Commentary

# Clinical data and role of ceritinib a second-generation ALK tyrosine kinase inhibitor for the treatment of ALK positive non-small cell lung cancer

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Rearrangements in anaplastic lymphoma kinase (*ALK*) gene and echinoderm microtubule-associated protein-like 4 (*EML4*) gene were first described in 2007. This genomic aberration is found in about 2–8% of non-small cell lung cancer (NSCLC) patients. In patients with adenocarcinoma lacking *EGFR* and *KRAS* mutations, the prevalence of EML4-ALK translocation could be as high as 42.8% (1). In these patients, *ALK* rearrangements serve as a key and strong oncogenic driver for NSCLC and represent a critical therapeutic target susceptible to targeted ALK kinase inhibition (2,3).

Crizotinib was the first ALK tyrosine kinase inhibitor (TKI) licensed for treatment of metastatic ALK-positive NSCLC based on the randomized phase 3 trial PROFILE 1014 (4). Despite the initial treatment response of crizotinib, disease progression inevitable develops after about 10 months of therapy. Different resistance mechanisms have recently been described. One relevant mechanism of resistance is the development of mutations in *ALK*. Novel ALK TKIs have been developed to overcome these mutations. Ceritinib is an oral second-generation ALK inhibitor showing clinical activity in crizotinib-resistant ALK-positive NSCLC but also in treatment-naive ALK-positive disease. Ceritinib has first been investigated in the multicenter, open-label, phase 1 trial ASCEND-1. The initial publication of the trial included 130 patients with advanced cancers harboring genetic alterations in *ALK* (5). In a first step, 59 patients were included in the dose-escalation phase and received ceritinib in doses of 50 to 750 mg. The maximum tolerated dose of ceritinib was 750 mg once daily; dose-limiting toxic events included diarrhea, vomiting, dehydration, elevated aminotransferase levels, and hypophosphatemia. This phase was followed by an expansion phase, in which an additional 71 patients. Among 114 patients with NSCLC who received at least 400 mg of ceritinib per day, the overall response rate (ORR) was 58% [95% confidence interval (CI), 48–67]. Among 80 patients who had received crizotinib previously, the ORR was 56% (95% CI, 45–67). Responses were observed in patients with various resistance mutations in *ALK* and in patients without detectable mutations. Among patients with NSCLC who received at least 400 mg of ceritinib per day, the median progression-free survival (PFS) was 7.0 months (95% CI, 5.6–9.5). The survival rate after 1 year was 65%.

The expansion cohort of this cohort did further include more patients and updated results have recently been published in *Lancet Oncology* (6). Between January 2011 and July 2013, 255 patients were enrolled and received at least 1 dose of ceritinib 750 mg/d, of whom 246 patients had an ALK positive NSCLC. The data cut-off for this updated analysis was April 14, 2014. At a median follow-up of 11.1 months, 60% of patients had discontinued ceritinib therapy. Of 147 patients having discontinued ceritinib, 98 patients (67%) stopped therapy due to disease progression. This update analysis is of high interest as it includes a large number of ALK positive patients with and without previous therapy with other ALK TKIs. Moreover, this analysis also includes data on intracranial activity of ceritinib in patients

with treated and untreated neurologically stable brain metastases.

The updated analysis of ASCEND-1 includes 246 patients with ALK positive NSCLC. Of these patients, 163 (66%) were pretreated with another ALK TKI. Of these pretreated patients all had received crizotinib, and five patients had also received alectinib. Other ALK TKIs have not been used before. Most of the pretreated patients (91%) had progressive disease on or within 2 weeks of the last dose of the previous ALK TKI. Baseline characteristics were consistent with those reported in other ALK TKI studies (7,8), and were irrespective of previous ALK TKI therapy. Briefly, most patients were heavily pretreated. In the ALK TKI naive cohort 81% of patients have previously received one or more lines of chemotherapy. In the ALK TKI pretreated population 84% of patients have additionally received one or more lines of chemotherapy. At study entry, half of the patients had asymptomatic or controlled brain metastases and 67% of these patients have previously received brain irradiation. On the basis of investigator assessment the proportion of ALK TKI naive patients who achieved an overall response was 72% (95% CI, 61–82). The proportion for ALK TKI pretreated patients was 56% (95% CI, 49–64). Median time to response was 6.1 weeks for both cohorts and therefore corresponds to the first radiographic evaluation. In addition to responses according to RECIST criteria, most of the patients in both groups reached a certain degree of tumor reduction when comparing measurable disease at baseline and one post-baseline assessment. For ALK TKI naive patients, median duration of response (DoR) was 17.0 months [95% CI, 11.3–non-estimable (NE)] and median PFS was 18.4 months (95% CI, 11.1–NE). Patients previously treated with another ALK TKI exhibited a median DoR of 8.3 months (95% CI, 6.8–9.7) and a median PFS of 6.9 months (95% CI, 5.6–8.7). In a prespecified exploratory analysis of the overall survival (OS), the median has not yet been reached (95% CI, 19.6–NE) in the ALK TKI naive patients and was 16.7 months (95% CI, 14.8–NE) in the ALK TKI pretreated population. It is important to mention that the results of the blinded independent review committee confirmed the investigator-assessed data.

With regard to patients with brain metastases outcome in these 124 patients was similar to those of the overall patient population. A retrospective analysis of intracranial response to ceritinib included 94 patients with independently confirmed brain metastases. Based on RECIST 1.1, 36 patients (38%) of these patients had measurable intracranial lesions at baseline (8 patients ALK TKI naive and 28 pretreated patients). The majority of these patients (69%) have received previous radiotherapy to the brain. Intracranial disease control was documented in 79% (95% CI, 54–94) of ALK TKI naive patients and 65% (95% CI, 54–76) of ALK TKI pretreated patients. Intracranial response rates in patients who had previously received radiotherapy to the brain were similar to those of patients not treated with brain irradiation.

