The Evolution of Frontline Therapy in *ALK*-Positive Advanced NSCLC: Which ALK TKI to Use Upfront?

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Abstract

Therapeutic options for advanced anaplastic lymphoma kinase (*ALK*)–positive non–small-cell lung cancer have changed dramatically since the 2011 approval of crizotinib. Since then, 3 additional agents have received FDA approval for use in the second-line setting after progression on crizotinib: ceritinib, alectinib, and brigatinib. Other investigational ALK inhibitors are under evaluation. As these agents represent newer-generation, more potent ALK inhibitors, interest in their use in the frontline setting has quickly grown. Here, we review frontline trials of ceritinib and alectinib, with comparisons drawn with crizotinib, the only FDA-approved frontline choice until the recent approval of ceritinib. With several new promising options, we attempt to better answer the question of which ALK tyrosine kinase inhibitor (TKI) should be favored upfront.

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Introduction

The identification of the *EML4-ALK* fusion oncogene in 2007 as a driver of pathogenesis, in the 2% to 7% of patients with non–small-cell lung cancer (NSCLC) who express it, has led to the development over the last decade of several targeted anaplastic lymphoma kinase (ALK) inhibitors.[1] The use of ALK inhibitors in advanced disease has transformed the treatment strategy of *ALK*-positive NSCLC, providing targeted therapeutic options that show significant progression-free survival (PFS) and overall survival (OS) benefit, with an impactful influence on patients and their disease course. There are currently 4 approved agents—crizotinib (Xalkori), ceritinib (Zykadia), alectinib (Alecensa), and brigatinib (Alunbrig)—with several others in active development.[2] Although crizotinib has historically represented the first-line agent of choice, it has quickly been challenged by the newer, more potent, second-generation ALK inhibitors ceritinib and alectinib, with ceritinib recently gaining FDA approval as a first-line option in May 2017. In order to best answer the question of which agent to use upfront, one must consider a variety of factors, including comparative trial data, adverse event (AE) profiles, and response rates, which will be reviewed here.

The use of crizotinib in *ALK*-positive lung cancer interestingly evolved when the drug, initially developed as a c-MET inhibitor, was in phase I development at the same time the *EML4-ALK* fusion oncogene was discovered. It was soon found that crizotinib was also a strong inhibitor of ALK phosphorylation and downstream signaling.[3] Crizotinib was first tested in a phase I trial evaluating 143 *ALK*-positive patients treated with escalating doses, reaching a recommended dose of 250 mg twice daily. Results showed an overall response rate (ORR) of 60.8% (95% CI, 52.3%-68.9%), a median duration of response (DOR) of 49.1 weeks (95% CI, 39.3-75.4 weeks), and a PFS of 9.7 months (95% CI, 7.7-12.8 months), with a well-tolerated profile.[4,5] In August 2011, crizotinib was granted accelerated approval by the FDA for treatment in patients with *ALK*-positive advanced NSCLC.

Crizotinib was later tested in 2 landmark phase III trials. In the PROFILE 1007 trial, 347 previously treated *ALK*-positive patients were randomized to either crizotinib or single-agent pemetrexed or docetaxel. At a follow-up of 1 year, crizotinib showed a statistically significant PFS benefit of 7.7 versus 3 months for single-agent chemotherapy (HR, 0.49; 95% CI, 0.37-0.64; P <.001) as well as improved ORR and DOR. Patients reported improved lung cancer symptoms and also greater global quality of life with crizotinib rather than chemotherapy. No significant difference in OS was found (20.3 vs 22.8 months; hazard ratio [HR], 1.02; 95% CI, 0.68-1.54; P = .54), likely a result of 64% crossover.[6]

With evident success in the second-line setting, crizotinib was then tested in the first-line setting in the PROFILE 1014 trial, in which 343 patients who were *ALK*-positive with no prior systemic treatment were randomized to crizotinib 250 mg twice daily or standard platinum doublet with cisplatin or carboplatin plus pemetrexed. The primary endpoint was PFS, which was met with a statistically significant benefit with crizotinib of 10.9 versus 7 months with chemotherapy (HR, 0.45; 95% CI, 0.35-0.60; P <.001). The ORR was 74% for crizotinib versus 45% for chemotherapy (P <.001), though the difference in OS was not significant (HR, 0.82; 95% CI, 0.54-1.26; P = .36), again likely due to a high crossover rate of 70% of patients. The most frequently occurring AEs in the crizotinib arm compared with chemotherapy were visual disturbances (71%), diarrhea (61%), and edema (49%). Overall, there was less permanent discontin-

uation of the drug compared with chemotherapy and a greater improvement in quality-of-life measures.[7] This trial solidified crizotinib as the standard of care in the frontline setting of metastatic *ALK*-positive NSCLC, for which it was approved in November 2013 as the first-line agent of choice.

