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Long-term Efficacy and Safety of Lorlatinib vs. Alectinib in Patients With and Without Brain/Central Nervous System Metastases: Matching-Adjusted Indirect Comparisons

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Objectives

- This study aimed to compare the long-term efficacy and safety of lorlatinib versus alectinib in previously untreated patients with anaplastic lymphoma kinase-positive (ALK+) metastatic non-small-cell lung cancer (mNSCLC) using matching-adjusted indirect comparisons (MAICs) based on the latest 5-year data from the CROWN trial (lorlatinib). Comparisons were conducted across three populations, including the intention-to-treat (ITT) population and patients with and without brain/central nervous system (CNS) metastases at baseline.

Conclusions

- This MAIC update provides long-term comparative data, further substantiating lorlatinib's effectiveness as a first-line treatment for ALK+ mNSCLC.
- Lorlatinib demonstrated superior long-term progression-free survival (PFS) compared with alectinib in the overall ITT population. Lorlatinib had a similar safety profile to alectinib in terms of adverse events (AEs) leading to treatment changes, although it was associated with a higher incidence of grade 3+ AEs.
- Lorlatinib significantly improved PFS in patients without baseline brain/CNS metastases over time and, despite the small sample sizes, demonstrated a numerical benefit over alectinib in patients with baseline brain/CNS metastases.

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Background

- Over the past decade, the treatment landscape for ALK+ mNSCLC has evolved with the introduction of newer generations of ALK tyrosine kinase inhibitors (ALK TKIs).[1]
- Second-generation (e.g., alectinib and brigatinib) and third-generation (e.g., lorlatinib) ALK TKIs have demonstrated greater efficacy as first-line treatments for ALK+ mNSCLC than crizotinib, a first-generation ALK TKI.[2-7]
- To date, no clinical trials have evaluated lorlatinib versus alectinib as first-line treatments for ALK+ mNSCLC, which necessitates alternative methods for comparative effectiveness research.
- An MAIC from an earlier 3-year data-cut of the CROWN trial showed that lorlatinib improved PFS compared with alectinib, although lorlatinib was associated with a higher rate of grade ≥3 adverse events (AEs).[8]
- The latest data-cut from October 31, 2023, allows for an updated long-term efficacy and safety analysis with extended follow-up data, including 5-year outcome data.

Methods

- An anchored MAIC was used to adjust for baseline differences in pre-selected effect modifiers, including the Eastern Cooperative Oncology Group Performance Score, presence of baseline brain/CNS metastases, and race (Asian vs. non-Asian).
- Published aggregate data for alectinib versus crizotinib were sourced from the ALEX[5] trial, and patient-level data for lorlatinib versus crizotinib were sourced from the CROWN trial.[9,10]
- Individual patient-level data from the CROWN trial were reweighted to match the average baseline characteristics of the patients in the ALEX trial, allowing for comparisons of outcomes across the two trials in similar populations.
- The MAIC analysis included both the ITT population and subpopulations with and without baseline brain/CNS metastases.
- Treatment effects for PFS were quantified using hazard ratios (HRs), as well as differences and ratios in annual probabilities and restricted mean survival time (RMST). AEs were compared based on rate ratios (RRs) and risk differences (RDs).
  - RMST can be interpreted as the average PFS time during the period from baseline up to a specific timepoint of interest. In this analysis, RMST was measured up to year 4 and year 5.5 (end of follow-up in ALEX and CROWN).
- Observed Kaplan-Meier (KM) data were used where possible. However, parametric survival models were required to extrapolate PFS from years 2 to 4 for crizotinib (CROWN) in the subgroup with brain/CNS metastases. Due to crizotinib's limited efficacy in the brain, all patients either experienced PFS events or were censored before 24 months, necessitating the use of parametric models to estimate PFS beyond this period.

