Commentary

Expanding opportunities for crizotinib resistance in *ALK*-positive lung cancer patients

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Anaplastic lymphoma kinase (*ALK*) gene rearrangements are present in 3–7% of patients with non-small cell lung cancer (NSCLC) and are more common among patients with a never/light smoking history, adenocarcinoma histology, a younger age, female gender and in patient with tumors with a wild-type status for the *EGFR* and *KRAS* genes (1).

Crizotinib (Xalkori; Pfizer, New York, USA), the first *ALK* inhibitor to be tested in the clinic, that co-targets ROS1 and MET tyrosine kinases, has proved superior to standard cytotoxic chemotherapy in first- and second-line settings for advanced *ALK*-positive NSCLC (2). Unfortunately, as seen with other targeted therapies, despite initial major responses to crizotinib, most *ALK*-positive NSCLC patients develop acquired resistance within the first year of treatment (3). Metastatic involvement of the central nervous system (CNS), pericardium, pleura and liver, is a frequent complication in patients with *ALK*-positive NSCLC and the CNS represents a dominant site of progression in *ALK*-positive patients treated with crizotinib (4). In addition, CNS progression on crizotinib contributes significantly to the high levels of morbidity and mortality observed among patients with *ALK*-rearrangements, a finding that is consistent with the low level of penetrance of crizotinib through the blood-brain barrier (4). In this context, several next-generation *ALK* inhibitors have been developed to enhance the anti-ALK activity, to overcome crizotinib acquired resistance and to increase activity in targeting CNS disease (5).

Patients with advanced *ALK*-positive NSCLC who develop resistance to crizotinib have an additional therapeutic option: alectinib (Alecensa; Roche, Basel, Switzerland), the third drug [after crizotinib and ceritinib (Zykadia™; Novartis, Basel, Switzerland)] for this molecular subset of NSCLC to garner FDA approval since the discovery of *ALK* as a therapeutic target in 2007. Alectinib is a highly selective, orally bioavailable, small molecule inhibitor of ALK, with potent *in vitro* activity against both wild-type and mutated *ALK*, and multiple kinases such as RET, LTK and GAK (6).

Recently, Shaw and colleagues evaluated the efficacy of alectinib in *ALK*-positive NSCLC patients who had progressed on crizotinib, in a US/Canadian population (phase II trial, n=87) (7). In their study, the objective response rate (ORR) was 48% (95% CI, 36–60%) among the 69 patients with measurable disease at baseline according to an independent review committee (IRC), and the median duration of response (DOR) was 13.5 months (95% CI, 6.7–not reached). A global study yielded remarkably similar results, the ORR was 50% (95% CI, 41–59%) among the 122 patients evaluable by IRC, and the median DOR was 11.2 months (95% CI, 9.6 months–not reached) (8).

Moreover, alectinib was well tolerated and patient adherence was acceptable. More than half (60%) of the patients had brain metastases at enrolment, almost two-thirds of whom had received previous brain radiation therapy. Of the 52 patients with measurable or non-measurable CNS disease at baseline, 21 (40%, 95% CI, 27–55) achieved an objective response, including 13 (25%) with a complete intracranial objective response, with a median DOR of 11.1 months (95% CI, 10.8–not reached). Control of CNS disease was achieved in 46 (89%, 95% CI, 77–96) patients (7).

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The response rate in the global study was 57% (95% CI, 39–74), and the median DOR was 10.3 months (95% CI, 7.6–11.2) (8). The intracranial response to alectinib is noteworthy since CNS metastases in NSCLC historically have had no effective treatment options. Aectinib shows efficacy in NSCLC patients with not only leptomeningeal carcinomatosis but also those with parenchymal CNS lesions. This suggests that alectinib has the potential to address the high unmet medical need facing patients with established brain metastases (9,10). The clinical control of CNS disease reported with alectinib is supported by the linear relationship between paired cerebrospinal fluid and free alectinib concentrations in plasma (11).

