Further Advances in the Management of Anaplastic Lymphoma Kinase–Mutated Non–Small-Cell Lung Cancer

This year (2017) marks the 10-year anniversary of the discovery of anaplastic lymphoma kinase (ALK) rearrangement in non–small-cell lung cancer (NSCLC). Since then, crizotinib, a first-in-class ALK inhibitor, has demonstrated significantly improved progression-free survival (PFS) over chemotherapy in treatment-naïve patients and in patients with platinum-refractory ALK-positive NSCLC. Similarly, ceritinib, a next-generation ALK inhibitor has also demonstrated statistically significant improved PFS over chemotherapy in treatment-naïve and in patients with chemotherapy- and crizotinib-refractory ALK-positive NSCLC. Likewise, alectinib, another next-generation ALK inhibitor, has demonstrated significantly improved PFS over crizotinib in patients with ALK inhibitor-naïve ALK-positive NSCLC in a study conducted in Japan (J-ALEX).

Brigatinib is a potent next-generation ALK inhibitor that can overcome multiple acquired mutations that confer resistance to ALK inhibitors such as crizotinib in preclinical models. On the basis of an ongoing phase II trial, brigatinib received Breakthrough Therapy designation from the US Food and Drug Administration in October 2014 for the treatment of patients with ALK-positive NSCLC that is resistant to crizotinib. The initial recommended phase II dosage of brigatinib was 180 mg once daily. During the phase II trial, occurrence of early-onset (usually within the first 7 days) pulmonary adverse events (AEs) were observed, which seemed to be dependent on the starting dose (2% AE incidence at 90-mg continuous daily dosing compared with 14% at 180-mg continuous daily dosing). In contrast, there were 0% AEs in this study when 90 mg brigatinib was administered once daily for 7 days, followed by an increase to 180-mg continuous daily dosing (90- to 180-mg dosing schedule). There were two early deaths attributed to brigatinib at 180-mg once daily dosing (sudden death on day 3; hypoxia on day 6). Two additional deaths at 180-mg once daily dosing occurred that were neither attributed to disease progression nor brigatinib (acute respiratory distress syndrome on day 17 and respiratory failure on day 81). The median PFS was 12.9 months for the 90-mg continuous dosing, 13.4 months for the 90- to 180-mg dosing regimen, and 10.8 months for the 180-mg continuous daily dosing regimen.

Taken together, an international randomized phase II trial (ALK Lung Cancer Trial of AP26113 [ALTA]) was launched to further define the efficacy and safety of two brigatinib regimens: 90-mg continuous dosing, 13.4 months for the 90- to 180-mg dosing regimen, and 10.8 months for the 180-mg continuous daily dosing regimen. Taken together, an international randomized phase II trial (ALK Lung Cancer Trial of AP26113 [ALTA]) was launched to further define the efficacy and safety of two brigatinib regimens: 90-mg continuous daily or 90-mg once daily dosing for 7 days and then stepping up to 180-mg continuous daily dosing, with overall response rate per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 as the primary end point.

The efficacy and safety results of the ALTA trial are reported by Kim et al in the article accompanying this editorial. Overall, brigatinib was generally well tolerated, with only 20% of patients receiving the Key points

- Crizotinib, a first-in-class ALK inhibitor, has demonstrated significantly improved progression-free survival (PFS) over chemotherapy in treatment-naïve patients and in patients with platinum-refractory ALK-positive NSCLC.
- Alectinib, another next-generation ALK inhibitor, has demonstrated significantly improved PFS over crizotinib in patients with ALK inhibitor-naïve ALK-positive NSCLC in a study conducted in Japan (J-ALEX).
- Brigatinib is a potent next-generation ALK inhibitor that can overcome multiple acquired mutations that confer resistance to ALK inhibitors such as crizotinib in preclinical models.
- On the basis of an ongoing phase III trial, brigatinib received Breakthrough Therapy designation from the US Food and Drug Administration.
Hypertension (grade ≥ 3) is a unique AE as the result of brigatinib (Table 1, original report). Early-onset pulmonary AEs were again observed in 6.4% of patients (14 of 219 patients; median time to onset, 2 days), all occurring at the 90-mg continuous daily dose and of which half were grade ≥ 3.

Pulmonary AEs were managed by dose discontinuation (n = 7; 50%), dose interruption (n = 6; 43%), or dose reduction without interruption (n = 1; 7%). One patient with dose interruption died as the result of pneumonia on day 7. This was an unplanned post hoc analysis, so it must be interpreted with caution.

In addition, the number of patients was small (10 patients with < 7 days postcrizotinib; four patients ≥ 7 days postcrizotinib developed early-onset pulmonary AEs).

Crizotinib is both a mild CYP3A4 inducer and a moderate CYP3A4 inhibitor; it can significantly inhibit the metabolism of erlotinib when the drugs are given together.