Results

ITT Population (Figure 1)

- Matching balanced differences in baseline characteristics across trials, reducing the effective sample size (ESS) by an acceptable ~15%. Lorlatinib demonstrated superior PFS compared with alectinib, reducing the risk of progression or death by 45% (HR: 0.55, 95% confidence interval [CI]: 0.34, 0.88).
- Lorlatinib extended mean PFS by 8.5 months up to year 4 and by 11.2 months up to year 5.5, with an adjusted RMST approximately 1.5 to 1.6 times higher than alectinib.
- PFS probabilities at years 1 to 5 were also significantly improved in terms of RDs with lorlatinib versus alectinib, ranging from 0.15 to 0.26 increases in annual PFS probabilities.
- Lorlatinib had a higher rate of grade ≥3 AEs than alectinib. Rates of treatment discontinuation, dose interruption, and dose reduction were similar between lorlatinib and alectinib.

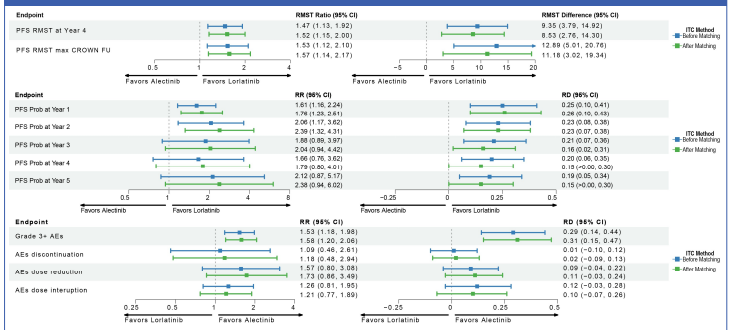
Population With Baseline Brain/CNS Metastases (Figure 2)

- Among patients with baseline brain/CNS metastases (ESS=64 of n=72), lorlatinib showed a benefit in PFS compared with alectinib, although this was not statistically significant because of the small sample size (HR: 0.47, 95% CI: 0.19, 1.20).
- At year 1, lorlatinib significantly improved PFS (RD: 0.30, 95% CI: 0.03, 0.57), and numerical benefits were observed in subsequent years.

Population Without Baseline Brain/CNS Metastases (Figure 2)

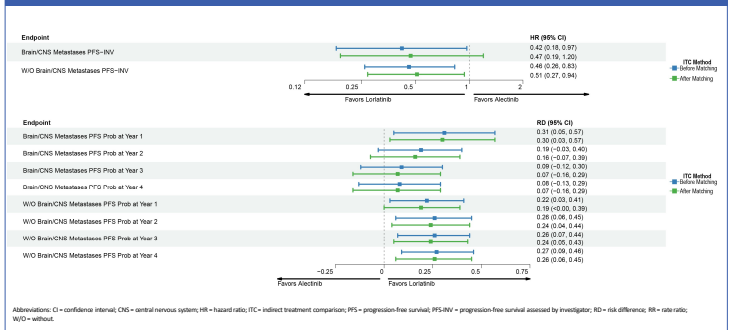
- Among patients without baseline brain/CNS metastases (ESS=195 of n=204), lorlatinib demonstrated superior PFS compared with alectinib (HR: 0.51, 95% CI: 0.27, 0.94).
- At year 1, lorlatinib was associated with a higher PFS compared with alectinib, although this result was not statistically significant. Over time, lorlatinib continued to show a consistent improvement in PFS, maintaining its advantage over alectinib and demonstrating a significant increase in PFS probabilities at years 2 to 4.

Figure 1: Lorlatinib (CROWN) versus Alectinib (ALEX) in the ITT Population



Abbreviations: AE = adverse event; CI = confidence interval; FU = follow-up; HR = hazard ratio; ITC = indirect treatment comparison; PFS = progression-free survival; PFS-INV = progression-free survival assessed by investigator; RD = risk difference; RMST = restricted mean survival time; RR = rate ratio. The difference in RMST is in terms of months.

Figure 2: Lorlatinib (CROWN) versus Alectinib (ALEX) in the Subpopulations With and Without Baseline Brain/CNS Metastases



Abbreviations: CI = confidence interval; CNS = central nervous system; HR = hazard ratio; ITC = indirect treatment comparison; PFS = progression-free survival; PFS-INV = progression-free survival assessed by investigator; RD = risk difference; RR = rate ratio; W/O = without.