Updated Efficacy and Safety From the Phase 3 CROWN Study of First-Line Lorlatinib vs Crizotinib in Advanced Anaplastic Lymphoma Kinase (*ALK*)–Positive Non-Small Cell Lung Cancer (NSCLC)

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Background

- Lorlatinib, a third-generation ALK inhibitor designed to cross the blood-brain barrier, offers higher potency and greater coverage of *ALK* resistance mutations than second-generation ALK inhibitors[1]
- In the planned interim analysis of the phase 3 CROWN study (NCT03052608), lorlatinib improved PFS and demonstrated IC activity in patients with untreated *ALK*-positive NSCLC[2]
  - At 18.3 months of median follow-up in the lorlatinib arm, median PFS was not reached (NR; 95% CI, NR-NR) with lorlatinib and was 9.3 months (95% CI, 7.6-11.1 months) with crizotinib (hazard ratio [HR], 0.28; 95% CI, 0.19-0.41; *P*<.001)
  - In patients with measurable baseline brain metastases, the frequency of confirmed IC response was greater with lorlatinib (82%) than crizotinib (23%)
- Based on the results of this study, the US Food and Drug Administration and regulatory authorities in Japan and Europe expanded lorlatinib approval to include first-line treatment in patients with metastatic NSCLC whose tumors are ALK positive[3-6]
- We report updated efficacy and safety data from the CROWN study after approximately 3 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 *ALK*-positive NSCLC (**Figure 1**)

Figure 1. Study design

Key eligibility criteria

- Stage IIIB/*IV ALK*+ NSCLC
- No prior systemic treatment for metastatic disease
- ECOG PS 0-2
- Asymptomatic treated or untreated CNS metastases were permitted
- ≥1 extracranial measurable target lesion (RECIST 1.1) with no prior radiation required

Randomized 1:1 N=296

- **Lorlatinib 100 mg QD n=149**
- **Crizotinib 250 mg BID n=147**

Stratified by:

- Presence of brain metastases (yes vs no)
- Ethnicity (Asian vs non-Asian)

Primary endpoint

- PFS[a] by BICR

Secondary endpoints

- Overall survival
- PFS by investigator
- ORR by BICR and investigator
- DOR, IC ORR, and IC DOR by BICR
- IC TTP by BICR
- TTR and IC TTR by BICR
- Safety
- Quality of life

No crossover between treatment arms was permitted

BID, twice daily; CNS, central nervous system; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; ORR, objective response rate; PS, performance status; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors; TTP, time to tumor progression; TTR, time to tumor response.
[a]Defined as the time from randomization to RECIST-defined progression or death due to any cause.

Results (Data Cutoff: September 20, 2021)

- Between May 2017 and February 2019, a total of 296 patients were randomly assigned to receive lorlatinib (n=149) or crizotinib (n=147)
- Median duration of treatment was 33.3 months with lorlatinib and 9.6 months with crizotinib
- Median duration of follow-up for PFS by BICR was 36.7 months with lorlatinib and 29.3 months with crizotinib
- Median PFS by BICR was NR (95% CI, NR-NR) with lorlatinib and 9.3 months (95% CI, 7.6-11.1 months) with crizotinib (HR, 0.27; 95% CI, 0.184-0.388; **Figure 2A**)
- PFS as assessed by the investigators was also longer with lorlatinib than crizotinib
  - Median PFS was NR (95% CI, NR-NR) with lorlatinib and 9.1 months (95% CI, 7.4-10.9 months) with crizotinib (HR, 0.19; 95% CI, 0.131-0.274)
- PFS benefit with lorlatinib compared with crizotinib was also observed in patients with (**Figure 2B**) and without baseline brain metastases (**Figure 2C**)
- Time to IC progression by BICR was longer with lorlatinib than crizotinib in the intention-to-treat (ITT) population (**Figure 3A**) as well as in patients with (**Figure 3B**) and without baseline brain metastases (**Figure 3C**)
  - 8 of 37 patients with baseline brain metastases and only 1 of 112 patients without baseline brain metastases had IC progression with lorlatinib treatment
- In patients with measurable baseline brain metastases, confirmed IC ORR by BICR was 83.3% with lorlatinib and 23.1% with crizotinib (**Table 1**)
  - 72.2% and 7.7%, respectively, had a complete IC response
- With longer follow-up, no new safety signals have emerged
- Grade 3/4 all-causality adverse events (AEs) occurred in 75.8% of patients in the lorlatinib arm and 57.0% in the crizotinib arm (**Table 2**)
  - The incidence of treatment-related grade 3/4 AEs in the lorlatinib arm was largely due to frequent occurrence of altered lipid levels such as hypercholesterolemia and hypertriglyceridemia (**Figure 4**)
- Treatment-related cognitive effects occurred in 20.8% of patients in the lorlatinib arm; however, most (27 of 31) cognitive effects were grade 1/2 and no grade 4 event was observed
- AEs leading to permanent treatment discontinuation were reported in 7.4% of patients in the lorlatinib arm and 9.9% in the crizotinib arm

