Poster 1279P

# First-line lorlatinib vs crizotinib in Asian patients with *ALK*+ non-small cell lung cancer (NSCLC): 5-year outcomes from the CROWN study


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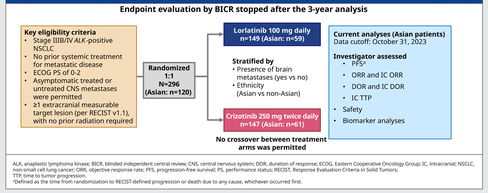
## Background

- Lorlatinib is a brain-penetrant, third-generation ALK tyrosine kinase inhibitor with antitumor activity in patients with *ALK*-positive NSCLC and has been approved in many countries as a first-line treatment in this patient population[1-4]
- At the planned interim analysis of the phase 3 CROWN study, after a median of 18.3 months of follow-up in the lorlatinib arm, PFS by blinded independent central review (BICR) was significantly longer with lorlatinib vs crizotinib (hazard ratio [HR], 0.28; 95% CI, 0.19-0.41; *P*<0.001)[1,5]
- After approximately 3 years of follow-up (data cutoff: September 20, 2021), a post hoc analysis reported that median PFS by BICR had still not been reached with lorlatinib[5,6]
  - The efficacy results from a subgroup of Asian patients in the CROWN study were consistent with those of the overall population[5]
- With a median follow-up of approximately 5 years in the overall CROWN study population, median PFS was not reached with lorlatinib and was 9.1 months with crizotinib (HR, 0.19; 95% CI, 0.13-0.27); the 5-year PFS rate with lorlatinib was 60%, and the probability of being free of IC progression was 92%[6]
- In this post hoc analysis (data cutoff: October 31, 2023), we report long-term outcomes in the Asian subgroup of the CROWN study after 5 years of follow-up

## Methods

- The CROWN study is an ongoing, international, randomized, phase 3 trial comparing lorlatinib with crizotinib in patients with previously untreated, advanced *ALK*-positive NSCLC (**Figure 1**)
  - The primary endpoint was PFS by BICR
- This is a post hoc analysis conducted after 5 years of follow-up to present efficacy, by investigator assessment only, including PFS, objective response rate (ORR), IC ORR, and IC time to progression (TTP); safety; and biomarker analyses in the Asian subgroup of the CROWN study
- Efficacy endpoints were analyzed using unstratified analyses in the Asian subgroup; efficacy and safety data were summarized descriptively

**Figure 1: Study design for post hoc analyses at 5 years in the Asian subgroup**




ALK, anaplastic lymphoma kinase; BICR, blinded independent central review; CNS, central nervous system; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; IC, intracranial; NSCLC, non-small cell lung cancer; ORR, objective response rate; PFS, progression-free survival; PS, performance status; RECIST, Response Evaluation Criteria in Solid Tumors; TTP, time to tumor progression.
[a]Defined as the time from randomization to RECIST-defined progression or death due to any cause, whichever occurred first.

## Results

### PATIENT DEMOGRAPHICS AND CLINICAL CHARACTERISTICS

- In the Asian subgroup, 120 patients (40.5% of the overall ITT population) were randomized to receive lorlatinib (n=59) or crizotinib (n=61)
- Demographics and baseline clinical characteristics were well balanced between patients in the lorlatinib and crizotinib treatment arms (**Table 1**)

**Table 1. Demographics and clinical characteristics of the CROWN Asian subgroup[a]**

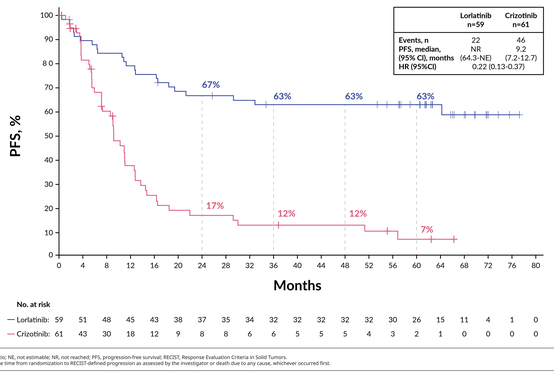
| | Lorlatinib (n=59) | Crizotinib (n=61) |
|---|---|---|
| **Age, median (range), years** | 61.0 (49.0-70.0) | 55.0 (47.0-66.0) |
| **Male, n (%)** | 32 (54.2) | 24 (39.3) |
| **Racial designation for Asian, n %** | | |
| Chinese | 25 (42.4) | 23 (37.7) |
| Japanese | 25 (42.4) | 23 (37.7) |
| Korean | 8 (13.6) | 13 (21.3) |
| Other | 1 (1.7) | 2 (3.3) |
| **ECOG PS, n (%)** | | |
| 0 | 21 (35.6) | 22 (36.1) |
| 1 | 37 (62.7) | 37 (60.7) |
| 2 | 1 (1.7) | 2 (3.3) |
| **Brain metastases at baseline, n (%)[b]** | | |
| Yes | 13 (22.0) | 16 (26.2) |
| Measurable disease | 3 (5.1) | 2 (3.3) |
| Disease not measurable | 10 (16.9) | 14 (23.0) |
| No | 46 (78.0) | 45 (73.8) |

ECOG, Eastern Cooperative Oncology Group; PS, performance status
[a]Asian patients in the full analysis set.
[b]Based on investigator assessment.

