Editorial

Recent studies move closer to answering questions about sequential therapy for anaplastic lymphoma kinase-rearranged non-small cell lung cancer

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Anaplastic lymphoma kinase (*ALK*) fusion gene resulting from gene rearrangement was first identified in anaplastic large-cell lymphoma (ALCL) and is characterized by the fusion of nucleophosmin (NPM) and *ALK* genes (1). Subsequently, this type of fusion gene was described for the first time in lung cancer by Soda *et al*. through cDNA expression screening of surgically resected specimens from lung adenocarcinoma patients (2). Unlike the fusion gene in ALCL, this gene results from a fusion between echinoderm microtubule-associated protein-like 4 (*EML4*) and *ALK*. The two genes are positioned in opposite directions on the short arm of chromosome 2, and the inversion of this region orients the genes in the same direction leading to the formation of the *EML4-ALK* fusion cancer gene (2). Although *ALK*, a receptor tyrosine kinase, dimerizes and becomes activated by ligand binding, the gene rearrangement has been shown to cause *ALK* binding to the coiled-coil domain leading to its constitutive dimerization and activation without ligand binding (3). A subsequent study showed that genetically modified mice with lung-specific expression of *EML4-ALK* develop lung adenocarcinoma demonstrating that *EML4-ALK* fusion gene is a potent cancer driver gene, and since then it has been the subject of global attention in the field of oncology (4). About 3–7% of non-small cell lung cancer is thought to be positive for this fusion gene, and many of the patients are young non-smokers with adenocarcinoma and with wild-type *EGFR* and *KRAS* genes (5-8). To date several drugs that target this fusion gene have been developed (9). Currently, one first generation and two second generation *ALK* inhibitors are available.

Crizotinib was the first approved first generation *ALK* inhibitor. Initially, crizotinib was used as a *MET* inhibitor in a phase I clinical trial (PROFILE1001) for solid tumors, but because it was found to exhibit inhibitory activity against multiple kinases including *ALK*, the clinical trial was expanded to include patients with *ALK* fusion gene-positive lung cancer (10). The clinical outcome was good with a final overall response rate (ORR) of 60.8% and a progression-free survival (PFS) of 9.7 months (10). The results of a subsequent phase II clinical trial provided similar ORR and PFS outcomes (PROFILE1005) (11). Based on these favorable clinical outcomes, crizotinib was granted an accelerated approval by the Food and Drug Administration (FDA) in 2011 for clinical use, just 4 years after its initial report. Crizotinib has been shown to be significantly effective for the treatment of patients with *ALK* fusion gene-positive lung cancer and it is presently one of the first-line treatments for this type of cancer. However, therapeutic problems such as progressive disease, relapse due to

acquired resistance and brain metastases have emerged (12-14). Later, a phase III trial (PROFILE1007) was conducted in 347 *ALK* fusion gene-positive non-small cell lung cancer patients who had previously undergone platinum-based chemotherapy (15). Patients were randomized to a crizotinib group or chemotherapy group (pemetrexed or docetaxel). Both PFS (7.7 *vs.* 3.0 months; HR =0.49, P<0.001) and ORR (65% *vs.* 20%; P<0.001) were superior in the crizotinib group. The median survival time (MST) was not significantly different (20.3 *vs.* 22.8 months; HR =1.02, P=0.54) between the two groups, but this lacks of survival benefit was interpreted as being due to the confounding effects of crossover (15).

