Editorial

The J-ALEX trial—is frontline alectinib a new standard of care?

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In patients with metastatic anaplastic lymphoma kinase (ALK) positive non-small-cell lung cancer (NSCLC), the options for therapy in both the first and second line setting are becoming increasingly complex. In the United States, both crizotinib and ceritinib are Food and Drug Administration (FDA) approved for use in the upfront setting, with ceritinib, alectinib, and most recently brigatinib, all having received FDA approval in the second line setting after progression of disease on crizotinib (1). Several other ALK tyrosine kinase inhibitors (TKIs) are under investigation, with lorlatinib having recently received breakthrough FDA designation as a second line treatment and ensartinib also showing significant efficacy in ALK TKI pre-treated patients (2,3).

In the frontline phase III trials PROFILE 1014 with crizotinib and ASCEND-4 with ceritinib, these agents were compared directly to platinum doublet chemotherapy in treatment naïve ALK positive advanced NSCLC patients. Both trials met the primary endpoint of improved progression-free survival (PFS) over standard chemotherapy (4,5). Crizotinib 250 mg twice daily compared to cisplatin or carboplatin plus pemetrexed showed a PFS benefit of 10.9 versus 7 months [hazard ratio (HR) 0.45, 95% confidence interval (CI) 0.35–0.60, P<0.0001] and an objective response rate (ORR) of 74% versus 45% with chemotherapy (4). In ASCEND-4, ceritinib at 750 mg daily resulted in a median PFS of 16.6 months compared to 8.1 months with four cycles of cisplatin or carboplatin plus pemetrexed followed by pemetrexed maintenance (HR 0.55, 95% CI 0.42–0.73). Ceritinib had an ORR of 72.5% versus 26.7% with chemotherapy (5). Crizotinib subsequently gained approval as the frontline agent of choice in November 2013, and ceritinib was approved as an upfront option by the FDA in May 2017.

In contrast to the study design of the above trials using chemotherapy as a comparator, the J-ALEX trial was the first randomized phase III trial to directly compare two ALK inhibitors (alectinib versus crizotinib) in the first line setting (6). Alectinib is a known potent second generation ALK inhibitor with significant central nervous system (CNS) penetration as well as activity against several known resistance mutations to crizotinib (7). In a phase I/II Japanese single arm trial of chemotherapy pre-treated, but ALK inhibitor naïve, ALK positive NSCLC patients, alectinib showed an ORR of 93.5% with a median PFS that was not reached at the time of data analysis (8). This impressive response and prolonged PFS set the stage for the larger phase III J-ALEX trial, whose study design and results herein will be discussed.

The J-ALEX trial was an open-label phase III multicenter trial conducted exclusively in Japan at 41 study sites. Between November 2013 to August 2015, 207 Japanese patients with stage IIIB/IV ALK positive NSCLC, who had previously received 0–1 lines of chemotherapy, but no prior ALK TKI, were randomized to alectinib 300 mg twice daily or crizotinib 250 mg twice daily. Patients had to be at least 20 years of age with ALK positivity confirmed by immunohistochemistry (IHC) and fluorescence in-situ hybridization (FISH), or real time polymerase chain reaction (RT-PCR) if inconclusive by the former tests.

Patients needed to have at least one measurable lesion and response was measured using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Patients were excluded if they previously received an ALK inhibitor, had current or previous radiographic evidence of interstitial lung disease, had symptomatic brain or leptomeningeal metastasis, or any type of effusion requiring drainage (6).

Patients were randomized 1:1 to receive alectinib or crizotinib, with further stratification according to performance status, disease stage, or treatment line. Patient characteristics were overall well balanced, with one exception being that brain metastasis were present in 27.9% of patients in the crizotinib group versus 13.6% in the alectinib group. Interestingly, about one third of patients in each arm had received one line of chemotherapy before entry. The primary end point was PFS with secondary endpoints being overall survival (OS), ORR, duration of response (DOR), time to response (TTR), health related quality of life, safety, and time to onset of brain metastasis if none at baseline, or time to progression of brain metastasis if present at baseline (6).

