Editorial



# The first cut is the deepest: changing clinical practice for ALK-positive lung cancer

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Approximately 4% of non-small-cell lung cancers (NSCLC), mostly adenocarcinomas, harbor oncogenic ALK gene fusions. Patients with such ALK-positive NSCLC tend to be younger, more frequently female and more frequently non-smokers (1,2). Based on superiority to chemotherapy two ALK-tyrosine kinase inhibitors crizotinib (3) and ceritinib (4) were approved for first-line therapy. Hence, both ESMO (5) and CAP (6) guidelines require screening of all NSCLC for ALK fusions, except pure squamous cell carcinomas from heavy smokers. As rapid and cost-effective screening by IHC followed by either by FISH or hybrid capture sequencing has been established, even in patients presenting with very advanced disease and urgent need for therapy first line therapies are possible and effective (7). An illustrative case is shown in *Figure 1* and presented in detail previously (7).

The median progression-free survival (PFS) of patients with ALK-positive NSCLC under treatment with crizotinib is 10.9 months (3). Many NSCLC eliciting acquired resistance to crizotinib respond to second-line therapies with ceritinib (8) and thus, current clinical practice in many countries is first-line therapy with crizotinib and immediate second-line ceritinib after emerging secondary resistance without mandatory re-biopsy. However, advanced ALK-positive NSCLC carries a high life-time risk of brain metastases at diagnosis, with the central nervous system (CNS) being the most common site of disease progression and limitation of therapies with tyrosine kinase inhibitors (TKIs) (9,10). Results from a new trial comparing the ALK-inhibitor alectinib versus crizotinib in treatment-naïve ALK-positive non-small-cell lung cancer (ALEX trial) are now changing the clinical stage profoundly (11).

Alectinib is a new TKI inhibiting the ALK-kinase more potently and eliciting activity against several mutations that confer resistance to crizotinib (12). In contrast to crizotinib and ceritinib, alectinib reveals good penetrance into the CNS and is not a substrate of P-glycoprotein, an efflux transporter which has been shown to clear xenobiotics from the CNS through the brain-blood barrier (13). Thus, alectinib seems to address one demanding clinical need in ALK-positive advanced lung cancer in delivering effective treatment of the CNS and protecting an organ-milieu which has been considered as undertreated by previous TKIs. Results from the ALEX trial, an open-label phase 3 trial comparing head-to-head crizotinib versus alectinib are likely to change treatment paradigms for ALK-positive lung cancer. In this randomized trial 303 patients with treatment naive, advanced ALK-positive NSCLC were treated either with alectinib (600 mg twice daily) or crizotinib (250 mg twice daily). The primary end point in this trial was investigator-assessed PFS, and further secondary end points were independent review committee-assessed PFS, time to CNS progression, objective response rate (ORR), and overall survival (OS) (11).

During clinical observation of patients in the ALEX trial an event of disease progression (or death) occurred in 62 of 152 patients (41%) in the alectinib group versus 102 of 151 patients (68%) in the crizotinib group. The rate of PFS was significantly higher with alectinib than with crizotinib (12-month event-free survival rate, 68.4% with alectinib

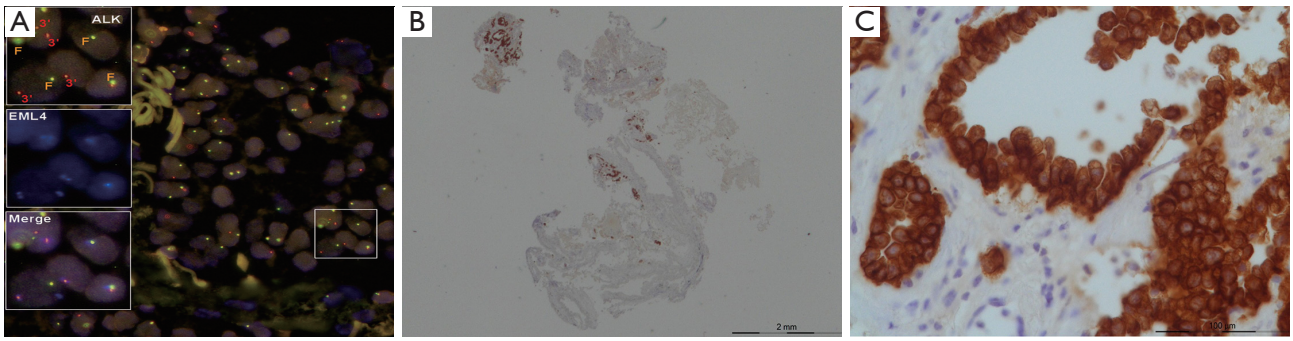


**Figure 1** Rapid screening for ALK-positive NSCLC by immunohistochemistry and subsequent validation by FISH (7). (A) Display of FISH image; (B) immunostaining 25× magnification; (C) immunostaining 400× magnification. NSCLC, non-small-cell lung cancers.

versus 48.4% with crizotinib; hazard ration for disease progression or death HR =0.47, P<0.001). Convincingly, the median PFS was not reached under treatment with alectinib. Consistently, all other secondary end points were in favor of alectinib. With regard to CNS progression only 18 patients (12%) treated with alectinib group had an event, in contrast to 68 patients (45%) treated with crizotinib (cause-specific hazard ration HR =0.16, P<0.001). The overall response rate did not differ to that extent with 126 responders in the alectinib group (response rate 82.9%) as compared to 114 patients in the crizotinib group (response rate 75.5%). Also the rate of adverse events was in favor of alectinib as grade 3 to 5 events were less frequent with alectinib than with crizotinib (41% versus 50%). Taken together PFS and CNS progression was highly in favor for alectinib, overall response was also in favor for alectinib with a lower rate of high-grade adverse events.

The results of this carefully conducted clinical trial represent a major step forward for patients with advanced ALK-rearranged NSCLC. Alectinib can now be considered the preferred choice of first-line treatment in patients with advanced ALK-rearranged lung cancer. However, even in the alectinib arm overall response occurred in approximately 83% but not in the remaining 17%. In this regard, it is good news that a series of new and potent TKIs with high activity against ALK and against many secondary resistance mutations in the kinase domain are currently under clinical development (14). Thus, it may be that alectinib is not the final victory in this race, but brigatinib, lorlatinib, entrectinib, and others still being on the track may prove superior. A common theme, however, emerging both from the ALEX trial and the recent first data from the FLAURA trial presented at ESMO 2017 (first-line treatment of EGFR-mutant advanced lung cancer with the third-generation EGFR inhibitor osimertinib) (15,16) indicate another important treatment paradigm: delivering the best TKI first rather than adding two lines of treatment with subsequent action upon acquired resistance. An old wisdom already put into lyrics by the song-writer Cat Stevens illustrates that "*The first cut is the deepest*".

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