Alectinib is a second generation *ALK* inhibitor with broader selectivity than crizotinib. Alectinib exhibits anti-tumor activity in the crizotinib-resistant L1196M mutation (16). A randomized, open-label, phase III trial (J-ALEX study) that directly compared alectinib and crizotinib in *ALK* inhibitor-naive patients was conducted in Japan. In February 2016, an independent data monitoring committee reviewed the clinical outcomes of a pre-planned interim analysis and recommended the early termination of the J-ALEX clinical trial because a statistically significant extension of PFS was observed in the alectinib monotherapy group (HR =0.34, P<0.0001). Based on these results, alectinib was granted the breakthrough therapy designation from FDA in September 2016, and considered as the first-line treatment for patients with *ALK*-positive non-small cell lung cancer. Ultimately, the study comprised a total of 207 patients with *ALK*-fusion gene-positive advanced/recurrent non-small cell lung cancer that were *ALK* inhibitor-naive and chemotherapy-naive or had previously received only one chemotherapy regimen (17). The hazard ratio of PFS in the alectinib monotherapy group in relation to the crizotinib monotherapy group was 0.34, indicating a statistically significant extension (P<0.0001) of PFS in the alectinib monotherapy group (17). The median PFS was 10.2 months in the crizotinib monotherapy group [95% confidence interval (CI): 8.2–12.0] but that of the alectinib monotherapy group (95% CI: 20.3– not estimated) had not been as yet reached at the time of the interim analysis (17). Currently, a global phase III trial (ALEX study) to directly compare the efficacy and safety of alectinib and crizotinib as first-line treatment is ongoing. A report at an academic conference showed that, according to an independent review committee, the disease progression or death risk decreased 50% in the alectinib group compared to the crizotinib group (HR =0.50, 95% CI: 0.36–0.70) and that the median PFS was 25.7 months in the alectinib group (95% CI: 19.9– not estimated) and 10.4 months in the crizotinib group (95% CI: 7.7–14.6).

Like alectinib, ceritinib is a second generation *ALK* inhibitor. Ceritinib exhibits broader selectivity and is a more potent *ALK* inhibitor *in vitro* than crizotinib (18). It crosses the blood brain barrier (BBB) *in vivo*, and is thought to be effective in tumors that are resistant to crizotinib (18). Ceritinib is also known to inhibit insulin-like growth factor 1 (IGF1**)** receptor in addition to *ALK* (18). An open-label phase I trial (ASCEND1) was conducted in *ALK* fusion gene-positive patients with locally advanced or metastatic cancer and with progressive disease despite standard therapy (19). The results showed a ORR of 72% in crizotinib-naive patients and 56.4% in crizotinib-treated patients (crizotinib-resistant patients) with a median PFS of 18.4 and 6.9 months, respectively (19). In a phase II clinical trial (ASCEND2) the ORR was 38.6% and the median PFS was 5.7 months in patients who had been previously treated with crizotinib (20). Ceritinib was also granted breakthrough therapy designation by the FDA in March 2013 and accelerated approval in April 2014 for the treatment of patients with *ALK*-positive non-small cell lung cancer that are intolerant to crizotinib and that have disease progression after crizotinib therapy. Subsequently, a randomized, open-label, global multicenter phase III trial (ASCEND4) was conducted to evaluate the safety and efficacy of ceritinib compared to standard cycles of chemotherapy and maintenance therapy in stage IIIB/IV *ALK*-positive advanced non-small cell lung cancer patients (21). Patients received either ceritinib 750 mg once a day orally or four cycles of pemetrexed-based standard platinum doublet chemotherapy (pemetrexed 500 mg/m^2 and cisplatin 75 mg/m^2 or carboplatin AUC 5–6) followed by pemetrexed maintenance (21). The 376 patients were randomly assigned to the ceritinib group (n=189; n=59 with brain metastasis) or chemotherapy group (n=187; n=62 with brain metastasis). The median PFS of patients receiving ceritinib as first-line treatment was 16.6 months (95% CI: 12.6–27.2). In contrast, the median PFS of patients receiving standard first-line therapy with platinum-based pemetrexed and maintenance therapy with pemetrexed was 8.1 months (95% CI: 5.8–11.1). The overall intracranial response rate (OIRR) of intracranial lesions in patients with measurable brain metastases was 57% (95% CI: 37–76; n=28) in the ceritinib group and 22% (95% CI: 9–42; n=27) in the chemotherapy group (21). Based on these clinical outcomes, the FDA broadened the indication of ceritinib in

May 26, 2017 as the first-line treatment for *ALK*-positive metastatic non-small cell lung cancer.