The success of crizotinib unfortunately is ultimately tempered by the development of drug-resistance mechanisms and disease progression, which on average occur toward the end of the first year of therapy, with central nervous system (CNS) metastasis being a common site of relapsed disease. These resistance mechanisms include secondary mutations within the ALK kinase domain, most notably the "gatekeeper" substitution L1196M, followed by a G1269A mutation, amplification of the ALK fusion gene, and activation of other receptor tyrosine kinase sites such as EGFR, cKIT, and IGF-1R.[8] In contrast to EGFR tyrosine kinase inhibitor (TKI) resistance, in which approximately 50% of the time a specific mutation (T790M) develops, in ALK patients, there is significant tumor heterogeneity as well as the presence of varying point mutations that can occur at nonactive sites, with only one-third of crizotinib resistant cases being an on-target mutation.[9,10]

Newer-Generation ALK Inhibitors

Given that crizotinib targets not only ALK, but MET and ROS1, several newer-generation ALK inhibitors have subsequently been developed, with higher affinity for inhibiting ALK, auto phosphorylation, resultant downstream signaling, and improved CNS penetration. These include ceritinib, alectinib, and brigatinib, all of which are FDA-approved for treatment after progression on or intolerance to crizotinib, with ceritinib also approved in the upfront setting. Other investigational agents include lorlatinib and ensartinib, with lorlatinib having achieved a breakthrough FDA designation as a second-line agent.[11,12] To further add to the complexity of ALK resistance, there are also differing activities of ALK inhibitors across *ALK* mutations, with varying selectivity profiles, making the understanding of the mechanism of resistance important to choosing an effective therapy.

The potency of ceritinib, alectinib, and brigatinib, and their demonstrated efficacy as second-line ALK inhibitors after progression on crizotinib, were shown in early phase I/II clinical trials, which led to approvals and also to interest in their use as first-line agents.[13-15] In the ASCEND-4 trial, 376 treatment-naïve stage IIIB/IV *ALK*-positive NSCLC patients were randomized to 750 mg daily of ceritinib or 4 cycles of platinum-based chemotherapy with cisplatin or carboplatin plus pemetrexed followed by pemetrexed maintenance. Crossover to the ceritinib arm was allowed if patients progressed on chemotherapy. *ALK* rearrangement was determined by immunohistochemistry. The primary endpoint was PFS, with secondary endpoints of ORR, DOR, OS, and intracranial response.[16]

The results showed a median PFS of 16.6 months in the ceritinib group versus 8.1 months in the chemotherapy arm (HR, 0.55; 95% CI, 0.42-0.73; P = .00001). This PFS benefit was observed in both patients with and without brain metastasis, with those without brain metastasis sustaining an impressive median PFS of 26.3 months versus 8.3 months in the chemotherapy group (HR, 0.48; 95% CI, 0.33-0.69). The ORR was also significantly improved for ceritinib (72.5% vs 26.7%) as well as the DOR (66.4 weeks vs 26.9 weeks). The OS data at the time of analysis were immature and did not cross the efficacy-stopping boundary, though it was not reached in the ceritinib group and was 26.2 months in the chemotherapy group (HR, 0.73; 95% CI, 0.50-1.08; P = .056). With regard to toxicity, notable AEs that were higher in the ceritinib arm compared with chemotherapy were diarrhea, nausea, and vomiting, as well as elevation in aminotransferases. Eighty percent of patients in the ceritinib group versus 45% in the chemotherapy group required dose adjustments or interruption of therapy, primarily as a result of gastrointestinal (GI) toxicity or liver function abnormalities. Five percent of patients discontinued therapy in the ceritinib group. Lung cancer–specific symptoms as evaluated by questionnaire were significantly improved for those randomized to the ceritinib arm versus chemotherapy arm.[16]

The study design of ASCEND-4 closely mirrored that of the PROFILE 1014 study in terms of the comparator chemotherapy arm, with similar results of witnessed control-arm PFS between the trials. No new AEs using a more potent ALK inhibitor were observed, although GI toxicity with ceritinib was an issue for a significant number of patients, requiring dose reductions. Data have been reported that decreasing the dose of ceritinib to 450 mg daily and taking with food may mitigate many of the GI toxicities seen with 750 mg daily.[17] The convincingly positive results of the ASCEND-4 trial across all subgroups led to the recent frontline FDA approval of ceritinib. The updated National Comprehensive Cancer Network NSCLC guidelines now include ceritinib alongside crizotinib as a category 1 option in the frontline setting in *ALK*-positive metastatic disease.[18]

