Brigatinib for treatment of anaplastic lymphoma kinase-rearranged metastatic non-small cell lung cancer

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ABSTRACT

Introduction: Crizotinib has been approved as a first-line treatment for patients with anaplastic lymphoma kinase (ALK)-rearranged advanced non-small-cell lung cancer (NSCLC). However, the majority of patients treated with crizotinib experience progression within 1 year, and the central nervous system (CNS) is the most common site of progression. Brigatinib, a potent and selective ALK inhibitor that can inhibit multiple crizotinib-resistant ALK mutants, has shown superior efficacy in advanced ALK-rearranged NSCLC, including in patients with CNS metastases.

Areas covered: We reviewed the characteristics of brigatinib, and its clinical efficacy and safety have been demonstrated in previous pivotal studies.

Expert opinion: Brigatinib was recently approved for use in ALK-rearranged NSCLC with acquired resistance to crizotinib as first-line treatment. Moreover, brigatinib is highly active in patients with CNS metastasis. The major concern about pulmonary adverse events was resolved with changes in treatment schedule. The mechanisms of resistance to brigatinib and the sequence of treatment with other ALK inhibitors are unresolved issues.

1. Introduction

Approximately 3–5% of non-small-cell lung cancer (NSCLC) harbors anaplastic lymphoma kinase (ALK) rearrangements [1,2]. ALK-rearranged NSCLC is typically associated with younger age, never smoker or light smoking, and adenocarcinoma histology. ALK rearrangements encode oncogenic proteins and are a target for tyrosine kinase inhibitors (Figure 1) [3–5]. ALK inhibitors have shown significant clinical benefits in patients with ALK-rearranged NSCLC and have become the standard first-line treatment for patients with advanced ALK-rearranged NSCLC [6].

Crizotinib, a first-generation ALK inhibitor, is an oral tyrosine kinase inhibitor targeting ALK, MET, and ROS1. In phase I study with 149 patients of advanced ALK-rearranged NSCLC, crizotinib at a dose of 250 mg twice daily was administrated and the overall response rate (ORR) was 60.8% and the median progression-free survival (PFS) was 9.7 months [7]. The multicenter, single-arm, phase II study of crizotinib in advanced ALK-rearranged NSCLC after progression on at least one line of cytotoxic chemotherapy showed also prolonged PFS (median PFS 8.5 months) and increased response rate (ORR 53%) [8]. Based on these data, the U.S. Food and Drug Administration (FDA) granted accelerated approval for crizotinib for treatment in advanced ALK-rearranged NSCLC in 2011.

However, the majority of patients develop resistance to crizotinib within 12 months [9]. Acquired resistance mechanisms include secondary mutations within the ALK tyrosine kinase domain, amplification of the ALK fusion gene, and activation of alternative signaling pathways [10,11]. In addition, ALK-rearranged advanced NSCLC shows a high frequency of central nervous system (CNS) metastasis owing to the limited CNS penetration of crizotinib [12,13]. Among second-generation ALK inhibitors (ceritinib, alectinib, brigatinib), alectinib and brigatinib have intracranial activity [9,14,15]. Lorlatinib, a third-generation ALK inhibitor, has also demonstrated intracranial tumor response [16].

In April 2017, the U.S. FDA approved brigatinib for patients with advanced ALK-rearranged NSCLC who have progressed on or cannot tolerate crizotinib. This review summarizes the data available for the use of brigatinib in treatment of NSCLC harboring ALK gene rearrangement.

2. Review of Brigatinib

2.1. Second-generation ALK inhibitors

To overcome crizotinib resistance, several potent and structurally different ALK inhibitors have been developed. Ceritinib (LDK378, zykadia) is 20 times more potent against ALK than crizotinib, and 58% of patients who failed crizotinib showed objective response to ceritinib [9,17]. Alectinib (CH5424802, alecensa) is another potent ALK inhibitor with an IC50 of 1.9 nmol per liter. Alectinib has activity against L1196M, one of the resistance mechanisms of crizotinib, and the ORR was 55% in patients who are refractory to crizotinib [15]. Based on these results, ceritinib and alectinib have been approved for treatment of refractory or relapsed ALK-
rearranged NSCLC resistant to crizotinib. In this article, we review the efficacy, toxicity, and clinical applications of brigatinib, a second-generation ALK inhibitor. Clinical outcomes including adverse events of brigatinib and other ALK TKIs are reviewed in Table 1.

