopecia or peripheral neuropathy that are grade >1 are allowed, if deemed irreversible.
[¶]If a patient has worsening neurological symptoms or signs due to brain metastasis, the patient must complete local therapy and be neurologically stable (with no requirement for an increasing dose of corticosteroids or use of anticonvulsants) for 7 days before randomization.
ALK: Anaplastic lymphoma kinase; ALT: Alanine aminotransferase; ANC: Absolute neutrophil count; AST: Aspartate aminotransferase; ECOG: Eastern Cooperative Oncology Group; eGFR: Estimated glomerular filtration rate; GI: Gastrointestinal; NSCLC: Non-small-cell lung cancer; PD: Progressive disease; PK: Pharmacokinetic; RECIST v1.1: Response Evaluation Criteria in Solid Tumors, version 1.1; TKI: Tyrosine kinase inhibitor; ULN: Upper limit of normal.

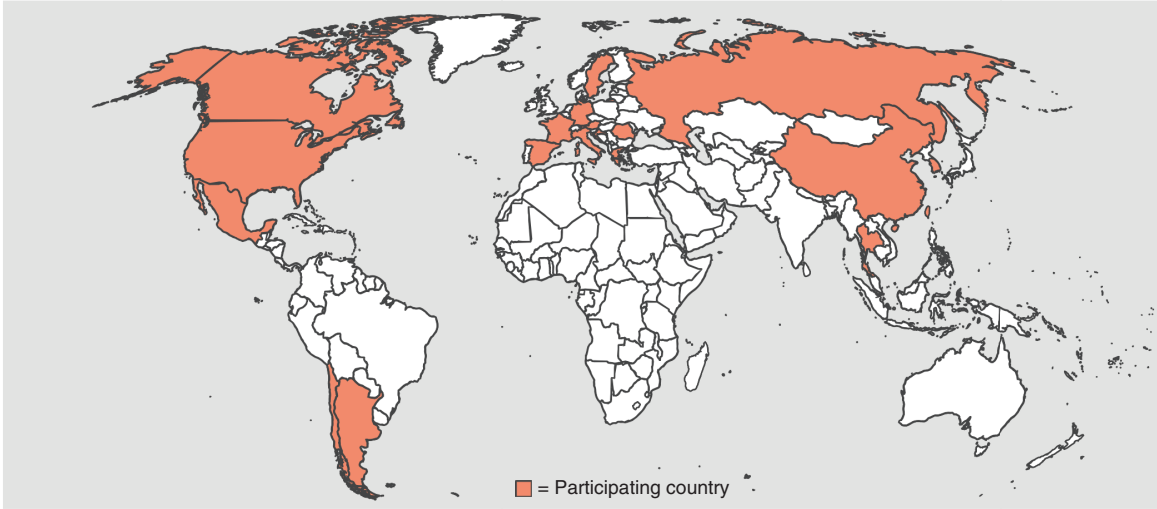

Figure 3. ALTA-3 trial locations. Patients are being recruited in Argentina, Austria, Canada, Chile, China, Croatia, France, Germany, Greece, Hong Kong SAR, Italy, Korea, Mexico, Romania, Russian Federation, Spain, Sweden, Taiwan, Thailand and the United States.

Planned study period

The trial opened for enrollment in May 2019. The overall time frame will depend upon the actual enrollment rate and event rate.

Study procedures

Tumor response and disease progression will be assessed using computed tomography (CT) or MRI of the chest, abdomen and brain. Imaging will be performed at screening and at 8-week intervals thereafter, through Cycle 12 after the initial dose, and every 3 cycles thereafter until the end of treatment. More frequent imaging is recommended at any time if clinically indicated. At screening, disease assessment must include CT or MRI imaging of the chest and abdomen (including adrenal glands) and contrast-enhanced (e.g., gadolinium) MRI of the brain, unless the contrast medium is medically contraindicated, in which case CT with contrast may be used. The same imaging modality at the same institution will be used at each assessment, if possible. All radiographic images will be submitted to an imaging core laboratory for central review. Confirmation of CR or PR will be performed at least 4 weeks after the initial response is observed. For patients who discontinue the study drug because of a reason other than PD by investigator's assessment, additional tumor assessment will be documented, if available, until disease progression or the start of subsequent systemic anticancer therapy.

