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LBA2

Lorlatinib vs crizotinib in the first-line treatment of patients (pts) with advanced ALK-positive non-small cell lung cancer (NSCLC): Results of the phase III CROWN study

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Background

Lorlatinib, a 3rd generation ALK tyrosine kinase inhibitor has shown overall and intracranial (IC) activity in advanced *ALK*+ NSCLC. We report interim data from an open label randomized, multicenter, phase III study of lorlatinib vs crizotinib in pts with untreated *ALK*+ NSCLC (NCT03052608).

Methods

Untreated pts with *ALK*+ Stage IIIB/IV NSCLC (104 study sites; 23 countries) were randomized 1:1 to oral lorlatinib (100 mg QD) or crizotinib (250 mg BID); stratified by presence of CNS metastases and ethnicity. The primary endpoint was progression-free survival (PFS) by blinded independent central review (BICR). PFS by investigator (INV), objective response (OR) and IC-OR by BICR, duration of response (DR), IC-DR, overall survival (OS) and safety were secondary endpoints. This planned interim analysis was conducted at 72% of 177 expected PFS events.

Results

Of 296 pts randomized, 291 received study treatment. At data cutoff (20 March 2020), median follow-up for PFS by BICR was 18.3 months (95% CI 16.4, 20.1) for lorlatinib (n=149) and 14.8 months (95% CI 12.8, 18.4) for crizotinib (n=147). PFS by BICR was significantly prolonged with lorlatinib vs crizotinib (HR 0.28; 95% CI 0.191, 0.413; stratified 1-sided p<0.001). Lorlatinib median PFS was NE (not estimable) (95% CI NE, NE) vs crizotinib 9.3 months (95% CI 7.6, 11.1). PFS by INV, OR and IC-OR by BICR were improved with lorlatinib vs crizotinib (Table). Grade 3–4 adverse events (AE)/AEs leading to treatment discontinuation: 72.5%/6.7% for lorlatinib; 55.6%/9.2% for crizotinib. The majority of Grade 3–4 AEs for lorlatinib were laboratory abnormalities, the most common of which were lipid abnormalities.Table: LBA2

	Lorlatinib (N=149)	Crizotinib (N=147)
12-month PFS rate by BICR (%)	78.1	38.7
(95% CI)	(70.3, 84.0)	(29.8, 47.5)
PFS by INV		
Median PFS, months (95% CI)	NE (NE, NE)	9.1 (7.4, 10.9)
HR (95% CI)	0.21 (0.144, 0.307)	
BOR by BICR, n (%)		
CR	4 (3)	0 (0)
PR	109 (73)	85 (58)
SD	19 (13)	41 (28)
Non-CR/Non-PD	3 (2)	3 (2)
Median DR, months (95% CI)	NE (NE, NE)	11.0 (9.0, 12.9)
IC BOR by BICR for pts with measurable brain metastases, n (%)		
Patients, n	17	13
CR	12 (71)	1 (8)

	Lorlatinib (N=149)	Crizotinib (N=147)
PR	2 (12)	2 (15)
SD	1 (6)	5 (39)
IC-DR*, range in months	3.9–31.4	5.4–11.1

BOR, best overall response; CR, complete response; PR, partial response; SD, stable disease, PD, progressive disease.
*censored in 86% and 33% of patients, respectively.

Conclusions

Lorlatinib resulted in a statistically significant and clinically meaningful improvement in PFS vs crizotinib and should be considered a new first-line treatment option for pts with *ALK+* NSCLC.

Clinical trial identification

NCT03052608.

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