Over the last few years, the introduction of several drugs acting against therapeutic targets has dramatically improved the prognosis of advanced non-small cell lung cancer (NSCLC), primarily for patients harboring epidermal growth factor receptor (EGFR) mutations and anaplastic lymphoma kinase (ALK) rearrangements. ALK rearrangements represent 3–7% of NSCLC, predominantly with adenocarcinoma histology and are mainly found in a light or non-smoker young population (1). Located on chromosome 2, they result in increased tyrosine kinase activity of the ALK receptor, promoting proliferation and tumor survival.

Several ALK inhibitors have revolutionized the management of advanced ALK-positive patients. Among them, three have been approval by the U.S. Food and Drug Administration (FDA): crizotinib, a first-generation ALK inhibitor, regardless of the treatment line, and two second-generation inhibitors, alectinib (CH5424802) and ceritinib (LDK378) in the crizotinib-resistant population. The European Medicines Agency (EMA) approved crizotinib and ceritinib in the same indications. Other ALK inhibitors, including brigatinib (AP26113), lorlatinib (PF-06463922) and entrectinib (RXDX-101), are currently in clinical development.

Alectinib is an oral highly potent, selective, second-generation ALK tyrosine kinase inhibitor targeting the ALK receptor. In the initial phase I/II studies in ALK-positive crizotinib-resistant patients, alectinib demonstrated high efficacy [overall response rate (ORR) over 50%], including patients with intracranial disease, and a good safety profile (2,3). In December 2015, Shaw et al. published in Lancet Oncology motivating results from a phase II study of alectinib in an ALK-positive crizotinib-resistant population (4). This provided further evidence for the importance of maintaining ALK inhibition after crizotinib failure, and highlighted the improvement of the therapeutic strategy in central nervous system (CNS) disease with next-generation inhibitors.

The study was a single-arm, multicenter, phase II trial designed to evaluate the activity and safety of alectinib in advanced ALK-positive NSCLC patients progressing under crizotinib. Twenty-seven North American centers participated, with enrollment over 12 months completed in August 2014. The primary endpoint was the ORR by response evaluation criteria in solid tumors (RECIST) version 1.1, assessed by an independent review committee (IRC). Secondary endpoints were efficacy in patients with CNS disease (IRC evaluation), ORR assessed by the investigators, safety, survival and patient-reported outcomes. The ORR was analyzed in all patients with measurable disease as per the IRC, who received at least one dose of alectinib. Other efficacy and safety endpoints were evaluated in the intention-to-treat population.

Patients with advanced stage IIIb-IV NSCLC were included, with a performance status 0-2, progressing under crizotinib. Patients could have received prior chemotherapy, but treatment with other ALK inhibitors was not permitted. As in other ALK inhibitor studies, patients with asymptomatic and neurologically stable CNS disease, including meningeal involvement were included. A total of 125 patients were screened and 87 were enrolled. Coherent with previous studies, the ALK-positive population was predominantly never smokers and had adenocarcinoma histology. All patients had progressed under crizotinib as the line before alectinib, and most (74%) had received...
chemotherapy. Fifty-two patients (60%) had CNS disease and none had meningeal carcinomatosis.

For the primary analysis with a median follow-up of 4.8 months, the ORR was 48% and 46% assessed by the IRC and the investigators respectively, with a median duration of response of 13.5 months. In an updated analysis performed after a median follow-up of 9.9 months, the ORR was 52% for the IRC and 51% as per the investigators. The ORR in patients with CNS involvement was 40%. Estimated median progression-free survival (PFS) was 8.1 months and overall survival (OS) at 1 year was 71% (Table 1).

The results of the global phase II study were reported in March 2016 by Ou et al. (9) in the Journal of Clinical Oncology, for a cohort of 138 ALK-positive crizotinib-resistant patients (61% CNS metastasis) treated in 56 centers in 16 countries, with a strong Asian representation. The ORR was 49% and was higher in chemotherapy-naïve patients, consistent with the data reported by Shaw et al.

