Lorlatinib Shows Overall and Intracranial Activity in *ALK*-Positive NSCLC

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Key Points

- Lorlatinib produced high systemic and intracranial response rates in treatment-naive and ALK tyrosine kinase inhibitor–experienced patients.
- In patients with ≥ 1 prior ALK tyrosine kinase inhibitor with or without chemotherapy, overall response rate was 47% and intracranial response rate was 63% in those with measurable lesions.

In a global phase II study reported in *The Lancet Oncology*, Solomon et al found that lorlatinib (Lorbrena) showed high overall and intracranial activity in patients with advanced *ALK*-positive non–small cell lung cancer (NSCLC) who were treatment-naive or who had received crizotinib (Xalkori) or multiple ALK tyrosine kinase inhibitors. Findings in this study supported the recent U.S. Food and Drug Administration approval of lorlatinib as second- or third-line treatment for *ALK*-positive metastatic disease.

Study Details

In the study, 276 patients with *ALK*-positive or *ROS1*-positive disease with or without central nervous system (CNS) metastases were enrolled between September 2015 and October 2016. Patients were enrolled into six different expansion cohorts (EXP1 through EXP6) on the basis of *ALK* and *ROS1* status and previous therapy. All patients were treated with oral lorlatinib 100 mg once daily continuously in 21-day cycles.

The primary endpoint was overall and intracranial tumor response on independent central review assessed in pooled subgroups of *ALK*-positive patients. Patients with measurable CNS metastases at baseline on independent central review were included in the intracranial response analysis.

The six cohorts included five cohorts of *ALK*-positive patients: 30 who were treatment-naive (EXP1); 59 who received previous crizotinib without (n = 27; EXP2) or with (n = 32; EXP3A) previous chemotherapy; 28 who received one previous noncrizotinib ALK tyrosine kinase inhibitor with or without chemotherapy (EXP3B); and 112 who had received two (n = 66; EXP4) or three (n = 46; EXP5) previous ALK tyrosine kinase inhibitors with or without chemotherapy. The sixth cohort, which is not included in the current efficacy analysis, consisted of 47 patients who were *ROS1*-positive with any previous treatment (EXP6). Safety data are from all six cohorts.

Responses in *ALK*-Positive Cohorts

In treatment-naive patients (EXP1), objective response was achieved in 27 (90.0%) of 30 patients; intracranial response occurred in 2 (66.7%) of 3 with measurable baseline CNS lesions.

In patients who had received at least one previous ALK tyrosine kinase inhibitor (EXP2 through EXP5), objective response was achieved in 93 (47.0%) of 198 patients and objective intracranial response was observed in 51 (63.0%) of 81 patients with measureable CNS lesions.

Objective response was achieved in 41 (69.5%) of 59 patients who had received only previous crizotinib (EXP2 and EXP3A), 9 (32.1%) of 28 patients with one previous noncrizotinib ALK tyrosine kinase inhibitor (EXP3B), and 43 (38.7%) of 111 who had received two or more ALK tyrosine kinase inhibitors (EXP4 and EXP5).

Among patients with measureable CNS lesions, objective intracranial response was observed in 20 (87.0%) of 23 patients in EXP2 and EXP3A, 5 (55.6%) of 9 in EXP3B, and 26 (53.1%) of 49 patients in EXP4 and EXP5.

Among the 198 patients in cohorts EXP2 through EXP5, overall complete response was observed in 2% of patients, partial response in 45%, and stable disease in 29%. With median durations of follow-up ranging from 6.9 to 7.2 months, median durations of response had not been reached overall or in any cohort. Among the 30 patients in the treatment-naive cohort (EXP1), overall complete response was observed in 3%, partial response in 87%, and stable disease in 7%. With median follow-up of 6.9 months, median duration of response had not been reached.

Among the 81 patients with measureable CNS disease in cohorts EXP2 through EXP5, complete intracranial response was observed in 20%, partial response in 43%, and stable disease in 25%. Median duration of intracranial response was 14.5

months, including 14.5 months in cohort EXP4 and EXP5 (≥ 2 prior tyrosine kinase inhibitors) and not reached in cohorts EXP2, EXP3A, and EXP3B. Among the three patients in the treatment-naive cohort (EXP1) with measureable disease, partial response was observed in two and stable disease in one. Median duration of response was not reached.

Adverse Events

The most common treatment-related adverse events of any grade and of grade ≥ 3 among all 275 patients were hypercholesterolemia (81%; 16% grade 3–4) and hypertriglyceridemia (60%; 16% grade 3–4). The next most common of any grade were edema (43%), peripheral neuropathy (30%), increased weight (18%), and cognitive effects (18%). The next most common treatment-related grade ≥ 3 adverse event was increased lipase (3%), with no other individual adverse event occurring in > 2% of patients. Serious treatment-related adverse events occurred in 7% of patients. Treatment-related adverse events led to treatment discontinuation in 3%. No treatment-related deaths were reported.

The investigators concluded, "Consistent with its broad *ALK* mutational coverage and CNS penetration, lorlatinib showed substantial overall and intracranial activity both in treatment-naive patients with *ALK*-positive non–small cell lung cancer, and in those who had progressed on crizotinib, second-generation ALK tyrosine kinase inhibitors, or after up to three previous ALK tyrosine kinase inhibitors. Thus, lorlatinib could represent an effective treatment option for patients with *ALK*-positive non–small cell lung cancer in first-line or subsequent therapy."

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Disclosure: See study authors' full disclosures at thelancet.com.