With the caveats of cross-trial comparison, phase II trials of two other next-generation ALK inhibitors (ceritinib and alectinib) in patients with crizotinib-refractory or intolerant ALK-positive NSCLC are listed in Table 1 for reference. 16–18 Brigatinib step-up dosing of 90 to 180 mg (the recommended dosing regimen) achieved an overall median PFS of 15.6 months and an intracranial PFS of 12.8 months, which are comparable if not numerically superior to ceritinib and alectinib in patients with crizotinib-refractory ALK-positive NSCLC. 8 19 The observation that a higher brigatinib dose regimen is more efficacious indicates that the signaling through ALK continues to be an oncogenic driver after progression on crizotinib in most patients with ALK-positive NSCLC. 20 The degree of brigatinib penetration to the CNS has not been reported. It is unknown whether brigatinib achieves CNS disease control because it is not a substrate of the active efflux system in the CNS, similar to what has been observed.
### TABLE 1 - Summaries of published phase II trials of second-generation anaplastic lymphoma kinase inhibitors in patients with crizotinib-refractory anaplastic lymphoma kinase–positive non–small-cell lung cancer

<table>
<thead>
<tr>
<th>Variable</th>
<th>Ceritinib</th>
<th>Alectinib</th>
<th>Brigatinib&lt;sup&gt;11&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ASCEND-2&lt;sup&gt;16&lt;/sup&gt;</td>
<td>NP28761, North America&lt;sup&gt;17&lt;/sup&gt;</td>
<td>NP28673, global&lt;sup&gt;18&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Selected patient characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients</td>
<td>140</td>
<td>87</td>
<td>138</td>
</tr>
<tr>
<td>Brain metastasis present, %</td>
<td>71.2</td>
<td>60</td>
<td>61</td>
</tr>
<tr>
<td>Received prior chemotherapy, %</td>
<td>100</td>
<td>74</td>
<td>80</td>
</tr>
<tr>
<td><strong>Overall efficacy measures</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median follow-up, months (95% CI)</td>
<td>11.3 (0.1 to 18.9)</td>
<td>9.9 (6.2 to 12.9)</td>
<td>11.0 (0.5 to 17.0)</td>
</tr>
<tr>
<td>ORR confirmed by blinded independent central review, % (95% CI)*</td>
<td>49.0 (39.0 to 59.1)</td>
<td>51.0 (40 to 61)</td>
<td>50.0 (41 to 59)</td>
</tr>
<tr>
<td>Median duration of response by blinded independent central review, months (95% CI)</td>
<td>9.7 (5.6 to 12.9)</td>
<td>13.5 (6.7 to NE)</td>
<td>11.2 (9.6 to NR)</td>
</tr>
<tr>
<td>Median progression-free survival by blinded independent central review, months (95% CI)</td>
<td>7.2 (5.4 to 9.0)</td>
<td>8.1 (6.2 to 12.6)</td>
<td>8.9 (5.6 to 11.3)</td>
</tr>
<tr>
<td><strong>Intracranial efficacy measures</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total no. of patients with measurable brain lesions</td>
<td>33</td>
<td>16</td>
<td>35</td>
</tr>
<tr>
<td>Intracranial ORR, % (95% CI)</td>
<td>39.4 (22.9 to 57.9)</td>
<td>75.0 (48 to 93)</td>
<td>51 (39 to 74)</td>
</tr>
<tr>
<td>Total no. of patients with measurable and nonmeasurable lesions</td>
<td>100</td>
<td>52</td>
<td>84</td>
</tr>
<tr>
<td>Variable</td>
<td>Ceritinib</td>
<td>Alectinib</td>
<td>Brigatinib</td>
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<td>-----------------------------------------------</td>
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<tr>
<td><strong>ASCEND-2</strong></td>
<td>NP28761, North America</td>
<td>NP28673, global</td>
<td>ALTA, 90 mg ALTA, 90 to 180 mg</td>
</tr>
<tr>
<td>Duration of intracranial control, months (95% CI)</td>
<td>NA</td>
<td>11.1 (10.8 to NE)</td>
<td>10.3 (7.6 to 11.2)</td>
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<tr>
<td>Adverse events</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Three most common, all grades (%)</td>
<td>Nausea (81.4), diarrhea (80.0), vomiting (62.9)</td>
<td>Constipation (36), fatigue (33), myalgia (24)</td>
<td>Constipation (33), fatigue (26), peripheral edema (25)</td>
</tr>
<tr>
<td>Three most common, ≥ grade 3 (%)</td>
<td>ALT elevation (17.1), γ-GT elevation (12.1), nausea (6.4), diarrhea (6.4), fatigue (6.4)</td>
<td>Blood CPK elevation (8), ALT elevation (6), AST elevation (9)</td>
<td>Dyspnea (3), ALT elevation (2), AST elevation (2)</td>
</tr>
</tbody>
</table>

*Patients with measurable target lesions.