### EFFICACY OUTCOMES

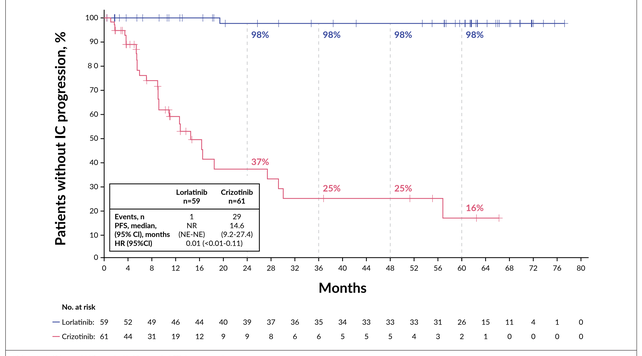
- After a median duration of follow-up of 62.4 months in the lorlatinib arm and 55.1 months in the crizotinib arm, the median PFS was not reached (95% CI, 64.3-not estimable) with lorlatinib and was 9.2 months (95% CI, 7.2-12.7) with crizotinib (HR, 0.22; 95% CI, 0.13-0.37; **Figure 2**)
- Median IC TTP was not reached in the lorlatinib arm and was 14.6 months (95% CI, 9.2-27.4) in the crizotinib arm (HR, 0.01; 95% CI, <0.01-0.11; **Figure 3**)
- Clinically meaningful improvements in ORR (81.4% vs 59.0%) and IC ORR (69.2% vs 6.3%) were observed with lorlatinib vs crizotinib, respectively (**Figure 4**)
- With lorlatinib, median PFS was not reached regardless of *EML4-ALK* variant subtype v1 or v3 or *TP53* mutation status (**Table 2**)

**Figure 2: PFS[a]**



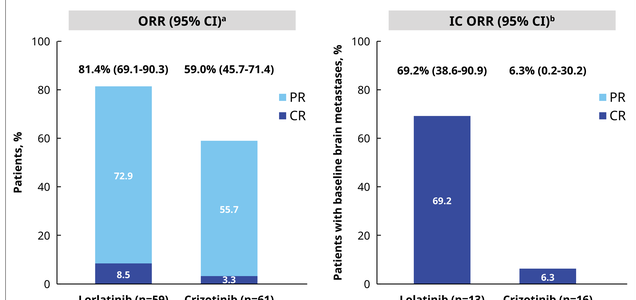

HR, hazard ratio; NE, not estimable; NR, not reached; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors.
[a]Defined as the time from randomization to RECIST-defined progression as assessed by the investigator or death due to any cause, whichever occurred first.

**Figure 3: IC TTP[a]**




HR, hazard ratio; IC, intracranial; NE, not estimable; NR, not reached; TTP, time to progression.
[a]Defined as the time from date of randomization to the date of the first documentation of progression of IC disease, based on either new brain metastases or progression of existing brain metastases.

**Figure 4: ORR and IC ORR**




CR, complete response; IC, intracranial; ORR, objective response rate; PR, partial response.
[a]Asian patients in the full analysis set.
[b]Asian patients in the full analysis set with baseline brain metastases.

