Lorlatinib versus Crizotinib in Patients with Advanced ALK-Positive Non-Small Cell Lung Cancer: 5-Year Outcomes From the Phase III CROWN Study

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Background: Non-small cell lung cancer (NSCLC) is the most common type of lung cancer, accounting for approximately 85% of all lung cancer cases. ALK-positive NSCLC is a type of lung cancer involved in a specific genetic abnormality which causes the anaplastic lymphoma kinase (ALK) gene to function abnormally, leading to the growth and spread of cancer cells. Although ALK-positive NSCLC only accounts for a small percentage of all NSCLC cases (~5-7%), patients with ALK-positive NSCLC often present with advanced-stage disease at diagnosis. Due to this reason, the primary goal of treatment for ALK-positive NSCLC is to control the cancer growth and improve the patients' quality of life. Knowing these patients are with ALK positive, targeted therapy, in this case, using medications that specifically target the abnormal ALK genes, would be the most effective treatment option for this type of cancer. The current guidelines recommend ALK tyrosine kinase inhibitors (TKIs) as the standard of care for patients with ALK-positive NSCLC. Lorlatinib (Lorbrena®) is a brain-penetrant, third-generation ALK TKI that is thought to have great coverage of ALK resistance mutations. Phase III CROWN study was comparing lorlatinib vs crizotinib, two ALK TKIs approved for ALK-positive NSCLC, in patients with previously untreated, advanced, ALK-positive NSCLC. Results showed improved benefit with lorlatinib over crizotinib. Although at a medium follow-up of 60.2 months, median progression-free survival (PFS) was still not reached with lorlatinib, the drug continued to show superior efficacy over crizotinib. Over 5 years, lorlatinib shows the longest PFS benefit compared to other single-agent targeted treatments with advanced NSCLC and across all metastatic solid tumors. On March 3, 2021, the FDA granted regulatory approval to lorlatinib for patients with metastatic NSCLC whose tumors are ALK-positive.

Objectives: Evaluate the long-term outcomes of lorlatinib versus crizotinib in patients with previously untreated, advanced, ALK-positive non-small cell lung cancer

Methods:

Study design

The CROWN study (NCT03052608) is an ongoing, international, open-label, randomized phase III trial comparing lorlatinib vs crizotinib in patients with previously untreated, advanced, ALK-positive NSCLC
Patients were randomly assigned 1:1 to receive lorlatinib 100 mg once daily or crizotinib 250 mg BID in 28-day cycles

End points

Primary endpoint: PFS by BICR per RECIST version 1.1
Secondary endpoint: Overall survival (OS): assessed at the time of the protocol-specified second interim analysis after at least 139 deaths have occurred (70% information fraction); PFS by investigator assessment; Objective response, intracranial objective response, time to intracranial progression, duration of response, and duration of intracranial response by BICR and investigator assessment; Safety; Patient-reported outcomes; Biomarker analyses

Follow-up

Per protocol, end point evaluation by BICR stopped after the 3-year analysis
Tumor assessments, including brain MRI, have been performed every 8 weeks in all patients throughout the study
Primary objective of the study was met at the prespecified interim analysis; therefore, this post hoc analysis conducted after 5 years of follow-up is to present efficacy by investigator assessment only, safety, and biomarker analyses

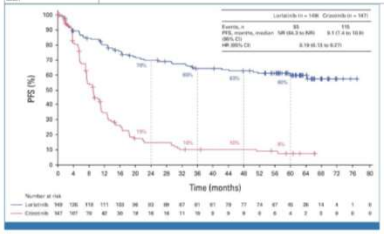
Results

Patient population / Characteristics

Total 296 patients were randomly assigned to the lorlatinib group (n = 149) or crizotinib group (n = 147)
5 patients in the crizotinib group did not receive treatment but were included in the intent-to-treat (ITT) population
At the data cutoff for the analysis (Oct 31, 2023), 74 of 149 (50%) patients treated with lorlatinib and 7 of 142 (5%) patients treated with crizotinib were continuing to receive the assigned treatment
Inclusion criteria
- ≥18 or ≥20 years of age, according to local regulations
- Had histologically or cytologically confirmed locally advanced or metastatic NSCLC with ALK status
- No previous systemic treatment for metastatic disease
- Patients with asymptomatic treated or untreated CNS metastases were eligible
- Have to have at least one extracranial measurable target lesion that had not been previously irradiated
- Have adequate bone marrow, pancreatic, renal, and liver functions