J-ALEX

The phase III J-ALEX trial was the first trial with data comparing 2 ALK inhibitors in the first-line setting. Conducted exclusively in Japan, this trial randomized 207 Japanese patients with stage IIIB/IV *ALK*-positive NSCLC, previously given 0 to 1 lines of chemotherapy, but ALK TKI naïve, to alectinib 300 mg twice daily or crizotinib 250 mg twice daily. The primary endpoint was PFS with secondary endpoints of OS, ORR, DOR, time to onset of CNS lesions in patients without any at baseline, time to progression of CNS lesions in those with lesions present at baseline, and quality of life. At the time of analysis, median PFS was not reached in the alectinib arm (20.3 months at the low end of the confidence interval) and was 10.2 months in the crizotinib arm (HR, 0.34; 99.7% CI, 0.17-0.70; P <.0001). The ORR of alectinib was 85.4% (95% CI, 78.6%-92.3%) versus 70.2%

(95% CI, 61.4%-79%) in the crizotinib arm. There was also an improved response to alectinib in the subgroup of patients with brain metastasis (HR, 0.08; 95% CI, 0.01-0.61). AEs of any grade favored alectinib, with the most common being constipation in the alectinib arm. In patients randomized to crizotinib, diarrhea, nausea, vomiting, visual disturbances, and transaminase elevations were significantly witnessed. No AEs resulting in a fatal outcome occurred. Survival data remain immature at present with only 9 events reported between the 2 groups.[19]

ALEX

With the J-ALEX trial conducted exclusively in Japan, the international ALEX trial was launched to assess whether these findings could be replicated on a global scale. Spanning 31 countries, the ALEX trial enrolled 303 treatment-naïve *ALK*-positive metastatic patients with NSCLC who were randomized to alectinib 600 mg twice daily or crizotinib 250 mg twice daily, with PFS as the primary endpoint. Secondary endpoints included OS, ORR, DOR, time to CNS progression, quality of life, and safety.[20] In addition to being an international study, the ALEX trial design differed from J-ALEX in that the dose of alectinib used was 600 mg twice daily compared with 300 mg twice daily, and the patients were treatment-naïve, whereas about one-third of patients in the J-ALEX trial had previously received 1 line of chemotherapy.

The results, like those of J-ALEX, were again compelling. Median PFS was not reached in the alectinib arm (17.7 months at the low end of the confidence interval) versus 11.1 months in the crizotinib arm (HR, 0.47; 95% CI, 0.34-0.67; P <.001). Nearly all subgroups benefited, with the exception of smokers and patients with an Eastern Cooperative Oncology Group score of 2, although these patients were represented in small numbers. 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. Of those patients without brain metastasis at baseline, time to CNS progression was significantly longer with alectinib, with a 12-month incidence rate of 9.4% (95% CI, 5.4%-14.7%) versus 41.4% (95% CI, 33.2%-49.4%) in the crizotinib cohort. Of those patients with measurable CNS metastasis at baseline, results showed an 81% (95% CI, 58%-95%) response rate in the alectinib arm versus 50% (95% CI, 28%-72%) in the crizotinib arm. An impressive 38% of patients in the alectinib arm achieved a complete response. In terms of grade 3 to 5 AEs, 41% of patients in the alectinib arm experienced such an event versus 50% in the crizotinib arm, with fewer rates of AEs leading to dose reduction, interruption, or discontinuation in those treated with alectinib. The median OS data are immature at present.[20]

Integrating the Results

So how can a clinician integrate the results of the PROFILE 1014, ASCEND-4, J-ALEX, and ALEX trials into deciding which ALK agent should be favored upfront? Crizotinib, ceritinib, and alectinib all show remarkable frontline overall response rates of 74%, 73%, and 80% to 85%, respectively.[7,16,19,20] Refer to the **Table** for trial comparisons. When taking into account comparative toxicities, the above trials demonstrate that although the spectrum of AEs is similar, alectinib seems to be better tolerated overall than are crizotinib or ceritinib, with less GI toxicity, nearly no visual disturbances, and less transaminase elevation. Increased peripheral edema and skin rash can be seen, however, as well as some generally mild myositis.[19]

With regard to CNS penetration, even with good control of systemic disease, about 40% to 50% of patients on crizotinib will develop brain metastases. Nonetheless, crizotinib still has modest penetration in the CNS. As evidenced by the PROFILE 1014 trial, of the 23% of patients with brain metastases, there was a nonsignificant trend toward improved time for intracranial progression in the crizotinib versus chemotherapy arm (HR, 0.60). At 24 weeks of follow-up in the patients with previously treated brain metastases, 56% were controlled in those receiving crizotinib versus 25% in those receiving chemotherapy.[7] The second-generation ALK inhibitors, however, have more robust CNS activity. In the ASCEND-4 trial, in patients with at least 1 brain metastasis, ceritinib had a 72.7% intracranial ORR versus 27.3% for chemotherapy.[16] In both the J-ALEX and ALEX studies, alectinib was significantly favored over crizotinib in the subset of patients with brain metastases.[19,20] It would thus seem reasonable that in patients who present with significant brain metastasis, an upfront second-generation agent should be considered over crizotinib. The survival data, when mature, will provide a more definitive answer.

