Alectinib in untreated anaplastic lymphoma kinase-positive non-small cell lung cancer

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Anaplastic lymphoma kinase (ALK) translocations are a validated molecular target in non-small cell lung cancer (NSCLC). ALK translocations result in the expression of a chimeric protein, exhibiting a constitutive ALK kinase activation, involved in cell proliferation, invasion and loss of apoptosis (1). ALK translocations are found in 4–7% of NSCLC, particularly in adenocarcinomas and in non-smokers (1). According to FDA and EMEA, standard first-line therapy for advanced ALK translocated NSCLC is crizotinib, a multi-target MET, ALK and ROS1 inhibitor (1,2). The use of second generation ALK inhibitors, such as ceritinib or alectinib, was initially validated at progression (3-5). More recently, these second generation ALK inhibitors were evaluated in first-line treatment. This year, ceritinib received FDA and EMEA approval in the first-line treatment for advanced ALK translocated NSCLC after the results of a phase III trial comparing ceritinib to platinum - pemetrexed chemotherapy with a benefit on progression-free survival of 16.6 vs. 8.1 months (6). Several clinical trials are underway comparing head to head different ALK inhibitors in phase III trials in ALK naïve patients, as brigatinib vs. crizotinib (NCT02737501) or lorlatinib vs. crizotinib (NCT03052608).

Alectinib, a powerful ALK inhibitor, has been shown effective in two phase II trials in crizotinib resistant ALK translocated NSCLC patients (3,7).

Recently, two phase III trials focused on alectinib in the first-line treatment in advanced ALK translocated NSCLC.

The J-ALEX study assessed alectinib versus crizotinib in a randomised phase III trial of ALK translocated advanced NSCLC in Japan (8). ALK translocation was confirmed by immunohistochemistry and fluorescent in situ hybridisation (FISH) or RT-PCR on tissue or cell samples. In this Japanese trial, 207 ALK inhibitor naïve patients were treated with either alectinib 300 mg twice daily, a lower dose than the 600 mg twice daily used outside Japan, or crizotinib 250 mg twice daily. At the pre-planned interim analysis, the study was stopped because the primary endpoint had been met (HR 0.34; P<0.0001). Median progression-free survival had not yet been reached with alectinib (95% CI, 20.3 months-not estimated) and was 10.2 months with crizotinib (8.2–12.0). Furthermore, alectinib compared to crizotinib showed a higher proportion of patients achieving an objective response (92% vs. 79%) and a smaller proportion of patients with grade 3 or 4 events (26% vs. 52%). These results provide the first head-to-head comparison of alectinib to crizotinib in a Japanese cohort.

These impressive results are confirmed in a second phase III trial, ALEX, comparing alectinib to crizotinib in ALK translocated advanced NSCLC (9). ALK translocation was determined only by immunohistochemistry. In this international trial, 55% of patients were non-Asian and included 303 patients treated with either alectinib 600 mg twice daily or crizotinib 250 mg twice daily. Median progression-free survival had not yet been reached with...
Alectinib (95% CI, 17.7 months–not estimated) and was 11.1 months with crizotinib (95% CI, 9.1–13.1). Furthermore, alectinib compared to crizotinib showed a higher proportion of patients achieving an objective response (82.9% vs. 75.5%) and a smaller proportion of patients with grade 3 or 4 events (41% vs. 50%). A particular interesting characteristic of alectinib is optimal brain penetration. Alectinib has shown central nervous system (CNS) efficacy. Only 18 patients (12%) in the alectinib group had a CNS progression compared to 68 patients (45%) in the crizotinib group (HR 0.16; 95% CI, 0.1–0.28; P<0.0001).

These two trials are a major advancement in the treatment of ALK translocated NSCLC. Indeed, J-ALEX and ALEX are the first randomized trial to directly compare ALK inhibitors in the first-line setting. The major concern is to evaluate the long-term benefit of frontline alectinib. Other second-generation ALK inhibitors, as ceritinib, brigatinib or lorlatinib, are highly effective after crizotinib progression. Whether more potent ALK inhibition in the frontline treatment, translates into greater efficacy upon sequential treatment with first-generation followed by second-generation ALK inhibitors at progression, is speculative. However, progression-free survival of frontline alectinib seems superior to combined progression-free survival in small series of crizotinib followed by ceritinib or alectinib treatment (17.4 and 18.4 months respectively).

Interestingly, ALK positivity by immunohistochemistry, as used in ALEX trial, seems to be sufficient to detect ALK translocation. FISH or RT-PCR will only be needed in the case of uncertain ALK protein expression (10).

J-ALEX and ALEX sustain alectinib as a new standard of care for first-line therapy of advanced ALK translocated NSCLC patients.

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Footnote

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References


