ALEX Trial: Alectinib vs Crizotinib in Untreated Advanced *ALK*-Positive NSCLC

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- In patients with advanced *ALK*-positive NSCLC, alectinib was associated with significantly prolonged progression-free survival compared with crizotinib.
- Alectinib produced higher intracranial response rates.

As reported at the recent ASCO Annual Meeting and in *The New England Journal of Medicine* by Peters et al, the phase III ALEX trial has shown improvement in progression-free survival with alectinib (Alecensa) vs crizotinib (Xalkori) in the first-line treatment of advanced *ALK*-positive non–small cell lung cancer (NSCLC).

Study Details

In the open-label trial, 303 patients from 98 sites worldwide were randomized between August 2014 and January 2016 to receive alectinib at 600 mg twice daily (n = 152) or crizotinib at 250 mg twice daily (n = 151). Randomization was stratified according to Eastern Cooperative Oncology Group (ECOG), Asian vs non-Asian race, and presence/absence of central nervous system (CNS) metastases. Treatment was continued until disease progression, unacceptable toxicity, or withdrawal of consent. The primary endpoint was investigator-assessed progression-free survival in the intention-to-treat population.

For the alectinib vs crizotinib groups: median age was 58 vs 54 years; 55% vs 58% were female; 45% vs 46% were Asian; 93% in both had an ECOG performance status of 0 or 1; 61% vs 65% were never smokers; 97% vs 96% had stage IV disease (all others had stage IIIB disease); 90% vs 94% had adenocarcinoma histology; 42% vs 38% had CNS metastases; treatment for CNS metastases included brain surgery in 4% vs 5%, radiosurgery in 19% vs 18%, and whole-brain radiotherapy in 63% vs 73%; and 17% vs 14% had received prior brain radiotherapy.

Progression-Free Survival

After a median follow-up of 18.6 months in the alectinib group and 17.6 months in the crizotinib group, disease progression or death had occurred in 41% of the alectinib group vs 68% of the crizotinib group. The 12-month event-free survival rates on investigator assessment were 68.4% (95% confidence interval [CI] = 61.0%–75.9%) in the alectinib group vs 48.7% (95% CI = 40.4%–56.9%) in the crizotinib group (hazard ratio [HR] = 0.47, $P < .001$). Median progression-free survival was not reached (95% CI = 17.7 months to not estimable) vs 11.1 months (95% CI = 9.1–13.1 months). On independent review committee assessment, median progression-free survival was 25.7 months vs 10.4 months (HR = 0.50, $P < .001$). The magnitude of

benefit with alectinib was generally consistent across subgroups; it was smaller in active smokers (8% vs 3% of groups) and in patients with an ECOG performance status of 2 (7% of both groups).

Objective response occurred in 82.9% vs 75.5% of patients (*P* = 0.09); median duration of response was not estimable vs 11.1 months. At data cutoff, death had occurred in 23% vs 26% of patients, with 12-month overall survival of 84.3% vs 82.5% (HR = 0.76, 95% CI = 0.48–1.20); median overall survival was not reached in either group.

CNS Responses

On independent review, CNS progression occurred in 12% of the alectinib group vs 45% of the crizotinib group (HR = 0.16, *P* < .001). Among patients with measurable CNS disease at baseline, CNS response occurred in 17 of 21 (81%) alectinib patients, including a complete response in 8, vs 11 of 22 (50%) crizotinib patients, including a complete response in 1. Median duration of intracranial response was 17.3 months vs 5.5 months. Among patients with measurable or nonmeasurable CNS disease at baseline, CNS response occurred in 38 of 64 (59%) alectinib patients, including a complete response in 29, vs 15 of 58 (26%) crizotinib patients, including acomplete response in 5.

Adverse Events

Adverse events of any grade that occurred at a ≥ 5% higher incidence in the alectinib group were anemia (20% vs 5%), myalgia (16% vs 2%), increased bilirubin (15% vs 1%), increased body weight (10% vs 0%), musculoskeletal pain (7% vs 2%), and photosensitivity reaction (5% vs 0%). Those adverse events more common with crizotinib included nausea (48% vs 14%), diarrhea (45% vs 12%), and vomiting (38% vs 7%). Grade ≥ 3 adverse events occurred in 41% of the alectinib group vs 50% of the crizotinib group. Those grade ≥ 3 adverse events most common in the alectinib group included increased alanine transaminase (ALT) and aspartate transaminase (AST) and anemia (5% each), and those grade ≥ 3 adverse events most common with crizotinib included increased ALT (15%) and AST (11%). Serious adverse events occurred in 29% vs 28%.

Adverse events led to treatment interruption in 19% vs 25%, dose reduction in 16% vs 21%, and treatment discontinuation in 11% vs 13%. Adverse events led to death in 5 (3%) vs 7 (5%) patients, with death considered related to study treatment in 0 vs 2 patients.

The investigators concluded: “As compared with crizotinib, alectinib showed superior efficacy and lower toxicity in primary treatment of *ALK*-positive NSCLC.”

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Solange Peters, MD, PhD, of Lausanne University Hospital, and **D. Ross Camidge, MD, PhD**, of the University of Colorado, Denver, contributed equally to *The New England Journal of Medicine* article.