Safety assessments

Adverse events will be monitored throughout the study and for 30 days after the end of study treatment. Adverse events will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events v4.03. Safety assessments also include physical and laboratory examinations, vital signs and ECGs. Assessment for early-onset pulmonary events will be performed on Day 8 before administration of study drug.

Patient-reported outcome assessments

The EORTC QLQ-C30, QLQ-LC13, QLQ-BN20 and EuroQoL-5 Dimensions-5 Levels (EQ-5D-5L) will be administered at screening, on Day 1 of every cycle (before any clinical measurements, assessments, evaluations or procedures are performed), at the time of treatment discontinuation, and 30 days after the last dose of study drug. Only the EQ-5D-5L will be administered in the follow-up period.

Tumor tissue & blood sample collection

Patients who have a prior ALK^+ result from an unapproved test (e.g., immunohistochemistry) must provide a tumor sample to the central laboratory before randomization. A pathologist will assess the tissue sample to ensure adequate tumor tissue is available. For patients for whom there is an available formalin-fixed, paraffin-embedded

tumor tissue that was acquired after progression on crizotinib, a sample will be requested for exploratory molecular genetic analysis. In patients without such tissue available, an optional biopsy for exploratory molecular genetic analysis may be obtained during screening if the patient has an amenable lesion. An optional biopsy will be obtained at the time of disease progression for patients who consent to the procedure and genetic testing of the sample. Circulating tumor DNA will be obtained at screening, on Day 1 of Cycle 3, and at the end of treatment. A blood sample will be collected for exploratory biomarker studies, including molecular genetic analysis of *ALK* and other genes implicated in tumor biology. Patients allocated to the brigatinib arm must provide blood samples for measurement of plasma concentrations of brigatinib. These blood samples will be collected at 1 and 4 h postdose on Day 1 of Cycle 1; predose and at 1 and 4 h postdose on Day 8 of Cycle 1 and Day 1 of Cycle 2; and predose on Day 1 of Cycles 3, 4 and 5. No PK blood samples will be collected from patients in the alectinib arm.

Health utilization data collection

Data on all medical care encounters (e.g., inpatient and outpatient admissions, home care and time of work loss) during the study will be collected from all patients, regardless of the reason for the medical care encounter. All encounters since the previous collection will be recorded at scheduled visits on Day 1 of each cycle, at end of treatment and 30 days after the last dose.

Outcome measures/end points

The primary end point is PFS as assessed by a blinded Independent Review Committee (BIRC) per RECIST v1.1. The key secondary end point is OS. Other secondary end points are: PFS as assessed by the investigator per RECIST v1.1; ORR as assessed by the investigator and BIRC per RECIST v1.1; DoR as assessed by the investigator and BIRC; time to response as assessed by the investigator and BIRC; intracranial ORR as assessed by the BIRC per modified RECIST v1.1; intracranial DoR as assessed by the BIRC per modified RECIST v1.1; time to iPD as assessed by the BIRC per modified RECIST v1.1; and HRQoL assessed with the global health status/quality of life (QoL) and other function and symptom domains from the EORTC QLQ-C30 (v3.0) and the EORTC QLQ-LC13. Safety end point assessments will include physical and laboratory examinations, vital signs and ECGs.

Exploratory end points are: CNS efficacy outcomes (intracranial ORR, intracranial DoR and time to iPD) as assessed by the BIRC per Response Assessment in Neuro-Oncology Brain Metastases criteria; molecular determinants of efficacy and safety with brigatinib and alectinib; HRQoL measured by EQ-5D-5L questionnaires; healthcare resource utilization; and items from the EORTC Quality of Life Brain Cancer Module (QLQ-BN20) used to assess morbidity related to CNS symptoms.