In a recent study, Shaw *et al.* (22) conducted a randomized open-label phase III trial of ceritinib in patients aged at least 18 years old with *ALK*-positive stage IIIB/IV non-small cell lung cancer that had received previous chemotherapy and crizotinib and that had subsequently progressive disease. Patients were randomly allocated at a ratio of 1:1 to oral ceritinib 750 mg/day (21-day cycle) or single-drug chemotherapy (pemetrexed 500 mg/m^2 or docetaxel 75 mg/m^2, every 21 days), and stratified based on performance status and on the presence or absence of brain metastases (22). Patients that discontinued chemotherapy because of disease progression crossed over to ceritinib group. The primary endpoint, PFS, was assessed every 6 weeks until 18 months and every 9 weeks. The median PFS was significantly improved by ceritinib (5.4 months, 95% CI: 4.1–6.9 months) compared to chemotherapy (1.6 months, 95% CI: 1.4–2.8 months) (HR =0.49, P<0.0001) (22). Serious adverse events were observed in 49/115 patients (43%) of the ceritinib group and in 36/113 patients (32%) of the chemotherapy group (22). Serious adverse events associated with treatment were similar between both groups. During the treatment period 13% (15/115) of patients in the ceritinib group and 4% (5/113) of patients in the chemotherapy group died. The cause of death in 13 (87%) of the 15 patients of the ceritinib group was disease progression and in 2 (13%) was an adverse event. However, none of these deaths was treatment-related according to the study investigator. All five deaths in the chemotherapy group were due to disease progression (22). These results indicate that treatment with a more potent *ALK* inhibitor provides a significant clinical benefit to patients after failure of crizotinib treatment, and that ceritinib is a more effective therapy than chemotherapy in this group of patients (22).

Based on the results from the J-ALEX and ALEX clinical trials, it can be anticipated that alectinib will be selected more often than crizotinib. However, as shown by the ASCEND5 study reported by Shaw *et al.*, there are discrepant views on what sequential therapy to follow. A retrospective study by Ito *et al.* showed that good clinical outcome can be achieved with alectinib after crizotinib (23). *ALK*-TKI may show differential responses depending on the *ALK* fusion variants (24,25). Therefore, further prospective clinical studies in a larger population that includes different ethnic groups are warranted.

More recently, on April 27, 2017, lorlatinib, a *ALK/ROS1* tyrosine kinase inhibitor was granted breakthrough therapy designation by the FDA for the treatment of patients with *ALK*-positive metastatic non-small cell lung cancer that have received prior therapy with an *ALK* inhibitor. Lorlatinib has shown anti-tumor activity in several secondary mutations including G1202R, which is a mutation that frequently occurs after therapy with *ALK* inhibitors (26,27). Lorlatinib is also a promising *ROS1* inhibitor that has shown significant efficacy in tumors with crizotinib-resistant S1986Y/F mutations (26). In addition, lorlatinib can be potentially effective in cases of brain metastasis because it can cross the blood-brain barrier and reach high concentration in the cerebrospinal fluid (28). Another new and promising *ALK* tyrosine kinase inhibitor is brigatinib. On April 28, 2017, brigatinib was approved by FDA after a short period of time for the treatment of patients with progressive or crizotinib-resistant metastatic *ALK*-positive non-small cell lung cancer. Brigatinib exhibits more potent anti-tumor activity than crizotinib and shows significant efficacy against several secondary mutations (29).

Currently, there are only three types of *ALK*-TKIs available for use in clinical practice. However, the clinical availability of lorlatinib and brigatinib is probably very close. Findings from recent prospective studies including the ASCEND5 trial and results from ongoing and upcoming studies will provide the clues to currently unanswered questions in the management of patients with *ALK*-rearranged NSCLC (22): which drug should be used first? Should another type of *ALK*-TKI or standard chemotherapy be selected for subsequent therapy? Should drug selection be based on the presence of secondary mutation or gene variant?

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Footnote

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

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