2.2. Chemistry and pharmacodynamics
Brigatinib (AP26113; trade name Alunbrig; ARIAD Pharmaceuticals, Cambridge, MA) is a potent, selective ALK inhibitor (IC\textsubscript{50}, 14 nmol/L) that combines around a bisanilinopyrimidine core that occupies the adenosine triphosphate-binding site of ALK. Brigatinib has several chemical features that increase affinity for ALK, such as the methoxy substituent, an extended solubilization group on the C2 aniline, a chlorine atom at C5, and a unique dimethylphosphine oxide functionality on the C4 aniline [22]. In addition, ALK mutations including L1198F and L1152R/P decrease the activity of ceritinib but not that of brigatinib. The small methoxy substituent of brigatinib can overcome a mutation of hinge residue L1198. Brigatinib has potent effects on at least 16 unique secondary mutations in ALK at 11 different amino acid residues (G1123, T1151, L1152, C1156, I1171, F1174, L1196, G1202, D1203, S1206, and G1269) that have been associated with resistance to crizotinib and/or the second-generation ALK inhibitors ceritinib and alectinib [22].

The kinase selectivity profile of brigatinib showed a high degree of selectivity. Among 289 screened kinases, brigatinib inhibited 11 native or mutant kinases, with IC\textsubscript{50} < 10 nmol/L. These included ROS1 and FLT3 (IC\textsubscript{50} values of 1.9 and 2.1 nmol/L, respectively). Brigatinib demonstrated more modest activity against T790M-mutant EGFR (IC\textsubscript{50} values of 29) and did not inhibit MET (IC\textsubscript{50} > 1000 nmol/L). In cellular assay, the activity of brigatinib was consistent with that of \textit{in vitro} kinase assay [22,23].

In a mouse xenograft model with either ALK-rearranged ALCL Karpas-299 or ALK-rearranged NSCLC H2228 cells, tumor regression was observed at significantly lower doses of brigatinib compared to crizotinib, in a dose-dependent manner. Tumor shrinkage was observed at 25 mg/kg/day (ALCL) and 10 mg/kg/day (NSCLC) of brigatinib compared to 100 mg/kg/day of crizotinib. The plasma levels of brigatinib in mice dosed at 25 mg/kg once daily were similar to those of human dosed at 90 mg once daily. Furthermore, superior potency with brigatinib was observed \textit{in vivo} in an orthotopic mouse brain tumor model compared to crizotinib, suggesting the enhanced CNS penetration and greater potency of brigatinib [22].

Figure 1. Mechanism of brigatinib in the EML4-ALK rearrangement and downstream signaling.
2.3. Pharmacokinetics and metabolism

In a phase I study, brigatinib showed favorable bioavailability with oral administration, and the median time to maximal plasma concentration ($C_{\text{max}}$) was 1–3 h. The mean terminal half-life was approximately 22–32 h at a steady state with biphasic elimination [24]. The area under the plasma concentration–time curve (AUC) and $C_{\text{max}}$ of brigatinib increased proportionally over a 60–240 mg once daily dose range after oral administration and exhibited linear pharmacokinetics (PK). The mean accumulation ratio after repeat dosing was 1.9–2.4. Following administration of brigatinib with a high-fat meal, $C_{\text{max}}$ was reduced by 13% with no effect on AUC compared to fasting conditions. Age, race, gender, body weight, and albumin concentration do not appear to affect exposure. Brigatinib is primarily metabolized by CYP2C8 and CYP3A4. At steady state, the AUC of active metabolite brigatinib was less than 10% of the AUC of brigatinib exposure (Box 1) [24,25].

