Editorial

Ceritinib—a second-generation ALK inhibitor overcoming resistance in ALK-rearranged non-small cell lung cancer

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For many years, standard first-line systemic therapy for metastatic non-small cell lung cancer (NSCLC) has consisted of platinum-based combination chemotherapy. The description of activating mutations in the epidermal growth factor receptor (EGFR) and the investigation of specific tyrosine kinase inhibitors (TKIs) inhibiting the EGFR signaling pathway changed this treatment paradigm. In the last few years, many genetic aberrations (mutations, translocations) have been described in NSCLC and some of them can be targeted by specific inhibitors. These genetic aberrations are believed to be the driver of lung cancer carcinogenesis and progression. Targeted therapies significantly increase overall response rates (ORR), disease-free survival (DFS) and overall survival (OS) compared to conventional chemotherapy. EGFR mutations are found in 10-15% of adenocarcinoma patients in Western countries. Chromosomal rearrangements of anaplastic lymphoma kinase (ALK) are detected in 1.6% to 8.6% of unselected NSCLC patients (1). ALK translocations are found nearly exclusively in lung adenocarcinomas, as opposed to other histopathological subtypes.

These rearrangements result in constitutively active ALK fusion proteins with potent transforming activity (2,3). These tumors are highly responsive to ALK TKIs. Crizotinib is an ATP-competitive small-molecule oral inhibitor of ALK, c-Met/hepatocyte growth factor receptor (HGFR), recepteur d'origine nantais (RON), and ROS receptor tyrosine kinases. Based on early-phase trials and a randomized trial in the second-line setting the ALK-TKI crizotinib was approved in 2011 [reviewed in (4)]. Recently, results from a randomized phase 3 trial in the first-line setting (PROFILE 1014) have been reported. Compared to standard chemotherapy with platinum/pemetrexed, crizotinib significantly improved ORR and progression-free survival (PFS) (5). Furthermore, crizotinib seems to also improve OS as shown in a non-randomized registry study (6). As it is the case with other targeted therapies for oncogene-addicted tumors, all patients with ALK-rearranged NSCLC who initially respond to crizotinib will have tumor progression usually within 1 to 2 years. In general, mechanisms of acquired drug resistance might be classified in two main categories. On one hand, the target gene itself can be altered either by mutation or by amplification. On the other hand, tumor cells might lose their dependency from the inhibited signaling pathway by activating alternative signaling pathways. In up to one third of relapsing patients, crizotinib resistance is mediated by secondary resistance mutations located in the ALK tyrosine kinase domain. The most commonly identified resistance mutation is the gatekeeper mutation L1196M (7). Based on the better understanding of resistance mechanisms to crizotinib, new therapeutic approaches have been developed.

Ceritinib (LDK378, Zykadia®, Novartis Pharmaceuticals, Basel, Switzerland) is an oral, small-molecule, ATP-competitive, TKI of ALK. In the preclinical setting ceritinib seems to be a more potent ALK inhibitor than crizotinib (8). Furthermore, ceritinib is able to overcome the secondary acquired L1196M gatekeeper mutation. In the phase 1 trial by Shaw *et al*. published in the New England Journal of Medicine 2014 ceritinib was tested in a dose-escalation phase in order to determine the maximal tolerated dose (MTD) (9). The MTD was determined to be 750 mg with the following dose-limiting toxicities (DLTs): diarrhea, vomiting, nausea, dehydration, elevated alanine aminotransferase level, and hypophosphatemia. All DLTs resolved on discontinuation of

treatment. Moreover, four cases of interstitial lung disease and one patient harboring asymptomatic grade 3 prolongation of the corrected QT interval that were possibly related to ceritinib have been described. At the MTD of 750 mg 62% of patients required at least one dose reduction. Among the 78 patients who were treated with the MTD of 750 mg ceritinib daily, the ORR was 59%. Patients previously treated with crizotinib (n=83) showed an ORR of 56% with ceritinib at a dose of 400 mg or more daily (45 patients) and 750 mg daily (28 patients). The ORR for patients not previously treated with crizotinib (34 patients) was 62%. Interestingly, responses were seen in untreated brain metastases in patients having received crizotinib before. The median PFS was 7.0 months in the whole cohort. For patients with previous crizotinib therapy the median PFS was 6.9 months whereas it was 10.4 months for ALK-TKI naïve patients. PFS was not different for patients with brain metastases (6.9 *vs*. 7.0 months, P=0.37). The OS at 1 year was 65%. Only 19 patients progressing during therapy with crizotinib underwent repeat tumor biopsy to investigate the mechanisms of resistance. Interestingly, all 19 patients showed an ALK rearrangement according to fluorescence in-situ hybridization (FISH). Five samples showed a secondary resistance mutation in the ALK tyrosine kinase domain and two samples had an ALK gene amplification. Tumor regression was observed in all the patients.

In summary, this large phase 1 trial clearly shows promising activity of ceritinib in ALK-positive NSCLC. Based on these promising clinical data of a large patient cohort (130 patients) the U.S. Food and Drug Administration (FDA) granted accelerated approval to ceritinib in April 2014. Responses were seen in crizotinib pretreated and crizotinib naïve patients. The activity of ceritinib in patients previously treated with crizotinib may be independent of the underlying mechanism of acquired resistance. Although only 19 patients with progression during crizotinib have had molecular analyses of a repeat tumor biopsy; responses were seen in patients with secondary mutations or amplifications. At least five patients harboring a secondary resistance mutation in the ALK tyrosine kinase domain have been treated with ceritinib and showed radiographic response among them three patients with the gatekeeper mutation L1196M. In contrast to crizotinib, ceritinib also shows activity in patients with brain metastases. The occurrence of central nervous system relapse is one of the main concerns in ALK-positive patients treated with crizotinib. Therefore, ceritinib seems to be an active drug in patients progressing on crizotinib. Furthermore, ceritinib might be a valuable option in ALK-positive patients with brain metastases irrespective of previous therapies. On the other hand, ceritinib also shows high activity in ALK-TKI naïve patients with a median PFS of 10.4 months. The question of timing and the sequence of different ALK-TKIs cannot be answered at the moment as there are no head-to-head comparisons. Currently, the only prospective randomized trial comparing two different ALK-TKIs is the ALEX trial investigating crizotinib and alectinib in the first-line setting. Alectinib is another second-generation ALK-TKI with high response rates in crizotinib-pretreated patients (10). Many questions in the use of ALK-TKIs are yet unanswered as for example the optimal dosing of ceritinib. Although responses have been observed with doses higher than 400 mg daily, the recommended dose is the MTD 750 mg daily. It is unclear if higher doses result in higher response rates. Furthermore we do not know how to treat primary crizotinib resistant patients (6% in the PROFILE 1007 trial). In the current trial these patients have not separately been investigated for response to ceritinib. Moreover, one of the main issues in the future will be treatment resistance to ceritinib. Recently, novel mutations in the ALK gene in patients progressing under ceritinib have been reported (8). Maybe newer ALK-TKIs like ASP3026, AP26113, and X-396 will be of benefit for these patients.

In conclusion, the phase I trial with expanded cohort shows high activity of ceritinib in ALK-positive patients irrespective of previous treatment with crizotinib. Ceritinib is a valuable treatment option for ALK-rearranged NSCLC patients.

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