Statistics

Analysis populations

The primary analyses of efficacy will be based on the intent-to-treat population, which will include all patients randomized to each regimen regardless of whether they are ALK^+ by an FDA-approved or other test or whether they receive study drug or adhere to the assigned dose. Safety analyses will be based on the population of patients receiving at least 1 dose of study drug.

Primary efficacy end point analysis

A two-sided stratified log-rank test (stratification factors: presence of intracranial brain metastases at baseline [yes vs no] and best prior response to crizotinib therapy as assessed by the investigator [CR/PR vs any other response/status unknown]) will be used to compare BIRC-assessed PFS in patients randomized to brigatinib versus alectinib. The overall (two-sided) type I error rate will be controlled at 0.05. PFS will be estimated for each treatment arm using the Kaplan-Meier method. HRs will be estimated using the stratified Cox regression model with the stratification factors described above.

Secondary efficacy end point analyses

The key secondary end point, OS, will be formally tested for statistical significance when PFS per BIRC is statistically significant. Investigator-assessed PFS, ORR, disease control rate and intracranial ORR will be analyzed by calculating the percentage of patients responding and associated two-sided 95% CIs. A Mantel-Haenszel test (using the stratification factors) will be performed to compare each end point between the two arms. Time to iPD, as assessed by the BIRC, will be compared between treatment groups in the full analysis set using a two-sided

stratified log-rank test. Time to iPD will be estimated for each treatment arm using the Kaplan-Meier method, and HRs will be estimated using the stratified Cox regression model with the stratification factors. Additional analyses in patients with measurable brain metastases and in patients without brain metastases will be performed in a similar manner. The DoR among responders and intracranial DoR among patients with brain metastases with an intracranial response will be estimated using the Kaplan-Meier method and compared between arms using stratified log-rank tests. Time to response will be summarized for responders using descriptive statistics.

Interim analysis

One interim analysis is planned to occur after approximately 70% (115 events) of the total expected events (progression or death) have been observed. An O'Brien-Fleming Lan-DeMets alpha spending function will be used to control the overall two-sided alpha level at 0.05. The study may be stopped if the observed HR meets the prespecified stopping rules for efficacy or futility. A gamma spending function will be used for the futility stopping boundary. Futility is nonbinding. If statistical significance is not achieved at the interim analysis, a final analysis is planned after 164 events have been observed. The efficacy and futility stopping boundaries used in the analysis will be adjusted based on the actual number of events observed at each analysis using the O'Brien-Fleming Lan-DeMets alpha and gamma spending function.

Rationale for number of patients

For sample size calculations, median PFS was assumed to be 9 months for alectinib and 15 months for brigatinib based on results of previous single-arm studies [23,35]. Approximately 246 patients will be randomized in a 1:1 fashion to receive brigatinib or alectinib. A total of 164 events (progression or death) among 246 randomized patients will provide 90% power to detect a 6-month improvement in PFS (HR, 0.60) based on a two-sided log-rank test controlled at the two-sided 0.05 level and adjusted for the proposed interim analysis plan. The number of events is fixed, but the enrollment number may change based on an assessment of the overall event rate pooled across treatment groups (before the close of enrollment).

Discussion & future perspective

After this study was initiated, alectinib replaced crizotinib as the preferred first-line therapy for advanced ALK$^+$ NSCLC [5] based on results of two Phase III trials (ALEX [NCT02075840] and J-ALEX [JapicCTI-132316]), which compared alectinib with crizotinib in the treatment-naive setting [11,36–38] and subsequently supported by the ALESIA trial (NCT02838420) [39]. However, as noted previously, many patients do not have access to alectinib and other next-generation ALK inhibitors as first-line therapy for ALK$^+$ NSCLC [33,34]. Due to the high rates of systemic and CNS progression with crizotinib, it is important to determine which next-generation ALK inhibitor is the best treatment for crizotinib-refractory ALK$^+$ NSCLC. Results of the ALTA-3 trial will provide important comparative data on the safety and efficacy of brigatinib compared with alectinib in the crizotinib-refractory setting. If positive, the results of ALTA-3 will build on the ALTA trial data and reaffirm the optimal approach with brigatinib over alectinib in crizotinib-resistant patients. In addition, exploratory analyses will investigate whether patients with different resistance mutations and biomarkers may derive benefit from brigatinib, further informing treatment selection and optimal drug sequencing in ALK+ NSCLC. The HRQoL and healthcare utilization data will also help assess the patient impact of brigatinib and alectinib.