Table 1 Summary of ALK inhibitors studies in crizotinib-naïve and resistant advanced NSCLC patients

<table>
<thead>
<tr>
<th>Drug</th>
<th>Study</th>
<th>Line</th>
<th>Phase</th>
<th>N</th>
<th>Crizotinib-naive</th>
<th>Crizotinib-resistant</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ORR [n (%)]</td>
<td>mPFS (m)</td>
</tr>
<tr>
<td>Crizotinib</td>
<td>PROFILE 1001</td>
<td>≥1st line</td>
<td>I</td>
<td>143</td>
<td>60.8</td>
<td>9.7</td>
</tr>
<tr>
<td></td>
<td>PROFILE 1005</td>
<td>≥2nd line</td>
<td>II</td>
<td>255</td>
<td>53</td>
<td>8.5</td>
</tr>
<tr>
<td></td>
<td>PROFILE 1007</td>
<td>≥2nd line</td>
<td>III</td>
<td>173</td>
<td>65</td>
<td>7.7</td>
</tr>
<tr>
<td></td>
<td>PROFILE 1014</td>
<td>1st line</td>
<td>III</td>
<td>172</td>
<td>74</td>
<td>10.2</td>
</tr>
<tr>
<td>Alectinib (RO5424802)</td>
<td>AF-001JP*</td>
<td>≥2nd line</td>
<td>I/II</td>
<td>43</td>
<td>93.5</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>AF-002JG</td>
<td>≥2nd line</td>
<td>I/II</td>
<td>44</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>NP28761</td>
<td>≥2nd line</td>
<td>II</td>
<td>69</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>NP28673</td>
<td>≥2nd line</td>
<td>II</td>
<td>122</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>J-ALEX*</td>
<td>1st line</td>
<td>III</td>
<td>103</td>
<td>91.6</td>
<td>NR</td>
</tr>
<tr>
<td>Ceritinib (LDK378)</td>
<td>ASCEND-1</td>
<td>≥2nd line</td>
<td>I</td>
<td>246</td>
<td>60/83 [72]</td>
<td>18.4</td>
</tr>
<tr>
<td></td>
<td>ASCEND-2</td>
<td>≥2nd line</td>
<td>II</td>
<td>140</td>
<td>–</td>
<td>–</td>
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<tr>
<td></td>
<td>ASCEND-3</td>
<td>≥2nd line</td>
<td>II</td>
<td>124</td>
<td>63.7</td>
<td>11.1</td>
</tr>
<tr>
<td>Brigatinib (AP26113)</td>
<td>NCT01449461</td>
<td>≥2nd line</td>
<td>I/II</td>
<td>65</td>
<td>7/7 [100]</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>ALTA**</td>
<td>≥2nd line</td>
<td>II</td>
<td>222</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Lorlatinib (PF-06463922)</td>
<td>NCT01970865</td>
<td>≥2nd line</td>
<td>I/II</td>
<td>41</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Entrectinib (RXDX-101)</td>
<td>NTC02097810</td>
<td>≥2nd line</td>
<td>I/II</td>
<td>7</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

*, Japanese population; preliminary data; **, randomized trial of brigatinib Arm A: 90 mg, Arm B: 180 mg; ***, 3 cohorts, 1 (with ALK and ROS1 alterations) allowed inclusion with progression under previous 2 ALK inhibitors; +, cohort of ALK and ROS1 rearrangement, allowing the inclusion with progression under previous 2 ALK inhibitors; NA, not available; NR, not reached.
Based on the initial phase I/II studies and the two phase II studies published by Shaw et al. and Ou et al., alectinib received conditional approval by the FDA in December 2015, for the treatment of advanced ALK-positive NSCLC resistant to crizotinib, while EMA approval is pending.

Alectinib also recently demonstrated significantly prolonged PFS and a favorable toxicity profile in the first-line setting. In this phase III study, alectinib was compared to crizotinib in a Japanese population (J-ALEX IA; JapicCTI-132316) (10). Median PFS was not reached in the alectinib arm compared to the 10.2 months in the crizotinib arm (Table 1). The safety profile and tolerability were, as expected, good.

**Next-generation ALK inhibitors: maintaining ALK inhibition is an effective strategy**

Although the first-generation ALK inhibitor crizotinib is active with 57–74% ORR, most patients progress within the first year, with a median duration of response of 11.3 months, the CNS being the most frequent site of progression (18). This has led to the development of next-generation inhibitors, highly potent and selective against ALK-positive disease, including CNS involvement. The second-generation ALK inhibitors include the aforementioned alectinib as well as ceritinib, while other inhibitors are currently in early clinical research.

Ceritinib is another oral second-generation ALK inhibitor with FDA approval, with a parallel development program to alectinib. According to data from the recently published, ASCEND-1, ASCEND-2, and ASCEND-3 phase I-II trials, ceritinib revealed activity and durable responses with manageable toxicity in ALK-positive patients, including those with CNS metastasis (Table 1).

