Poster 979P

Long-term intracranial safety and efficacy analyses from the phase 3 CROWN study

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Conclusions

- At the 3-year follow up from the phase 3 CROWN study, the time to intracranial (IC) progression by blinded independent central review (BICR) was longer with lorlatinib than with crizotinib in patients with non-small cell lung cancer (NSCLC) with and without baseline brain metastases
- Central nervous system (CNS) adverse events (AEs) with lorlatinib involved disturbances of cognition, mood, speech, and psychosis
- These CNS effects can be managed by dose reduction or discontinuation
- CNS AEs led to only 2 patients permanently discontinuing treatment
- The incidence and prevalence of CNS AEs decreased over the 3-year time period
- Long-term analysis confirmed that CNS AEs remained manageable over time and lorlatinib dose reduction did not impact IC efficacy

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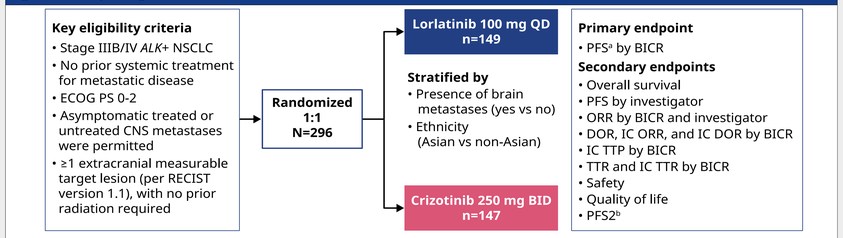
Background

- Lorlatinib is a brain-penetrant, third-generation anaplastic lymphoma kinase (ALK) inhibitor tyrosine kinase inhibitor (TKI) approved for the treatment of patients with metastatic NSCLC whose tumors are *ALK* positive[1,2]
- Results from the ongoing phase 3 CROWN study (NCT03052608) showed durable systemic and IC benefit with lorlatinib vs crizotinib in patients with treatment-naive *ALK*-positive NSCLC[2]
- Updated results from this study, with approximately 3 years of follow-up, continued to demonstrate superior progression-free survival (PFS) with lorlatinib vs crizotinib[3]
- As reported in clinical studies, a broad spectrum of CNS toxicities can occur in patients receiving lorlatinib[2,5]
- In the CROWN study, lorlatinib demonstrated increased frequencies of CNS toxicities, including disturbances of cognition, mood, speech, and psychosis, compared with crizotinib[2,3]
- We evaluated the long-term IC safety and efficacy of lorlatinib from the 3-year 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**)
  - 296 patients were randomized 1:1 to receive oral lorlatinib (100 mg once daily) or crizotinib (250 mg twice daily)
- AEs were classified and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03
- CNS AEs were categorized as cognitive, mood, speech, or psychotic events
- The incidence of new events was calculated within the following time intervals of lorlatinib treatment: <6 months, 6 months - 1 year, 1-2 years, 2-3 years, and >3 years
- IC time to progression (TTP) was defined as the time from randomization to the first objective progression of CNS disease (either new brain metastases or progression of existing brain metastases)
- IC TTP landmark analysis was performed according to dose reduction within 16 weeks

Figure 1: Study Design

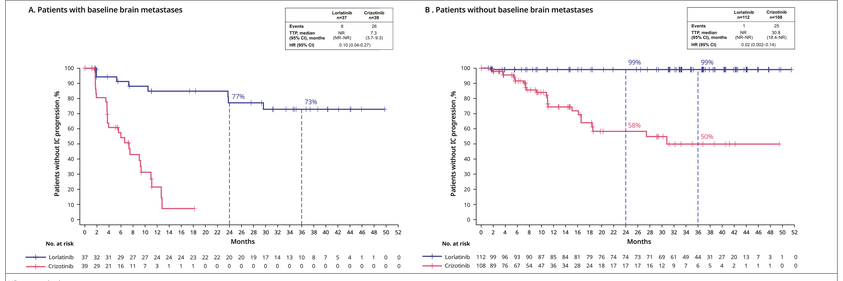


BID, twice daily; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; ORR, objective response rate; PS, performance status; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors; TTP, time to tumor progression; TTR, time to tumor response.
[a]Defined as the time from randomization to RECIST-defined progression as assessed by the independent radiologist or death due to any cause, whichever occurred first.
[b]Defined as the time from randomization to the date of progression of disease on first subsequent systemic anticancer therapy or death due to any cause, whichever occurred first.