Conclusion

The ALTA-3 study is investigating the efficacy and tolerability of brigatinib compared with alectinib as second-line therapy for ALK$^+$ NSCLC. The results of this study will help define the role of brigatinib in the management of ALK+ NSCLC. Study accrual is ongoing, with a targeted enrollment of 246 patients.

Executive summary

Background

- Crizotinib, the first ALK-tyrosine kinase inhibitor (TKI) approved as first-line treatment for metastatic ALK$^+$ non-small-cell lung cancer (NSCLC), provides improved progression-free survival (PFS) versus chemotherapy.
- However, the PFS benefit and intracranial efficacy of crizotinib have limitations, likely related to inadequate intracranial penetration and the development of secondary mutations linked to resistance.
- Several ALK TKIs including alectinib have subsequently been developed that have better brain penetration and/or more potent inhibition of ALK with acquired resistance mutations and are superior to crizotinib in the first-line setting.
- Brigatinib was designed to have potent activity against a broad array of *ALK* mutants and demonstrated potentially best-in-class efficacy in crizotinib-refractory patients (Phase II ALTA trial) and marked efficacy in patients with ALK TKI-naive ALK$^+$ NSCLC (Phase III ALTA-1L trial).
- Given the existence of patients initiating or continuing crizotinib treatment, there is a need for head-to-head comparisons of brigatinib with alectinib in patients with crizotinib-refractory ALK$^+$ NSCLC.

The ALTA-3 study

- ALTA-3 is a Phase III, randomized, open-label, comparative, multicenter, international study in adults with locally advanced or metastatic ALK$^+$ NSCLC who had disease progression while on crizotinib.
- Patients will be randomized 1:1 to receive brigatinib 180 mg qd with a 7-day lead-in at 90 mg qd or alectinib 600 mg twice daily.
- Approximately 246 patients will be enrolled.
- The primary efficacy end point is PFS as assessed by a Blinded Independent Review Committee (BIRC) per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.
- Secondary end points are overall survival (key secondary end point); PFS, as assessed by the investigator per RECIST v1.1; overall response rate, as assessed by the investigator and BIRC per RECIST v1.1; duration of response, as assessed by the investigator and BIRC; time to response, as assessed by the investigator and BIRC; intracranial objective response rate, as assessed by the BIRC per modified RECIST v1.1; intracranial duration of response, as assessed by the BIRC per modified RECIST v1.1; time to intracranial progressive disease, as assessed by the BIRC per modified RECIST v1.1; and health-related quality of life.
- Safety end point assessments include adverse events, physical and laboratory examinations, vital signs and electrocardiograms.

Conclusion

- The ALTA-3 trial will provide important comparative data on the safety and efficacy of brigatinib compared with alectinib in patients with locally advanced or metastatic ALK$^+$ NSCLC that has progressed on crizotinib.
- The results of this study will help define optimal ALK inhibitor sequence after progression on ALK TKI therapy.

Author contributions

S Popat, S Lu, G Song and X Ma contributed to study design. S Popat and S Lu contributed as study investigators. S Lu and JCH Yang enrolled patients. Collection and assembly of data were done by X Ma. S Popat and X Ma contributed to data analysis. S Popat contributed to manuscript preparation. All authors contributed to data interpretation, manuscript review and revisions and final approval of manuscript.

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