### Box 1. Drug summary.

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Brigatinib (AP26113)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase</td>
<td>Approved</td>
</tr>
<tr>
<td>Indication</td>
<td>Alunbrig® is indicated for patients with metastatic ALK-rearranged non-small-cell lung cancer who have progressed on or are intolerant to crizotinib.</td>
</tr>
<tr>
<td>Pharmacology description/mechanism of action</td>
<td>Brigatinib combines around a bisanilinopyrimidine core that occupies the ATP-binding site of ALK and inhibits the kinase activity of ALK, IGF-1R. Brigatinib induces a dose-dependent antitumor effect in in vitro and in vivo models.</td>
</tr>
<tr>
<td>Route of administration</td>
<td>Brigatinib is administered orally</td>
</tr>
<tr>
<td>Chemical structure</td>
<td></td>
</tr>
</tbody>
</table>

![Chemical structure of brigatinib](image)

### Table 1. Clinical outcomes of 2nd generation ALK inhibitors in ALK-rearranged NSCLC patients

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>ORR (%)</th>
<th>Intracranial ORR (%)</th>
<th>Median PFS (mo)</th>
<th>Most common AEs</th>
<th>Most common Gr 3-4 AEs</th>
<th>Treatment related death</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brigatinib</td>
<td>Phase I/II (n=71) 30-300mg qd</td>
<td>74</td>
<td>53</td>
<td>13.4</td>
<td>Nausea (53%)</td>
<td>Lipase ↑ (9%)</td>
<td>Sudden death (n=1)</td>
<td>[20]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Fatigue (43%)</td>
<td>Dyspnea (6%)</td>
<td>Hypoxia (n=1) Unknown cause</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Diarrhea (41%)</td>
<td>Hypertension (5%)</td>
<td>(n=1)</td>
<td></td>
</tr>
<tr>
<td>Alectinib</td>
<td>Phase II (n=110) 180mg qd*</td>
<td>55</td>
<td>67</td>
<td>15.6</td>
<td>Diarrhea (34%)</td>
<td>CK↑ (11%)</td>
<td>Intestinal perforation (n=1)</td>
<td>[24]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Nausea (32%)</td>
<td>Hypertension (4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CK↑ (32%)</td>
<td>Pneumonitis (4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Phase II global (n=122) 600mg bid</td>
<td>50</td>
<td>57</td>
<td>8.9</td>
<td>Constipation (33%)</td>
<td>Dyspnea (3%)</td>
<td></td>
<td>[28]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Fatigue (26%)</td>
<td>Fatigue (1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Peripheral edema (25%)</td>
<td>Headache (1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Phase II single center (n=87) 600mg bid</td>
<td>48</td>
<td>75</td>
<td>8.1</td>
<td>Constipation (36%)</td>
<td>CK↑ (8%)</td>
<td>Hemorrhage (n=1)</td>
<td>[29]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Fatigue (33%)</td>
<td>ALT↑ (6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Myalgia (24%)</td>
<td>AST↑ (5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ceritinib</td>
<td>Phase I (n=163) 750mg qd</td>
<td>56</td>
<td>36</td>
<td>6.9</td>
<td>Diarrhea (86%)</td>
<td>ALT↑ (30%)</td>
<td>Ischemic hepatitis (n=1)</td>
<td>[30]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Nausea (81%)</td>
<td>Diarrhea (6%)</td>
<td>N/a</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Vomiting (61%)</td>
<td>Hyperglycemia (6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ceritinib</td>
<td>Phase II (n=140) 750mg qd</td>
<td>36</td>
<td>45</td>
<td>5.7</td>
<td>Nausea (81%)</td>
<td>Diarrhea (80%)</td>
<td></td>
<td>[31]</td>
</tr>
</tbody>
</table>

*180mg qd with 7-day lead-in at 90mg, AE: adverse event, CK: blood creatinine phosphokinase, Gr: grade, NSCLC: non-small cell lung cancer, ORR: overall response rate, PFS: progression-free survival*
2.4. Clinical efficacy

2.4.1. Phase I/II study

A total of 137 patients with ALK-rearranged NSCLC with or without prior crizotinib were enrolled in a phase I/II clinical trial (NCT01449461). The study included dose-escalation cohorts and dose-expansion cohorts [24]. Dose-limiting toxicities were observed at a dose of 240 mg once daily (grade 3 increased alanine aminotransferase) or 300 mg once daily (grade 4 dyspnea). Confirmed ORR was 62% in patients with advanced ALK-rearranged NSCLC previously treated with crizotinib and 100% in crizotinib-naïve patients. The most common grade 3 or 4 adverse events were increased lipase (9%), dyspnea (6%), and hypertension (5%). Of note, serious adverse events occurring in ≥ 5% of patients were dyspnea (7%), pneumonia (7%), and hypoxia (7%) [24,27].