Results (Data cutoff: September 20, 2021)

- In the CROWN study, 149 patients received lorlatinib, and 147 received crizotinib
- 76 patients had brain metastases (n=37, lorlatinib; n=39, crizotinib), and 220 did not have brain metastases (n=112, lorlatinib; n=108, crizotinib)
- In patients with baseline brain metastases, the hazard ratio (HR) for IC TTP was 0.10 (95% CI, 0.04-0.27), favoring lorlatinib over crizotinib; in those without baseline brain metastases, the HR was 0.02 (95% CI, 0.002-0.14; **Figure 2**)
- Of the 149 patients treated with lorlatinib, all-causality CNS AEs occurred in 37 (25%) in <6 months, 14 (11%) between 6 months and 1 year, 18 (15%) between 1 and 2 years, 10 (10%) between 2 and 3 years, and only 2 (2%) treated for >3 years (**Table 1**)
- The incidence and prevalence of CNS AEs by severity over time are shown in Figures 3 and 4, respectively

Figure 2: IC TTP by BICR in patients with or without brain metastases



NR, not reached.

Figure 3: Incidence of treatment-emergent CNS AEs by time and grade

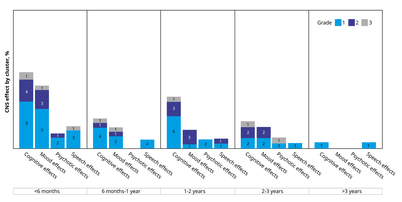
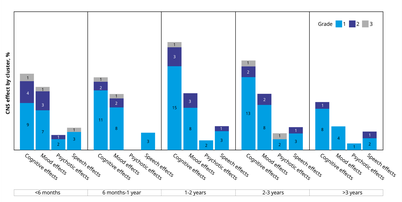
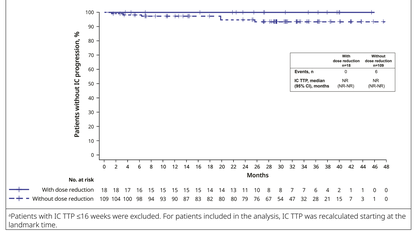


Figure 4: Prevalence of treatment-emergent CNS AEs by time and grade



- In total, 103 CNS AEs have been reported, and of these, 61 events (59%) were managed without any intervention (**Table 2**)
  - Of 61 events, 32 (52%) resolved spontaneously, 1 (2%) improved, and 28 (46%) did not resolve
- 26 events were managed with dose reduction and/or dose interruption with or without concomitant medication
- CNS AEs led to permanent discontinuation in 2 patients
- Landmark analysis of IC TTP showed comparable efficacy in patients with or without lorlatinib dose reduction within 16 weeks (**Figure 5**)

Figure 5: IC TTP based on BICR by first lorlatinib dose reduction within 16 weeks[a]



[a]Patients with IC TTP ≤16 weeks were excluded. For patients included in the analysis, IC TTP was recalculated starting at the landmark time.

Table 1: CNS AEs observed over time with lorlatinib

Patients with events[a]	Time interval				
	<6 months n=149	6 months-1 year n=129	1-2 years n=117	2-3 years n=98	>3 years n=92
Any CNS AE, n (%)	37 (25)	14 (11)	18 (15)	10 (10)	2 (2)
Cluster term					
Cognitive effects[b]	21 (14)	7 (5)	11 (9)	5 (5)	1 (1)
Mood effects[c]	17 (11)	5 (4)	4 (3)	4 (4)	0
Speech effects[d]	6 (4)	2 (2)	2 (2)	1 (1)	1 (1)
Psychotic effects[e]	4 (3)	0	2 (2)	2 (2)	0

[a]Patients were only counted once per time interval within each cluster. n was the number of patients at risk during the specified time period.
[b]Any event from HLGT Cognitive and attention disorders and disturbances, Deliria (incl confusion), or Mental impairment disorders.
[c]Any event from HLGT Anxiety disorders and symptoms, Depressed mood disorders and disturbances, Manic and bipolar mood disorders and disturbances, Mood disorders and disturbances NEC, or Personality disorders and disturbances in behavior.
[d]Any event from HLT Speech and language abnormalities.
[e]Any event from SMQ narrow Psychosis and psychotic disorders or PT of Psychotic symptom.

Table 2: Outcomes of treatment-emergent CNS AEs following dose management

Intervention	Outcome n=103				
	Resolved	Partially resolved	Not resolved	Not applicable	Total
No intervention, n (%)	32 (31)	1 (1)	28 (27)	0	61 (59)
Concomitant medication only, n (%)	8 (8)	0	6 (6)	0	14 (14)
Dose reduction only, n (%)	3 (3)	0	1 (1)	0	4 (4)
Dose interruption only, n (%)	12 (12)	2 (2)	1 (1)	0	15 (15)
Dose reduction + dose interruption, n (%)	2 (2)	0	0	0	2 (2)
Dose reduction + concomitant medication, n (%)	0	0	0	0	0
Dose interruption + concomitant medication, n (%)	1 (1)	0	3 (3)	0	4 (4)
Dose reduction + dose interruption + concomitant medication, n (%)	0	1 (1)	0	0	1 (1)
Permanent treatment discontinuation, n (%)	0	0	0	2 (2)	2 (2)
Total, n (%)	58 (56)	4 (4)	39 (38)	2 (2)	103 (100)