At the time of planned interim analysis, median PFS was not reached in the alectinib arm (20.3 months at the low end of the CI) and was 10.2 months in the crizotinib arm (HR 0.34, 99.7% CI 0.17–0.70). The ORR of alectinib in the intention to treat population was 85.4% (95% CI 78.6–92.3) versus 70.2% (95% CI 61.4–79) in the crizotinib arm. In the subgroup of patients with brain metastasis, there was also a strikingly improved response to alectinib (HR 0.08, 95% CI 0.01–0.61). For patients with brain metastatic lesions at baseline, the HR for the time to progression of a brain metastatic lesion or death was 0.16 (95% CI 0.02–1.28), and for patients without brain metastatic lesions at baseline, the HR for the time to onset of a brain metastatic lesion or death was 0.41 (95% CI 0.17–1.01). All grade adverse events favored alectinib with the most common side effects in the alectinib arm being constipation (35%), nasopharyngitis (20.4%), and dysgeusia (18.4%). In the crizotinib arm, nausea (74%), diarrhea (73.1%), vomiting (57.5%), visual disturbances (54.8%), dysgeusia (51.9%), constipation (44.2%), and transaminase elevations (31%) were all significantly increased. In terms of OS, the data remains immature at present. Based on these results, the authors concluded that alectinib should become the new standard of care as first line treatment for ALK positive advanced NSCLC (6).

The results of this study are certainly compelling. With the major study drawbacks being that it was (I) conducted exclusively in Japanese patients; (II) there was a relatively large percentage of patients having already been exposed to chemotherapy; and (III) there was a significantly larger percentage of patients with brain metastasis in the crizotinib arm compared to the alectinib arm, overall, the study was well done, and the latter two factors did not seem to negatively impact results. The most important question that emerged after initial results of J-ALEX were presented at ASCO in 2016 was should alectinib replace crizotinib in the upfront setting? No survival data had been reported and experts appropriately debated whether these results could be applied to a broader population. In Japan, the impressive PFS benefit combined with a more tolerable side effect profile and improved CNS penetration, led to Japanese approval of alectinib as a first line choice. Though, for the rest of the world, there remained some skepticism with the highly anticipated results of the ALEX trial awaited to see if results of J-ALEX could be confirmed on a global scale.

The wait for the ALEX results was only a year with J-ALEX presented at ASCO 2016 and ALEX at ASCO 2017 with simultaneous publication in June 2017. The ALEX trial was an international phase III trial launched across 161 locations in 31 countries, with 303 treatment naïve ALK positive metastatic NSCLC patients randomized to alectinib 600 mg twice daily or crizotinib 250 mg twice daily, with PFS again being the primary endpoint (9). Secondary endpoints included time to CNS progression, ORR, DOR, OS, quality of life, and safety. After a follow up of 17.6 months in the crizotinib arm and 18.6 months in the alectinib arm, median PFS was not reached in the alectinib arm versus 11.1 months with crizotinib (HR 0.47, 95% CI 0.34–0.67, P<0.001). The effect was seen across nearly all subgroups with the exception of smokers and patients with an ECOG of 2, though these represented small numbers of patients. Time to CNS progression was also significantly longer with alectinib, with a 12-month incidence rate of CNS progression of 9.4% (95% CI 5.4–14.7) with alectinib versus 41.4% (95% CI 33.2–49.4) in the crizotinib arm. Among those patients with measurable CNS metastasis at baseline, 81% (95% CI 58–95) had a response in the alectinib arm versus 50% (95% CI 28–72) in the crizotinib arm, with 38% in the alectinib arm having achieved a complete response. ORR was 82.9% (95% CI 76–88.5) in the alectinib arm versus 75.5% (95% CI 67.8–82.1) in the crizotinib arm with 41% patients in the alectinib arm experiencing grade 3–5 adverse events versus 50% in the crizotinib arm. Median OS data at the time of analysis was immature but did not clearly favor either arm (9).