A randomized phase II trial in patients with crizotinib-refractory ALK-rearranged NSCLC (ALTA, NCT02094573) evaluated two different regimens of brigatinib, 90 mg once daily (n = 112, Arm A) and 180 mg once daily with a 7-day lead-in (n = 110, Arm B). A total of 222 patients were enrolled. Among these patients, 69% (n = 154) had CNS metastasis, and 74% (n = 164) received prior chemotherapy. Investigator-assessed confirmed ORR was the primary end point. The ORR was 45% (97.5% CI, 34–56%) in Arm A and 54% (97.5% CI, 43–65%) in Arm B. Of note, intracranial ORR was 42% in patients with measurable brain metastasis (11 of 26 patients) on the 90 mg dose and 67% with the 180 mg dose (12 of 18 patients). With an 8.0 month median follow-up, investigator-assessed median PFS was 9.2 months (95% CI, 7.4–15.6) and 12.9 months (95% CI, 11.1–not reached) in Arm A and Arm B, respectively. The most common adverse events of any grade were nausea, diarrhea, headache, and cough, which were mainly confined to grades 1 and 2 [27–29].

Recent updated results of ALTA were presented nearly 1.5 years after the last patient was enrolled. As of 21 February 2017, 36 (32%) patients in Arm A and 45 (41%) patients in Arm B remained in the study. The median follow-up (range) was 16.8 months (0.1–28.5) in Arm A and 18.6 months (0.1–32.0) in Arm B. The median PFS was 9.2 months (95% CI, 7.4–12.8) in Arm A and 16.7 months (95% CI, 11.6–not reached) in Arm B. Median overall survival was not reached in Arm A (95% CI, 20.2–not reached) and was 27.6 months (95% CI 27.6–not reached) in Arm B. The duration of intracranial response in patients with measurable brain metastasis was not reached in Arm A and was 16.1 months in Arm B. The intracranial PFS was 28.5 months (95% CI, 19.3–not reached) in Arm A and 18.4 months (95%, 12.6–not reached) in Arm B. This long-term follow-up ALTA study demonstrated that brigatinib continues to show substantial efficacy with an acceptable safety profile in both arms [28,29]. Based on these results, brigatinib was approved as a breakthrough designation therapy by the U.S. FDA and was granted orphan drug designation for treatment of ALK-rearranged NSCLC patients.

2.4.2. Phase III study

Based on the ALTA study, a randomized phase 3 trial of brigatinib at 180 mg (with lead-in) versus crizotinib in patients with ALK inhibitor-naïve advanced ALK+ NSCLC has completed accrual (ALTA-1L, NCT02737501).

2.4.3. Efficacy for CNS metastasis

Approximately 30% of patients with ALK-rearranged NSCLC have CNS metastasis at diagnosis, and up to 70% of patients treated with crizotinib experience CNS progression [30]. Brigatinib yielded promising intracranial efficacy in previous studies. In a phase I/II study (NCT01449461), 53% of patients with measurable brain metastasis showed objective response, and the estimated median duration of intracranial response was 18.9 months [24]. In a randomized phase II trial (ALTA, NCT02094573), confirmed intracranial objective response was 67% in patients with measurable brain metastases treated with 180 mg with a 7 day lead-in at 90 mg. The intracranial PFS in patients with any brain metastasis at baseline was 18.4 months, which is quite promising [29].

2.5. Safety and tolerability

Brigatinib showed an acceptable safety profile in previous studies. In a phase I/II study (NCT01449461), dose-limiting toxicities were reported during the dose-escalation phase, which included grade 3 increased alanine aminotransferase at 240 mg once daily and grade 4 dyspnea at 300 mg once daily. Nausea (53%), fatigue (43%), and diarrhea (41%) were the most common adverse events (AEs) and were mostly grades 1 and 2. Serious pulmonary AEs were also noted, such as dyspnea (7%), pneumonia (7%), and hypoxia (5%). Grade 3–4 pulmonary AEs typically occur within 24–48 h at a dose of 180 mg once daily in dose escalation and an initial phase II expansion. To reduce early pulmonary events, a 7 day lead-in at 90 mg regimen was explored, and no pulmonary toxicities were reported [24,27]. Updated results of the ALTA study demonstrate that pulmonary adverse events with early onset (median day 2, range 1–9), including dyspnea, hypoxia, cough, and pneumonia, occurred in 14 (6%) of 219 treated patients with 7 (3%) grade ≥ 3 events. Interestingly, all of these events occurred at 90 mg in both arms, and no such events occurred after escalation to 180 mg. These events were well managed with steroids and antibiotics [28,29].