Figure 2: PFS by BICR

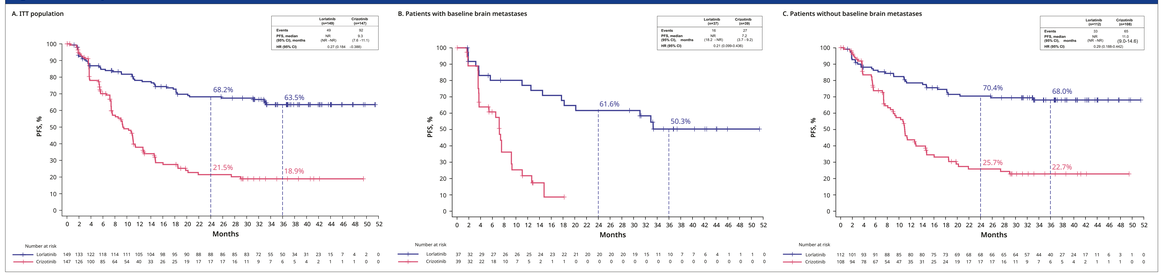


Figure 3: Time to IC progression by BICR

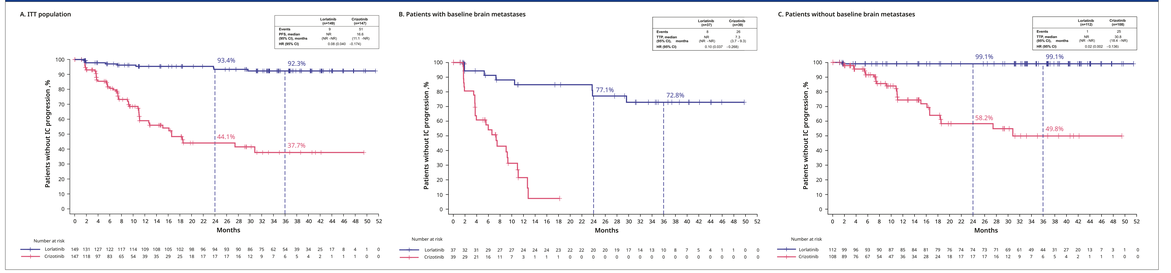


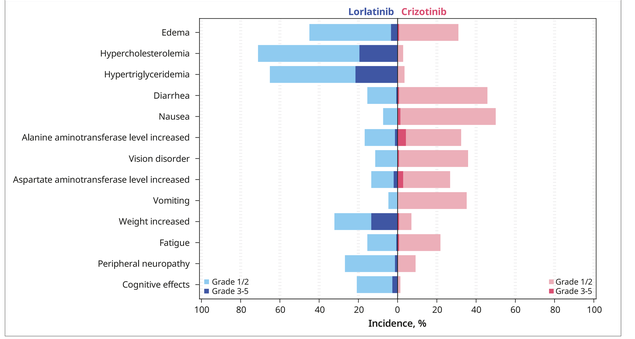
Table 1: Summary of overall and IC response by BICR

	Lorlatinib	Crizotinib
ITT population, n	**149**	**147**
Confirmed ORR by BICR, n (%)	115 (77.2)	86 (58.5)
Complete response	4 (2.7)	0
DOR, median (95% CI), months	NR (NR-NR)	9.6 (9.0-12.9)
Patients with any brain metastases at baseline, n	**37**	**39**
Confirmed IC ORR by BICR, n (%)	24 (64.9)	7 (17.9)
Complete IC response	22 (59.5)	5 (12.8)
IC DOR, median (95% CI), months	NR (NR-NR)	9.4 (6.0-11.1)
Patients with ≥1 measurable brain metastasis at baseline, n	**18**	**13**
Confirmed IC ORR by BICR, n (%)	15 (83.3)	3 (23.1)
Complete IC response	13 (72.2)	1 (7.7)
IC DOR, median (95% CI), months	NR (NR-NR)	10.2 (9.4-11.1)

Table 2: Summary of AEs

	n (%)	
	Lorlatinib (n=149)	Crizotinib (n=142)
Any-grade AE	149 (100.0)	140 (98.6)
Treatment related	145 (97.3)	133 (93.7)
Grade 3/4 AE	113 (75.8)	81 (57.0)
Treatment related	94 (63.1)	54 (38.0)
Death	10 (6.7)	7 (4.9)
Treatment related	2 (1.3)	0
Any serious AE	57 (38.3)	44 (31.0)
Treatment related	13 (8.7)	9 (6.3)
AEs leading to dose reduction	32 (21.5)	21 (14.8)
AEs leading to temporary discontinuations	84 (56.4)	69 (48.6)
AEs leading to permanent treatment discontinuation	11 (7.4)	14 (9.9)

Figure 4: Any-grade treatment-related AEs in ≥20% of patients within either treatment arm



Conclusions

- With approximately 18 months of additional follow-up since the interim analysis of the phase 3 CROWN study, lorlatinib continued to show superior overall and intracranial (IC) efficacy compared with crizotinib in patients with *ALK*-positive NSCLC
  - Progression-free survival (PFS) by blinded independent central review (BICR) remained longer with lorlatinib than crizotinib; 3-year PFS was 63.5% with lorlatinib and 18.9% with crizotinib
  - Time to IC progression was longer with lorlatinib than crizotinib
- These efficacy benefits with lorlatinib compared with crizotinib were observed not only in patients with baseline brain metastases but also in patients without baseline brain metastases
  - In patients without baseline brain metastases, only 1 of 112 patients had evidence of IC progression, suggesting a protective effect against development of brain metastases on lorlatinib treatment
- No new safety signals were observed with longer follow-up
- These updated long-term data from CROWN confirm the efficacy of lorlatinib over crizotinib in patients with treatment-naive *ALK*-positive NSCLC and support the use of lorlatinib in these patients with and without baseline brain metastases

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