Although data from phase II studies with alectinib or ceritinib are available, to date there are no advanced data from randomized clinical trials directly comparing the ALK inhibitors, with the only available results being the preliminary outcome of the J-ALEX phase III study, comparing alectinib vs. crizotinib in the first-line setting, reported at the 2016 American Society of Clinical Oncology (ASCO) meeting (10). In the discussion of Shaw et al., an indirect comparison is established between alectinib and ceritinib in relation to the ORRs of 48% and 38%, respectively, suggesting outcomes slightly higher with alectinib. However, these comparisons should be taken with caution, given the different patient cohorts and small patient numbers and early stage of development.

Interestingly, Tans et al., published an adjusted comparison study from separate clinical trials, between ceritinib and crizotinib in the first-line setting in ALK-positive previously-treated patients, with external controls (19). Ceritinib was associated with longer OS (1-year OS was 83% vs. 66% with crizotinib) and median PFS (13.8 vs. 8.3 months), with no difference in response.

A number of other next-generation ALK inhibitors are currently in development. Brigatinib is a second-generation ALK inhibitor with dual inhibition against ALK and EGFR (14), lorlatinib is a highly potent, reversible, ATP-competitive third-generation inhibitor of ALK and ROS1 (16), and entrectinib is a highly active ALK, ROS1 and NTRK1-3 inhibitor (17). All three have shown promising activity, including in intracranial disease, in preclinical models and early clinical studies.

In summary, next-generation inhibitors, such as alectinib, are typically characterized by high clinical activity, with ORRs of 39% to 69% and median PFS between 6 and 12 months, in ALK-positive patients progressing under crizotinib (Table 1). These finding are strong arguments consolidating the maintenance of selective ALK inhibition in a population progressing under crizotinib, as part of the therapeutic arsenal in ALK-positive patients.

**Crizotinib resistance: selecting ALK inhibitors according to molecular profile**

Over the last few years, characterization of the crizotinib-resistant ALK-positive population has improved with the identification of resistance mechanisms, with the acquisition of mutations within the ALK tyrosine kinase domain accounting for approximately 30% of cases. The most common are “the gatekeeper” ALK L1196M and the ALKG1269A mutations. Other known mechanisms include ALK amplifications and bypass signaling pathways (20). One limitation noted by Shaw et al. in their study was the absence of the identification of secondary mutations, due to non-mandatory tumor biopsy after progression under crizotinib. This is key data with potentially important molecular evidence to orientate the optimal treatment sequence.

The new-generation ALK inhibitors have a very selective profile against ALK, and favorable sensitivity for several mutations. In preliminary studies, alectinib and ceritinib had similar inhibition profiles for specific mutations, including the sensitive L1196M mutation and the resistant G1202R mutation. However, in most cases the susceptibility
spectrum is different, supporting selection of a subsequent ALK inhibitor based on the subtype of resistance mutation. Novel third-generation ALK inhibitors, such as lorlatinib, have a wide range of activity in comparison with second-generation agents. Recently, p-glycoprotein (P-gp) overexpression was proposed as a crizotinib and ceritinib-resistance mechanism, but not for alectinib or lorlatinib (21). In this study, resistance to ceritinib was reversed using a P-gp inhibitor associated with the ALK inhibitor.

The multiple ongoing studies will help uncover the real impact of the resistance mutational status in the selection of suitable therapy after progression under crizotinib.

CNS involvement: improving the outcome

The CNS is a major and very common site of metastasis in advanced ALK-rearranged lung cancer patients, with up to 30% having brain metastasis at diagnosis. Although most patients experience clinical benefit with early objective response with crizotinib, up to 60% progress with CNS involvement, the most common site (18). One of the strongest arguments explaining this, is that crizotinib has poor penetration through the blood-brain barrier.

The next-generation ALK inhibitors have been developed in response to this, improving activity in CNS disease by increasing their capacity to penetrate the CNS. In the study reported by Shaw et al., efficacy in CNS disease was a secondary objective. Of the 52 patients with CNS involvement at baseline (60%), only 16 had measurable disease. The CNS ORR was 75% (four complete and eight partial responses), and 40% including non-measurable disease. CNS duration of response was 11.1 months (95% CI, 10.8-not reached). The 17 patients receiving previous radiation therapy had a 67% ORR (10 complete responses). These findings are notable, considering that most of the patients were treated with alectinib in third-line, and also suggest intracranial activity independent of radiotherapy. Alectinib showed an equally impressive 57% intracranial ORR in the global phase II study (9), while ceritinib had a 45% ORR in CNS disease in the phase II ASCEND-2 (12). In addition, while the inclusion of patients with meningeal carcinomatosis was allowed, none were included. Although meningeal carcinomatosis treated with next-generation ALK inhibitors has been reported, solid evidence of management and response in this population is lacking (22).