**Table 2: Frequency of *EML4-ALK* fusion variants and *TP53* mutations and response to treatment**

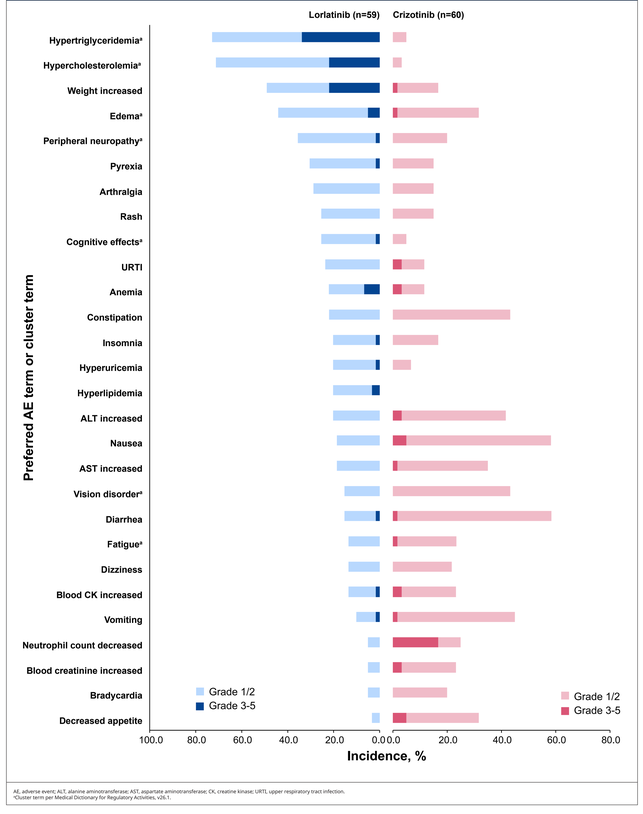
| | n (%) | | ORR (95% CI), % | | DOR, median (95% CI), months | | PFS, median (95% CI), months | | |
|---|---|---|---|---|---|---|---|---|---|
| | Lorlatinib[b] | Crizotinib[c] | Lorlatinib | Crizotinib | Lorlatinib | Crizotinib | Lorlatinib | Crizotinib | HR (95% CI) |
| ***EML4-ALK* variant 1** | 6 (10.2) | 11 (18.3) | 100 (54.1-100) | 45.5 (16.7-76.6) | NR (62.5-NE) | 9.2 (3.7-NE) | NR (64.3-NE) | 9.0 (5.5-13.7) | 0.11 (0.01-0.92) |
| ***EML4-ALK* variant 3** | 11 (18.6) | 13 (21.7) | 81.8 (48.2-97.7) | 69.2 (38.6-90.9) | NR (NE-NE) | 11.0 (5.3-NE) | NR (6.5-NE) | 9.2 (5.4-14.6) | 0.15 (0.04-0.58) |
| ***TP53* mutation positive[a]** | 20 (45.5) | 19 (39.6) | 70.0 (45.7-88.1) | 57.9 (33.5-79.7) | NR (NE-NE) | 8.0 (5.3-12.9) | NR (12.7-NE) | 7.2 (5.1-11.1) | 0.28 (0.11-0.69) |
| ***TP53* mutation negative[a]** | 24 (54.5) | 29 (60.4) | 91.7 (73.0-99.0) | 58.6 (38.9-76.5) | NR (62.5-NE) | 11.0 (7.4-12.9) | NR (29.3-NE) | 9.1 (6.0-12.8) | 0.13 (0.06-0.31) |

ALK, anaplastic lymphoma kinase; DOR, duration of response; EML, echinoderm microtubule-associated protein-like; HR, hazard ratio; NE, not evaluable; NR, not reached; ORR, objective response rate; PFS, progression-free survival; TP, tumor protein.
[a]Analysis only in patients with detectable cell-free DNA.
[b]For *EML4-ALK* analysis, n=59, and for *TP53* mutation analysis, n=44.
[c]For *EML4-ALK* analysis, n=60, and for *TP53* mutation analysis, n=48.

### SAFETY OUTCOMES

- All-cause adverse events (AEs) observed in the lorlatinib arm (**Figure 5**):
  - Any-grade, grade 3/4, and serious AEs occurred in 100%, 81.4%, and 49.2% of patients
  - The higher incidence of grade 3/4 AEs with lorlatinib was largely due to grade 3/4 hypertriglyceridemia (33.9%), hypercholesterolemia (22.0%), and increased weight (22.0%)
  - Any-grade central nervous system AEs included cognitive effects (25.4%), mood effects (11.9%), psychotic effects (5.1%), and speech effects (3.4%)
  - AEs led to dose reduction (23.7%), temporary treatment discontinuation (69.5%), or permanent treatment discontinuation (13.6%) in patients, all of which were reported during the first 26 months
- There was no correlation between patients who had a reduction in lorlatinib dose and baseline body weight
- Treatment-related AEs leading to permanent treatment discontinuation were reported in 5.1% of patients with lorlatinib and 8.3% of patients with crizotinib

**Figure 5: All-cause AEs in ≥20% of patients in either treatment arm**




AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase; URTI, upper respiratory tract infection.
[a]Cluster term per Medical Dictionary for Regulatory Activities, v26.1.

## Conclusions

- After 5 years of follow-up in the phase 3 CROWN study (NCT03052608), in the Asian subgroup of patients with advanced anaplastic lymphoma kinase (*ALK*)-positive non-small cell lung cancer (NSCLC) treated with lorlatinib:
  - Median progression-free survival (PFS) has still not been reached in the lorlatinib arm
  - The 5-year PFS rate was 62.8% in the lorlatinib arm
  - The probability of being free of intracranial (IC) progression was 97.6%
- No new safety signals were observed in the Asian subgroup with longer follow-up, and the safety profile was consistent with that observed in the overall population of the phase 3 CROWN study
- *ELM4-ALK* variant subtypes v1 or v3, and *TP53* mutation status were not predictive of PFS
- These data support the use of first-line lorlatinib in Asian patients with advanced *ALK*-positive NSCLC

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