TABLE. Frontline ALK TKI Trials.

Trial	Treatment	Number of Patients (N)	Median PFS (months)	ORR (%)	Median OS (months)
PROFILE 1014	Crizotinib 250 mg BID vs Cisplatin/carboplatin + pemetrexed	343	10.9 vs 7 (P<.001)	74 vs 45	No difference (P = .36)
ASCEND-4	Ceritinib 750 mg daily vs Cisplatin/carboplatin + pemetrexed	376	16.6 vs 8.1 (P<.00001)	72.5 vs 26.7	NR vs 26.2 (P = .056)
J-ALEX	Alectinib 300 mg BID vs Crizotinib 250 mg BID	207	NR vs 10.2 (P<.0001)	85.4 vs 70.2	Data immature
ALEX	Alectinib 600 mg BID vs Crizotinib 250 mg BID	303	NR vs 11.1 (P<.001)	82.9 vs 75.5	Data immature

BID, twice daily; NR, not reached; PFS, progression-free survival; ORR, overall response rate; OS, overall survival

Certainly based on the head-to-head comparison posed in both J-ALEX and ALEX, alectinib demonstrated an improved PFS, ORR, and CNS response over crizotinib in the front line, and its toxicity profile was preferable. Even without mature OS data, it would be hard to picture alectinib not being granted FDA approval as a first-line option in the near future. It now represents a "preferred" frontline agent compared with crizotinib and ceritinib in the most recently updated NCCN guidelines.[18] Both the 300 mg twice-daily dose as used in J-ALEX and the 600 mg twice-daily dose used in ALEX appear highly effective, with a response rate of more than 80% and median PFS that is yet to be reached. Like most drugs, higher dosages can come with higher toxicity, and alectinib at 300 mg twice daily appeared to be better tolerated than 600 mg twice daily. Twenty six percent of patients in J-ALEX experienced at least 1 grade 3 or 4 AE on alectinib 300 mg twice daily compared with 41% with at least a grade 3 AE on alectinib 600 mg twice daily in the ALEX trial. Despite encouraging CNS responses in both J-ALEX and ALEX, it is difficult to compare the 2 trials in this regard, because J-ALEX had significantly fewer patients with measurable brain lesions in comparison with ALEX (13.6% vs 42%). At present, alectinib 600 mg twice daily remains the recommended dose in the United States when used as a second-line agent.

With alectinib showing overall superiority to crizotinib, and being on pace to replace crizotinib as a new standard of care in the frontline setting, an important question arises: Is frontline alectinib better than sequential therapy with crizotinib followed by alectinib or another second-generation ALK TKI? One can conjecture that when assessing PFS, the answer depends on which drugs are used. Although PFS comparisons between trials should always be taken with caution, given that the low end of the confidence interval in ALEX with regard to PFS was 17.7 months with alectinib, this already is trending toward exceeding the median PFS of upfront crizotinib followed by alectinib or ceritinib in the second line, which is around 10 to 11 months for crizotinib[7] plus 7 to 8 months with alectinib or ceritinib.[21,22] However, this calculation changes if the recently approved brigatinib is used as a sequential therapy to crizotinib, as it was the first ALK TKI to show more than a 12-month PFS benefit in the second-line setting.[15] Therefore, it can be said that the verdict is still out on sequential therapy, regarding first-in-class crizotinib versus upfront use of the newer-generation ALK TKIs. Time and more mature survival data will likely settle this.

Conclusions

In sum, the current landscape of first-line treatment for *ALK*-positive stage IIIB/IV disease is quickly, excitingly evolving. Several ALK TKIs are emerging as effective options, with crizotinib and ceritinib already FDA-approved in the frontline setting, and alectinib undoubtedly soon to follow. In addition, phase III trials of brigatinib versus crizotinib as well as ensartinib versus crizotinib in ALK treatment-naïve patients are underway, and their results are likely to eventually add to the pot of upfront therapies.[23,24] The decision of which ALK inhibitor to use first has become complex, and without yet firm survival data to support 1 agent over another, it is fair to say that clinician decisions will vary, and drug tolerance, resistance patterns, quality-of-life measures, patient preference, accessibility, and cost should be carefully assessed and evaluated for each individual patient. Based on available data, alectinib appears to be the most promising agent of the group, and time will tell if it eventually wins out. One thing is for sure: There is indeed much hope for patients with advanced *ALK*-positive NSCLC who, before August 2011, were left with chemotherapy as their sole treatment choice. Now, just about 6 years later, they can take advantage of a list of effective ALK inhibitors that, as time progresses, only appears to be growing.

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