Cancer Network

October 17, 2025 – Crizotinib results removed

Frontline Alectinib Upholds OS Benefit in Advanced ALK+ NSCLC

Author(s)Gina Mauro

Final results of the phase 3 ALEX trial (NCT02075840), which were presented during the European Society for Medical Oncology (ESMO) Congress 2025.1

Data showed that at a median follow-up of 53.5 months with alectinib, the median overall survival (OS) was 81.1 months (95% CI, 62.3-not estimable) The 7-year OS rate was 48.6% with alectinib.

“This is probably one of the longest OS [rates] we’ve ever reported for patients with stage IV non–small cell lung cancer. Fifty percent of patients alive at 5 years in a randomized phase 3 study of stage IV lung cancer, I think this is actually an achievement.”

The long-term OS improvement with alectinib was observed across most patient subgroups, except for active smokers (HR, 1.75) and those with an ECOG performance status of 2 (HR, 1.47). In those with central nervous system (CNS) metastases, however, data showed that the largest benefit was observed in patients who had undergone radiation (HR, 0.62).

Earlier results of ALEX led to the FDA approval of alectinib in April 2024 in the frontline setting for patients with advanced ALK-positive NSCLC.2,3

In the open-label, multicenter phase 3 ALEX trial, patients with advanced ALK-positive NSCLC were randomly assigned to receive 600 mg of twice-daily alectinib or 250 mg of twice-daily crizotinib until disease progression, unacceptable toxicity, withdrawal from study, or death. No crossover was permitted before disease progression. Patients also underwent imaging every 8 weeks.

Patients must have been 18 years or older, have no prior systemic therapy, and an ECOG performance status of 0 to 2. Stratification factors included ECOG performance status (0 or 1 vs 2), race (Asian vs non-Asian), and baseline CNS metastases (yes vs no).

The primary end point was investigator-assessed progression-free survival (PFS) via RECIST v1.1 criteria, with secondary end points being independent review committee–assessed PFS, time to CNS progression, objective response rate, duration of response, OS, and safety.

Prior reported data of the final PFS analysis, which had a data cutoff date of November 30, 2018, showed an investigator-assessed median PFS of 34.8 months with alectinib  At a median follow-up of 48.2 months, OS data were immature, and the median OS was not reached with alectinib.

At the ESMO Congress 2025, Mok, who serves as the Li Shu Fan Medical Foundation endowed Professor and chairman of the Department of Clinical Oncology at the Chinese University of Hong Kong, presented on the final OS analysis and long-term safety data after an additional 6 years of follow-up from the prior OS analysis. The data cutoff date was April 28, 2025.

CNS metastases via an independent review committee were present in 42.1% of alectinib-treated patients and 17.1% received prior brain radiation.

Additional data showed that the next 1 or more lines of ALK TKI therapy included lorlatinib (18.4%), brigatinib (10.5%), crizotinib (9.2%), ceritinib (6.6%), ensartinib (0.7%), NVL 655 (0.7%), and APG 2449 (%).

In exploring the OS of patients with CNS metastases at baseline, the median OS was 63.4 months in those on alectinib (n = 59). For those without CNS metastases on alectinib, the median OS was 94.0 months.9

Furthermore, in the group of patients who received prior brain radiation, the median OS was 92.0 months with alectinib (n = 2). Those who did not have prior brain radiation had a median OS of 46.9 months with alectinib (n = 34).

Investigator-assessed DOR in responders was a median of 42.3 months (95% CI, 31.3-51.3) with alectinib (n = 126).

The most common adverse effects (AEs) that led to dose reductions or discontinuations with alectinib comprised increased blood bilirubin (5.3%). Grade 3 to 5 AEs were 57.9%, and serious AEs were 46; treatment-related AEs were 82.2%. AEs with alectinib that led to death, treatment discontinuation, dose reduction, and dose interruptions occurred in 6.6%, 17.8%, 23.0%, and 32.2%, respectively.

The most common grade 3 to 5 AEs included anemia (7.2%), increased alanine aspartase (5.3%, pneumonia (5.3%, urinary tract infection (5.3%), increased ALT (4.6%), increased blood bilirubin (4.6%), increased blood CPK (3.3%), neutropenia (0%).

Two percent of on-study deaths (n = 3) of unknown cause, with no autopsy performed, were suspected to be unrelated to alectinib.

References

Mok TSJ, Camidge DR, Dziadziuszko R, et al. Final overall survival (OS) and safety analysis of the Phase 3 ALEX study of alectinib vs crizotinib in patients with previously untreated, advanced ALK-positive (ALK+) non-small cell lung cancer (NSCLC). Ann Oncol. Published online ahead of print October 17, 2025. doi:10.1016/j.annonc.2025.09.018

Peters S, Camidge DR, Shaw AT, et al. Alectinib versus crizotinib in untreated ALK-positive non–small-cell lung cancer. N Eng J Med. 2017;377(9):829-838. doi:10.1056/NEJMoa1704795

FDA approves Genentech's Alecensa as first adjuvant treatment for people with ALK-positive early-stage lung cancer. News release. Genentech. April 18, 2024. Accessed October 17, 2025. https://shorturl.at/zSV29

Mok T, Camidge DR, Gadgeel SM, et al. Updated overall survival and final progression-free survival data for patients with treatment-naive advanced ALK-positive non-small-cell lung cancer in the ALEX study. Ann Oncol. 2020;31(8):1056-1064. doi:10.1016/j.annonc.2020.04.478