ALTA, ALK Lung Cancer Trial of AP26113; ASCEND-2, Activity and Safety of Ceritinib in Patients With ALK-rearranged Non-Small-Cell Lung Cancer 2; CPK, creatinine phosphokinase; γ-GT, γ-glutamyltransferase; NA, not available; NE, not evaluable; NR, not reached; ORR, overall response rate.
with alectinib. Brigatinib joined crizotinib, ceritinib, and alectinib on April 28, 2017, as the fourth ALK inhibitor to be approved in the United States on the basis of the ALTA trial.

Many acquired mutations that render resistance to ALK inhibitors such as crizotinib have been identified, which confer differential sensitivity to various next-generation ALK inhibitors. Treatment schemes on the basis of the presence of a particular resistance mutation have been proposed. The solvent-front mutation ALK G1202R is the most recalcitrant mutation and the most common emerging ALK resistance mutation to next-generation ALK inhibitors. There was one crizotinib-refractory patient with ALK G1202R, who achieved a confirmed partial response to brigatinib in ALTA. However, the treatment details, including metastatic burden, time to response, and duration of response of the patient, were not reported.11 Although brigatinib has demonstrated in vitro activity against G1202R (kinase IC50 = 4.9 nM), there was a significant shift in cellular IC50 values from wildtype echinoderm microtubule-associated protein-like 4 (EML4)-ALK (IC50 = 14 nM) to mutant G1202R (IC50 = 184 nM). Lorlatinib, which is another next-generation ALK inhibitor designed for CNS penetration, has in vitro activity against G1202R mutation, also demonstrates a significant shift in cellular IC50 from wildtype EML4-ALK (IC50 = 3.6 nM; BaF3 cells) to mutant G1202R (IC50 = 113 nM; BaF3 cells). An inhibitor designed specifically to overcome solvent-front resistance mutations, including ALK G1202R, has recently commenced a first-in-human phase I clinical trial (ClinicalTrials.gov identifier: NCT03093116).

Besides intracranial disease progression and emergence of acquired ALK resistance mutations, a number of other resistance mechanisms have been defined for ALK inhibitors. These include amplification of ALK28,29 or c-KIT,29 classic chemotherapy resistance mechanism of increased efflux of ALK inhibitor by overexpression of P-glycoprotein,30 and activation of the bypass pathways such as MEK and SRC21 that can potentially lead to morphologic transformation such as epithelial-mesenchymal transition22 or histologic transformation to SCLC. In addition, the BIM deletion polymorphism that is unique to Asian individuals can confer intrinsic resistance to crizotinib in Asian patients with ALK-positive NSCLC.33 Hence, to be able to truly personalize treatment of patients with ALK-positive NSCLC in the next decade with the advent of multiple ALK inhibitors, we must understand the biology of ALK-positive NSCLC in addition to being able to detect the presence of ALK-positive NSCLC. Although > 10 fusion partners have been identified in ALK-positive NSCLC,19 the EML4-ALK fusion remains the most common ALK fusion protein in ALK-positive NSCLC. There is emerging evidence that various EML4-ALK variants may confer differential response to crizotinib34,35 as the result of either retention of the HELP domain in the EML4 fusion partner,36 differential protein stability of the various EML4-ALK variants,37 and/or the difference in cellular location of the various EML4-ALK variants.38 In the future, we have to identify all possible resistance mechanisms to allow rational sequential and/or combination ALK inhibitor therapy rather than empirical sequencing of ALK inhibitors on the basis of the latest availability of any individual ALK inhibitor.

Key points
- Brigatinib joined crizotinib, ceritinib, and alectinib on April 28, 2017, as the fourth ALK inhibitor to be approved in the United States on the basis of the ALTA trial.
- Many acquired mutations that render resistance to ALK inhibitors such as crizotinib have been identified, which confer differential sensitivity to various next-generation ALK inhibitors.
- There was one crizotinib-refractory patient with ALK G1202R, who achieved a confirmed partial response to brigatinib in ALTA.
- Lorlatinib, which is another next-generation ALK inhibitor designed for CNS penetration that has in vitro activity against G1202R mutation, also demonstrates a significant shift in cellular IC50 from wildtype EML4-ALK (IC50 = 3.6 nM; BaF3 cells) to mutant G1202R (IC50 = 113 nM; BaF3 cells).
- Besides intracranial disease progression and emergence of acquired ALK resistance mutations, a number of other resistance mechanisms have been defined for ALK inhibitors.

References


35. Woo CG, Seo S, Kim SW, et al: Differential protein stability and clinical responses of EML4-ALK fusion variants to various

