Brigatinib vs Crizotinib in ALK TKI–Naïve ALK+ NSCLC: Final Results From ALTA-1L

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**Introduction**

• The first-generation ALK inhibitor crizotinib does not show sufficient activity in patients with treatment-naive advanced ALK (ALK+) non–small cell lung cancer (NSCLC).

• In most patients, development of progressive disease within 1 year due to acquired ALK resistance mutations and/or poor central nervous system (CNS) penetration.

• The CNS is the most common site for progression in patients with ALK+ NSCLC treated with crizotinib.

• Brigatinib, an oral, selective, anion-dependent ALK inhibitor with preclinical activity against acquired ALK resistance mutations, was evaluated in patients with ALK+ NSCLC in the phase 1/2 ALTA-1L study.

• The study met statistical significance at the first preplanned interim analysis (94% of events).

• At the median follow-up analysis (70% of expected events), brigatinib demonstrated durable progression-free survival (PFS) versus crizotinib at 4 years (P=0.001).

• Among patients with brain metastases at baseline, the HR for brigatinib-associated PFS (3.95; 95% CI, 1.95–8.02) was significantly (P=0.001).

• Overall survival was still rising at the end point analysis (HR: 0.63 [95% CI, 0.47–0.87]).

• We report the final efficacy and safety data from long-term follow-up of patients in ALTA-1L.

**Methods**

• Complete methods for ALTA-1L (NCT02737501) have been previously published.

• ALK+ patients aged 18 years with stage IIIIB/IVA ALK+ NSCLC who had not received prior ALK inhibitor therapy and had received prior systemic chemotherapy for locally advanced/metastatic disease were randomized to 2 arms.

• Patients with asymptomatic or subclinical CNS metastases were included.

• Patients were randomized to receive brigatinib 180 mg (97 arm) or 140 mg (40 arm) bid or crizotinib 250 mg bid.

• Investigators were permitted biomarker-directed therapy at any time in 90% of patients.

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• Patients were stratified by centrally reviewed brain metastases.

• The primary end points were overall survival, progression-free survival (PFS), CNS safety, CNS progression-free survival (PFS) and investigator-assessed CNS progression.

• All events were centrally reviewed.

• Data were collected from patient records, medical records, and independent third-party source verification.

• Patients received systemic therapy for at least 4 weeks in all treatment arms.

• The study included 271 patients from 8 countries.

• Data were analyzed for patients who had received at least one dose of trial medication (intent-to-treat population).

• The study cohort included 97 (36%) of 271 patients receiving brigatinib 180 mg bid, 40 (15%) patients receiving brigatinib 140 mg bid, and 134 (49%) patients receiving crizotinib 250 mg bid.

• Patients treated with crizotinib as first-line therapy were included.

• Study patients were treated with either crizotinib or brigatinib.

• Patients from both the crizotinib and brigatinib arms were crossed over to brigatinib if approved by the investigator and after the patient met certain criteria.

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**Results**

• Last patient last contact was January 2021, approximately 3.5 years after the last patient was enrolled.

• Median (range) follow-up for brigatinib 43.0 (0.4–60.7) months, crizotinib 15.2 (3.1–61.5) months.

• 86 patients (65%) in the brigatinib arm and 59 patients (53%) in the crizotinib arm were still on study drug at end of study in both arms.

• 68 patients (50%) from the crizotinib arm were crossed over to brigatinib after disease progression.

• Median (range) duration of brigatinib treatment in these 68 patients was 17.3 (7.1–35.9) months.

• Lesion assessed intervals for overall survival were calculated by the Kaplan–Meier method.

• All adverse events, serious adverse events, and adverse events leading to drug discontinuation were counted as first events for a given patient regardless of their timing.

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• In sensitivity analyses adjusting for treatment crossover in the crizotinib arm, the OS HR was 0.96 (95% CI, 0.51–1.82 [P=0.82]) by the MASM approach.

**Summary**

• The combination of ALK kinase inhibitors in non–small cell lung cancer is a promising strategy for patients with ALK+ NSCLC.

• Brigatinib demonstrated significantly improved progression-free survival (PFS) versus crizotinib, with a 40% reduction in the risk of progression or death.

• Median and overall survival were still rising at the end point analysis.

• Results support brigatinib as an overall standard treatment option for ALK+ NSCLC.