Of equal importance, alectinib's side effects were mild, predominantly grade 1 or 2, including constipation (36%), fatigue (33%), myalgia (24%), and peripheral edema (23%). The most common grade 3 and 4 adverse events were changes in laboratory values, including increased blood creatine phosphokinase (8%), increased alanine aminotransferase (6%), and increased aspartate aminotransferase (5%). Two patients died, with only one death from hemorrhage, judged related to study treatment (7).

Based on the findings of both studies (US/Canadian and global), a phase III trial of first-line alectinib *vs.* crizotinib in treatment-naive *ALK*-positive advanced NSCLC patients is currently recruiting patients (ALEX trial, NCT02075840).

Currently, several other next-generation ALK inhibitors with increased potency and specificity are undergoing preclinical and clinical testing (5). However, with still more *ALK* inhibitors in pharmaceutical pipelines, some fundamental questions need to be addressed, for instance, how to properly sequence these agents (5,10).

In addition, optimum combinations of *ALK* inhibitors with targeted or cytotoxic agents (e.g., other tyrosine kinase inhibitors and inhibitors of heat-shock protein 90, NCT01579994) (12), or local treatments (e.g., whole-brain irradiation or radiosurgery in selected patients with emergent brain metastasis) (13) deserve clinical evaluation. Moreover, immunotherapy has recently revolutionized cancer treatment, including in advanced NSCLC patients (14). Combining immune checkpoint agents and *ALK* inhibitors may represent an opportunity to improve efficacy in crizotinib-resistant NSCLC patients. In this context, two early phase trials are ongoing: (I) for safety and efficacy assessment of ceritinib combined with anti-PD1 treatment with nivolumab in patients with pretreated *ALK*-positive NSCLC (NCT02393625), and (II) a modified phase I trial with ipilimumab combined with mutation-specific targeted therapy (crizotinib or erlotinib) stratified for the presence of *ALK* rearrangements or *EGFR* mutations (NCT01998126) (5).

Crizotinib resistance mechanisms include *ALK* gene mutations (e.g., 1151Tins, L1152R, C1156Y, L1196M, G1202R, S1206Y, G1269A) in approximately 30% of resistant patients, *ALK* fusion gene amplification in almost 8% of cases, *EGFR* mutations and autophosphorylation, *KRAS* mutations, cKIT pathway activation, induction of autophagy, and epithelial-mesenchymal transition (15). Comprehensive profiling assays will continue to refine the mutational landscape of *ALK*-positive NSCLC and identify co-existent genomic alterations that may modify response and resistance to *ALK*-directed therapies, underlying the variability in the response duration observed clinically. The second generation *ALK* inhibitors, ceritinib and alectinib, can overcome some of the resistance mechanisms, which may partly explain the improved response rates observed in clinical trials. Alectinib is effective against crizotinib resistant *ALK* mutations including L1196M, G1269A, F1174L, R1275Q and C1156Y, but is inactive against I1171, G1202R, S1206Y mutations (7,16). In addition, several mechanisms underlying alectinib resistance have been reported recently (17,18). In view of the broad spectrum of mechanisms generating *ALK* resistance, selection of next-generation *ALK* inhibitors should be tailored based on molecular genotyping. However, serial biopsies have some limitations in clinical practice in patients with relapsed NSCLC: they may be technically difficult or impossible and could incur serious risks to patients. Blood-based assays (circulating free DNA or circulating tumor cells—CTCs, as a liquid biopsy) offer an attractive alternative source for tumor tissue analysis, which is easily accessible, repeatable, non-invasive, and has the potential to identify predictive biomarkers to tailor therapies on a personalized basis. Based on two recent reports on the potential use of *ALK* FISH or immunocytochemistry (ICC) to detect *ALK* rearrangements in CTCs, a multicenter prospective clinical trial is ongoing to assess the sensitivity of FISH/ICC assays and the prevalence of resistant mutations in CTCs from NSCLC patients treated with *ALK* inhibitors (STALKLUNG01 trial, NCT02372448) (19,20).

In the last few years, novel potent *ALK* inhibitors with promising results and a good toxicity profile have become available. Alectinib holds promise for crizotinib-resistant NSCLC patients. Given the heterogeneity of the mechanisms involved in resistance, it is important to emphasize the need to find ways to prevent resistance from developing at all in these patients.

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