The trial design of ALEX differed from J-ALEX in that the study population included patients from multiple countries, the dose of alectinib used was 600 mg twice daily compared to 300 mg twice daily, and the patients were treatment naïve, whereas those in the J-ALEX trial could have received chemotherapy initially. The results of both trials nonetheless closely mirrored each other and clearly demonstrated that in the frontline setting, alectinib is superior to crizotinib in terms of PFS, ORR, CNS response, and toxicity. In J-ALEX, 300 mg twice daily compared to 600 mg twice daily in ALEX, appears to have comparable response rates and potentially lower adverse events with 26% of patients in J-ALEX experiencing at least one grade 3 or 4 adverse event versus 41% in the ALEX trial with at least a grade 3 side effect. In terms of CNS response, in J-ALEX, there were only 13.6% of patients with measurable brain lesions in the alectinib arm compared to 42% in the ALEX trial, thus despite appreciable CNS responses in both, it is difficult to draw dosage comparisons with the small CNS positive sample size in J-ALEX. Nonetheless, these data confirm the significant CNS penetration of alectinib, a further added benefit of second generation ALK inhibitors over first-in-class crizotinib.

With the success of both J-ALEX and ALEX showing superiority of alectinib over crizotinib in the frontline setting, an important question that arises is the following: Is it better to start with a second generation ALK inhibitor such as alectinib or ceritinib, or is sequential therapy with crizotinib followed by a second generation ALK inhibitor at the time of progression preferable? With OS data being immature in the J-ALEX and ALEX trials, one can hypothetically analyze PFS. If the average PFS on first line crizotinib as seen in the PROFILE 1014 trial is around 11 months and that of alectinib or ceritinib at time of progression on crizotinib is around 7–8 months (10,11), then a goal second generation frontline agent would exceed 19 months to be considered superior to the sequential approach. In both the J-ALEX and ALEX trials, alectinib at the time of analysis had not reached a median PFS, though with the low ends of the PFS CIs being 20.3 and 17.7 months in J-ALEX and ALEX respectively, the trend is certainly in excess of 19 months. The newest approved second line agent brigatinib has shown in a phase I/II trial of previously treated ALK positive NSCLC patients to result in a median PFS of 13.2 months, the first ALK TKI to show over a year PFS in at least the second line setting (12). This pushes forward even further the sequential PFS hypothetical margin if crizotinib is used upfront followed by a drug like brigatinib.

Therefore, selection of a first line agent is perhaps slightly more complex than meets the eye. Overall though, the results of J-ALEX and ALEX with upfront alectinib are convincing and reproducible, clearly showing a PFS benefit, as well as improved tolerability and CNS penetration with alectinib over crizotinib. It would be hard to imagine alectinib not being FDA approved as a first line choice and replacing crizotinib as a new standard of care. Furthermore, if the survival data is positive, alectinib will undoubtedly be the first choice ALK inhibitor in ALK positive advanced NSCLC patients. The use of ceritinib upfront remains a little less clear, and its popularity may be limited by increased GI toxicity at the standard dosing, though this can be mitigated with lower dosing and with taking the medication with food.

Without firm survival data to support one ALK inhibitor over another, it is fair to say that each patient should be approached individually with regard to therapy, with several factors being taken into account. Access to various ALK inhibitors, side effects of individual drugs, underlying comorbidities, patient preference, cost, presence of CNS metastasis, and the projected effect of sequential therapy, are all important considerations. ALK positive NSCLC treatment is also becoming more and more dictated by ALK resistance mutations, with these mutations being more common after treatment with second generation ALK inhibitors, and the G1202R mutation conferring resistance to all second generation drugs (13). Perhaps it may matter less what ALK inhibitor a patient starts on, rather than how they are sequentially managed based on their evolving tumor biology, matching a specific ALK inhibitor that demonstrates sensitivity to a specific mutation. Other resistance mechanisms play a role as well and will be considered in the subsequent therapy. This level of personalized care may ultimately be how to prolong life the longest in this subset of NSCLC patients.

In conclusion, it is incredible to think that before August 2011, chemotherapy was the only option for ALK positive NSCLC patients with advanced disease. Now, a total of four FDA approved ALK therapies exist, with more in development. In the frontline setting, crizotinib and ceritinib remain the FDA approved options, though this therapeutic landscape will shortly change in light of the aforementioned results of the J-ALEX and ALEX trials. Additionally, both brigatinib and ensartinib are currently undergoing evaluation compared to crizotinib as frontline agents, and these results may further alter the upfront

treatment algorithm (14,15). The future of treatment of ALK positive NSCLC is undoubtedly promising with multiple therapeutic options in both the frontline setting and after progression.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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