2.6. Resistance to brigatinib

Similar to crizotinib with ALK-rearranged NSCLC, acquired resistance invariably develops after treatment with second-generation ALK inhibitors. Given the more potent nature of second-generation ALK inhibitors, there are more varied mechanisms of resistance. These include ALK resistance mutations and activation of bypass pathways such as MAPK reactivation, SRC activation, PI3KCA mutation, and MET amplification. The exact resistance mechanism to brigatinib has not been fully determined. Recently, Ganior et al reported that, among 6 patients who underwent repeat biopsy and next generation sequencing after progression on brigatinib, 5 received prior crizotinib. None of these patients were treated with other second-generation ALK inhibitors. A total of 71% of brigatinib-resistance specimens had ALK resistance mutations, and G1202R was the most common mutation, followed by E1210K, D1203N, and S1206Y/C mutations [31].
3. Conclusion
Brigatinib showed superior activity against ALK resistance mutations and encouraging efficacy in CNS metastasis. To date, one phase I/II study and one randomized phase II study have been published. Brigatinib at 180 mg once daily (with 7 day lead-in at 90 mg) demonstrated promising clinical efficacy, including 55% confirmed ORR and over 15 months of median PFS. Furthermore, intracranial ORR was nearly 70% and median intracranial PFS was 18.4 months in crizotinib refractory ALK-rearranged NSCLC. To evaluate the role of brigatinib as first-line treatment in patients with crizotinib naïve ALK-rearranged NSCLC, the ALTA-1L (NCT02737501) trial is ongoing.

4. Expert opinion
Acquired resistance to crizotinib as first-line treatment for ALK-rearranged NSCLC develops in most applicable patients. Brigatinib is highly active in crizotinib refractory patients. Moreover, high efficacy and long CNS progression-free survival were observed in patients with CNS metastasis. During the development of brigatinib, pulmonary adverse events with early onset were raised as a major concern. However, serious events were eliminated through changes in the treatment schedule, indicating a tolerable drug. Although a small number of patients were treated with brigatinib as first-line therapy, the response rate and PFS were quite encouraging. Given the high efficacy of brigatinib even in salvage therapy with high CNS efficacy, an ongoing phase III trial comparing brigatinib with crizotinib in ALK inhibitor naïve NSCLC patients will elucidate the role of brigatinib as first-line therapy.

The mechanisms of resistance to brigatinib in crizotinib refractory ALK-rearranged NSCLC have not been fully elucidated. Similarly, the mechanism of resistance to upfront use of brigatinib is unknown. Therefore, repeat biopsy is essential to identify the exact resistance mechanism and to guide treatment decision.

Another major challenge is the sequence of treatment. Ceritinib and alectinib have already been established as first-line therapy. There is a high possibility that brigatinib can be positioned as first-line therapy in ALK-rearranged NSCLC. In the near future, several second- or third-generation ALK inhibitors, such as ceritinib, brigatinib, alectinib, and lorlatinib, will be available as first-line therapy. It remains to be determined which of these ALK TKIs should be chosen as first-line therapy or what sequence of agents should be used to maximize prolonged survival in ALK-rearranged NSCLC patients. Given the complexity of biology and the dynamic nature of resistance to ALK inhibitors, real-time molecular profiling using cell-free DNA as a noninvasive method will guide the treatment strategies and suggest the ideal sequence of brigatinib and other ALK inhibitors in the future.

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Declaration of interest
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References
Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

7. First demonstration of superior efficacy of ALK inhibitor (crizotinib) over cytotoxic chemotherapy in first line therapy for advanced ALK-rearranged NSCLC.