Median duration of exposure to ceritinib 750 mg daily for all 246 patients was 38.6 weeks with a median average daily dose of 664.2 mg and a median relative dose intensity of 82.8%. Overall, 181 patients (74%) had at least 1 dose interruption, and 152 patients (62%) had at least 1 dose reduction. One fifth of patients were in need of 2 dose reductions. At least one adverse event (AE) was reported for all patients in this study with 97% of patients being reported as having a study drug related AE. At least one grade 3–4 AE was reported in 81% of patients and at least one serious adverse event (SAE) was reported in 48% of patients. Treatment-related grade 3–4 AEs were reported in 51% of patients and treatment-related SAEs were reported in 12% of patients. The most common grade 3–4 AEs were gastrointestinal toxicities (diarrhea, nausea, vomiting), increased liver enzymes, increased lipase serum levels and hyperglycemia. Twenty-six patients (11%) discontinued treatment due to AEs, of which 35% were suspected to be related to ceritinib. Two on-treatment deaths were deemed to be related to study drug, one due to interstitial lung disease and the other due to multiorgan failure that occurred in the context of infection and ischemic hepatitis.

In summary, the updated report of ASCEND-1 is important as it confirms clinical activity of ceritinib in patients with *ALK* rearranged NSCLC patients that have progressed in previous therapy with crizotinib and therefore confirm the role of ceritinib as an effective second-line treatment option. Moreover, the reported activity of ceritinib in patients with brain metastases both in the brain and extracerebral is important in a population that has a high rate of intracerebral metastases.

Further trials confirmed the role of ceritinib in the setting of ALK positive NSCLC. The ASCEND-3 study was a phase II study of ceritinib in previously treated ALK TKI naive patients. Updated results have recently been presented during the ESMO congress in Copenhagen (9). This single-arm phase II study included 124 patients with ALK positive NSCLC that were ALK TKI naive and have had up to three lines of previous chemotherapy,

 

asymptomatic or neurologically stable brain metastases and a WHO performance status of 0 to 2. Patients were treated with ceritinib 750 mg daily until disease progression or unacceptable toxicity. After a median follow-up of 25.9 months 48.4% of patients were still on study drug. The ORR by independent review was 63.7% (95% CI, 54.6–72.2) and the median PFS was 18.4 months (95% CI, 10.9–26.3). The median OS as not reached at the current data cut-off. The survival rate at 24 months was 67.5% (95% CI, 58.0–75.2). A decrease in tumor burden from baseline was shown in 108/114 patients (94.7%). ORR for patients with brain metastases at baseline (n=49) was 57.1% (95% CI, 42.2–71.2) compared to 74.7% (95% CI, 63.3–84.0) for patients without brain metastases. The respective PFS rates were 10.8 months (95% CI, 7.3–16.6) and 19.6 months (95% CI, 14.5–not reached), respectively. The documented intracranial disease control rate was 76.9% (95% CI, 46.2–95.0).

The ASCEND-5 trial was a randomized open-label trial for patients with metastatic ALK positive NSCLC previously treated with crizotinib and one or two prior lines of chemotherapy regimens including a platinum-based doublet chemotherapy (10). Patients were randomized to either chemotherapy (pemetrexed or docetaxel) or ceritinib 750 mg once daily. Cross-over from chemotherapy to ceritinib was allowed following confirmed progressive disease according to blinded, independent review committee. The current report is based on a median duration of follow-up of 16.5 months. Sixty-four point seven percent of patients on chemotherapy crossed over to ceritinib. Median PFS was 1.6 *vs.* 5.4 months with a hazard ratio (HR) of 0.49 (95% CI, 0.36–0.67). With a P value of <0.001 ceritinib significantly prolonged PFS compared to chemotherapy. At the data cut-off, median OS was similar for both arms. Ceritinib also significantly improved the ORR (6.9% *vs.* 39.1%).

In conclusion, current evidence supports the use of ceritinib in crizotinib-pretreated ALK positive NSCLC patients. There is a well-documented activity of drug in patients with brain metastases that is a frequent localization of the disease in this patient population (11). Ceritinib is currently approved for ALK-positive adenocarcinoma patients progressing on crizotinib. As discussed in this overview, ceritinib also showed intriguing activity in ALK positive NSCLC patients that were ALK TKI naive. Several other ALK TKIs (e.g., alectinib, brigatinib, ensartinib, entrectinib, lorlatinib) are currently investigated in clinical trials. Alectinib is one of the most advanced new generation ALK TKI and was recently approved by the FDA for the treatment of patients with ALK positive metastatic NSCLC who have progressed on or are intolerant to crizotinib (12). This approval was based on two single-arm trials including 225 patients treated with alectinib 600 mg orally twice daily (8,13). The ORRs by independent review committee in these studies were 38% (95% CI, 36–52) and 44% (95% CI, 36–53); the median DoR were 7.5 and 11.2 months. In a pooled analysis of 51 patients with measurable disease in the central nervous system at baseline, the CNS ORR was 61% (95% CI, 46–74); the CNS DOR was 9.1 months. The results of a randomized trial conducted in Japan, J-ALEX, assessing alectinib 300 mg BID versus crizotinib in 207 ALK inhibitor-naive patients with ALK positive NSCLC, were recently reported to show a PFS advantage for alectinib over crizotinib (14). The ALEX study will determine whether similar findings are observed in a global population treated with alectinib 600 mg BID.

Studies are still needed to address optimal sequencing of ALK inhibitors in the treatment of patients with metastatic ALK-positive NSCLC.

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*Ethical Statement:* The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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