Efficacy

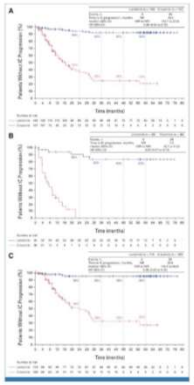
	Lorlatinib	Crizotinib
Median duration of follow-up	60.2 months (95% CI, 57.4 to 61.8)	55.1 months (95% CI, 36.8 to 62.5)
Disease progression or death with lorlatinib vs crizotinib	HR 0.19 (95% CI, 0.13 to 0.27)	
Median PFS	NR (95% CI, 64.3 to NR)	9.1 months (95% CI, 7.4 to 10.9)
4- and 5-year PFS, respectively	63% and 60% (95% CI, 51 to 68)	10% and 8% (95% CI, 3 to 14)
Among patients with baseline brain metastases	HR for disease progression or death with lorlatinib versus crizotinib was 0.08 (95% CI, 0.04 to 0.19) Median PFS Lorlatinib NR (95% CI, 32.0 to NR) Crizotinib 8 months (95% CI, 3.7 to 7.6) 5-year PFS Lorlatinib 53% (95% CI, 35 to 66) Not evaluable with crizotinib as all patients progressed or died or were censored within 2 years	
Among patients without baseline brain metastases	HR for disease progression or death with lorlatinib versus crizotinib was 0.24 (95% CI, 0.16 to 0.36) Median PFS Lorlatinib NR (95% CI, 64.3 to NR) Crizotinib 10.8 months (95% CI, 9.0 to 12.8) 5-year PFS Lorlatinib 63% (95% CI, 52 to 71) Crizotinib 10% (95% CI, 5 to 18)	
Proportion of patients with a confirmed objective response by investigator assessment	81% (95% CI, 73 to 87)	63% (95% CI, 54 to 70)
Median duration of response	NR (95% CI, NR to NR)	9.2 months (95% CI, 7.5 to 11.1)
Patients with measurable and/or nonmeasurable baseline brain metastases	Intracranial objective response was greater with lorlatinib than with crizotinib (60 versus 11%) Intracranial complete response was reported in 45% and 5% of patients, respectively. Median duration of intracranial response was NR (95% CI, NR to NR) and 12.8 months (95% CI, 7.5 to NR)	
Time to intracranial progression by investigator assessment	Longer with lorlatinib than with crizotinib, with an HR of 0.06 (95% CI, 0.03 to 0.12) Lorlatinib NR (95% CI, NR to NR) Crizotinib 16.4 months (95% CI, 12.7 to 21.9)	
Probability of being free of intracranial progression at 5 years	92% (90% CI, 85 to 96)	21% (90% CI, 10 to 35)
Among patients with baseline brain metastases	HR for time to intracranial progression favored lorlatinib over crizotinib at 0.03 (95% CI, 0.01 to 0.13) Probability of being free of intracranial progression at 5 years Lorlatinib 63% (90% CI, 64 to 93) Not evaluable with crizotinib	
Among patients without baseline brain metastases	HR for time to intracranial progression was 0.05 (95% CI, 0.02 to 0.13), favoring lorlatinib over crizotinib Probability of preventing development of brain metastases Lorlatinib 96% (95% CI, 85 to 98) Crizotinib 27% (90% CI, 14 to 43)	
The cumulative incidence of progression of brain metastases as the first event, with adjustment for the competing risks of progression other than brain metastases and death	Lower in the lorlatinib group than in the crizotinib group In the lorlatinib group, according to investigator assessment, only 4 of 114 patients without baseline brain metastases developed intracranial lesion(s), which occurred during the first 16 months of treatment	



Safety

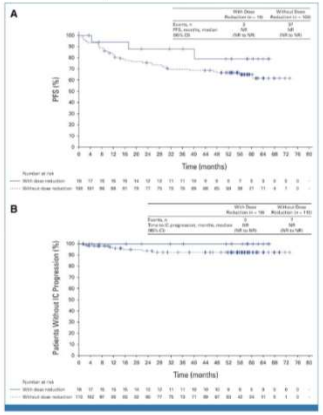
Table 2. Summary of AEs

Safety Population	Lorlatinib (n = 149)	Crizotinib (n = 142)
All causality AEs, No. (%)		
Any grade	149 (100)	140 (99)
Grade 3/4	116 (77)	81 (57)
Grade 5	14 (9)	7 (5)
Serious	65 (44)	45 (32)
Leading to temporary drug discontinuation	92 (62)	68 (48)
Leading to dose reduction	34 (23)	31 (15)
Leading to permanent drug discontinuation	16 (11)	10 (7)
Treatment-related AEs, No. (%)		
Any grade	145 (97)	133 (94)
Grade 3/4	99 (66)	55 (39)
Grade 5	2 (1)	0
Serious	14 (9)	6 (4)
Leading to temporary drug discontinuation	58 (39)	51 (36)
Leading to dose reduction	21 (21)	19 (13)
Leading to permanent drug discontinuation	8 (5)	6 (4)



Efficacy in patients who had dose reduction

Post hoc analyses conducted in patients with and without lorlatinib dose reduction within the first 16 weeks
Dose reduction did not seem to impact median PFS or time to intracranial progression



Discussion: In the CROWN study analysis, lorlatinib demonstrated superior long-term efficacy compared to crizotinib in patients with untreated advanced ALK-positive NSCLC, achieving the longest reported progression-free survival (PFS) exceeding five years. Lorlatinib also showed high intracranial response, effectively managing pre-existing brain metastases and preventing new brain metastases. Although lorlatinib was associated with a higher rate of grade 3/4 adverse events, these were manageable, and no new safety signals emerged. Overall, these findings establish lorlatinib as a leading treatment option, setting a new standard for targeted therapies in advanced NSCLC.

References: Solomon BJ, Liu G, Felip E, et al. Lorlatinib Versus Crizotinib in Patients With Advanced *ALK*-Positive Non-Small Cell Lung Cancer: 5-Year Outcomes From the Phase III CROWN Study. *J Clin Oncol*. Published online May 31, 2024. doi:10.1200/JCO.24.00581