In conclusion, these findings provide preliminary support to approach the challenge of CNS disease in ALK-positive lung cancer patients, with new-generation inhibitors as part of the therapeutic arsenal. The therapeutic algorithm in the CNS is changing, with a need to identify candidates for local treatment (few brain metastasis with controlled extracranial disease) or who should be switched to second-generation inhibitors (multiple brain metastasis or progressing extracranial disease) (23), such as alectinib, which are highly active in intracranial disease.

Toxicity profile: taking safety into consideration

Shaw et al. (4) showed alectinib has a favorable safety profile, coherent with previous reports. Most adverse events were grade 1–2, the most frequent being constipation (36%), fatigue (33%), peripheral edema (25%) and myalgia (21%). Grade 3–4 events were mainly asymptomatic laboratory abnormalities: increased creatinine phosphokinase (8%), alanine aminotransferase (6%) and alanine aminotransferase (5%), which were manageable with dose adjustment. Only two patients (2%) discontinued treatment for adverse events, both for grade 3 liver profile abnormalities, and 16% required dose reduction. Two deaths were reported, one due to hemorrhage in a patient on anticoagulant therapy, which the investigator considered related to the study treatment. These findings are globally comparable to the second phase II global study (9).

The ceritinib profile is, in contrast, quite different, but is also manageable (11-13). The most common all-grade toxicity was gastrointestinal, mainly diarrhea and nausea, reported in approximately 80% of patients. The most common grade 3–4 events were laboratory liver abnormalities. In ASCEND-2, serious adverse events were reported in 17% of patients and dose interruptions in 76%. For brigatinib, the most common toxicities were also gastrointestinal, along with pneumonitis-like pulmonary events reported in around 8% of patients. As for lorlatinib, hypercholesterolemia was the most frequent event, while CNS events and peripheral neuropathy were also reported.

Overall, alectinib and the other next-generation inhibitors have demonstrated activity associated with good safety and favorable toxicity profiles.

ALK administration: should the optimal inhibitor be given first or subsequently?

In the current scenario, crizotinib might be viewed as the weaker ALK inhibitor with poor control of CNS involvement. In contrast, a recently reported interesting case described an impressive response in a patient harboring...
a crizotinib-resistant mutation following re-challenge with crizotinib after lorlatinib (24), suggesting that crizotinib can overcome resistance mutations to third-generation ALK inhibitors, and in this scenario, should stay in the game.

The second-generation ALK inhibitors have reported clear survival benefits in both crizotinib-naive, as well as resistant patients. However, the magnitude of benefit differs between the two populations. While alectinib and ceritinib in crizotinib-naive patients have shown response rates around 70% to 90% and PFS exceeding 11 months, in crizotinib-resistant patients, results are less impressive with response rates below 50% and median PFS around 6 to 8 months, emphasizing the impact of previous ALK inhibitors on the efficacy of subsequent inhibitors (Table 1).

On one hand, efficacy in crizotinib-naive patients has been the main argument for the clinical development of alectinib and ceritinib in first-line versus crizotinib. In the PROFILE 1014 study with crizotinib versus platinum-based chemotherapy as front-line therapy, crizotinib showed an ORR of 74% and median PFS of 10.2 months (8). The recent results from the J-ALEX study showed that alectinib improved these outcomes, with a response rate of more than 90% and median PFS not yet reached (Table 1).

On the other hand, there is still no evidence as to whether the treatment with a next-generation ALK inhibitor and sequential crizotinib is better than crizotinib and sequential alectinib or ceritinib. The preliminary results from J-ALEX are impressive but are yet to be confirmed. These and the upcoming results from the global ALEX study (NCT02075840) will be critical in contributing to defining the optimal sequence of ALK inhibitors. A key unanswered question to be addressed is whether there is need for new clinical trials to define the appropriate order for each inhibitor, including crizotinib.

Conclusions

Alectinib is a second-generation ALK inhibitor, which is effective and well-tolerated in ALK-positive NSCLC patients, demonstrating high activity in CNS disease. Along with ceritinib, they are currently the standard treatment in crizotinib-resistant patients. It is still unclear whether OS will be increased by the sequence of administration of ALK inhibitors, from first to last generation, or if the ‘strongest’ inhibitor should be given upfront. The role of molecular alterations in guiding this sequence, as well as of local treatments is also unclear. The toxicity profile will be an important factor when selecting the optimal ALK inhibitor.

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Footnote

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References

8. Camidge DR, Bang YJ, Kwak EL, et al. Activity and safety of crizotinib in patients with ALK-positive non-small-cell...
Mezquita and Besse. Sequencing ALK inhibitors: alectinib in crizotinib-resistant patients


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