ALK+ NSCLC: Is it time to rethink first-line targeted therapy?

Written by The Life Science Feed Editorial Team · Published 6 August 2026 · Edited by Mara Voss

Advanced anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC) presents a persistent challenge, particularly with the high incidence of brain metastases and the rapid development of resistance to first-generation ALK inhibitors. Clinicians have long sought therapies that offer durable control, especially within the central nervous system. Lorlatinib, a third-generation ALK tyrosine kinase inhibitor (TKI), emerged as a potential answer to these unmet needs.

KEY TAKEAWAYS

- The Pivot: Lorlatinib demonstrated superior intracranial and systemic efficacy over crizotinib as a first-line treatment for ALK-positive advanced NSCLC.
- The Data: The 5-year progression-free survival rate was 60% for lorlatinib vs 8% for crizotinib (HR 0.28; 95% CI, 0.20-0.39).
- The Action: Consider lorlatinib as a preferred first-line option for patients with ALK-positive advanced NSCLC, especially those with or at high risk for brain metastases.

Non-small cell lung cancer accounts for approximately 85% of all lung cancer diagnoses, and a subset of these, around 3-5%, harbor rearrangements in the ALK gene. This specific genetic alteration drives tumor growth and proliferation, making it a critical therapeutic target. Before the advent of targeted therapies, patients with ALK-positive NSCLC faced a grim prognosis, often receiving platinum-based chemotherapy with limited long-term benefits. The introduction of ALK inhibitors revolutionized treatment, but first-generation agents like crizotinib, while effective, frequently led to resistance and were particularly challenged by central nervous system (CNS) progression, a common site of metastasis in this patient population.

The need for more potent and CNS-penetrant ALK inhibitors became clear as clinicians observed patients developing resistance and experiencing disease progression in the brain. Second-generation ALK TKIs offered improvements, but the quest for a therapy that could provide sustained systemic and intracranial control continued. Lorlatinib, specifically designed to overcome resistance mutations that emerge with earlier ALK inhibitors and to achieve high CNS penetration, entered clinical development to address these critical gaps in care.

The numbers behind the shift

The CROWN trial, a pivotal Phase III, randomized, open-label study, directly compared lorlatinib to crizotinib in 296 treatment-naive patients with advanced ALK-positive NSCLC. Patients were randomized 1:1 to receive either lorlatinib 100 mg once daily or crizotinib 250 mg twice daily. The primary endpoint was progression-free survival (PFS) as assessed

by a blinded independent central review (BICR). Secondary endpoints included overall survival (OS), objective response rate (ORR), intracranial ORR, and safety. The trial enrolled patients from 106 sites across 23 countries, ensuring a diverse patient population. Eligibility criteria included an ECOG performance status of 0-2 and documented ALK rearrangement. Patients with asymptomatic brain metastases were included, reflecting the real-world clinical scenario.

Lorlatinib significantly extended PFS compared to crizotinib. At a median follow-up of 36.7 months, the median PFS for lorlatinib was not reached, while for crizotinib it was 10.9 months (HR 0.28; 95% CI, 0.20-0.39; P60% for lorlatinib compared to 8% for crizotinib, a stark difference demonstrating durable benefit. This sustained efficacy across a prolonged follow-up period highlights lorlatinib's profound impact on disease control.

The intracranial activity of lorlatinib was particularly striking. Among patients with measurable brain metastases at baseline (N=37 in the lorlatinib arm, N=32 in the crizotinib arm), the intracranial objective response rate (ORR) was 82% (95% CI, 67-92) for lorlatinib, compared to 23% (95% CI, 10-42) for crizotinib. Complete intracranial responses were observed in 71% of lorlatinib-treated patients versus 15% of crizotinib-treated patients. The median intracranial duration of response was not reached for lorlatinib, while it was 9.4 months for crizotinib. This superior intracranial efficacy is critical, as CNS progression often dictates prognosis and quality of life for these patients.

For patients without baseline brain metastases, the incidence of new brain metastases was substantially lower with lorlatinib. Only 3% of patients in the lorlatinib arm developed new brain metastases, compared to 31% in the crizotinib arm (HR 0.06; 95% CI, 0.02-0.18). This prophylactic effect against CNS progression underscores lorlatinib's potent CNS penetration and its ability to prevent one of the most debilitating complications of ALK-positive NSCLC. The overall objective response rate (ORR) was 78% (95% CI, 70-84) for lorlatinib versus 39% (95% CI, 32-47) for crizotinib. The median duration of response was not reached for lorlatinib, but was 11.0 months for crizotinib.

Safety profiles differed between the two agents. Lorlatinib was associated with higher rates of hypercholesterolemia (84% vs 4%), hypertriglyceridemia (64% vs 5%), and peripheral neuropathy (34% vs 9%). These metabolic effects were generally manageable with lipid-lowering agents and dose modifications. Grade 3 or 4 adverse events occurred in 72% of lorlatinib patients and 56% of crizotinib patients. Discontinuations due to adverse events were 7% for lorlatinib and 6% for crizotinib. While the adverse event profile of lorlatinib requires careful monitoring, particularly for metabolic changes, the benefits in PFS and intracranial control often outweigh these considerations for eligible patients.

The CROWN trial's open-label design is an obvious caveat, as it introduces potential for bias, particularly in subjective assessments of adverse events. But the primary endpoint, PFS, was assessed by a blinded independent central review, mitigating some of this concern. The trial was not powered to detect differences in overall survival at the initial analysis, and that gap matters. Longer follow-up is necessary to determine if the substantial PFS benefit translates into a significant OS advantage, which is the ultimate goal in cancer therapy. Still, the magnitude of PFS benefit and the profound intracranial efficacy provide strong evidence for its first-line use.

The patient population in CROWN was predominantly Asian (50% in the lorlatinib arm, 47% in the crizotinib arm), which is consistent with the higher prevalence of ALK rearrangements in this demographic. But the trial also included a substantial proportion of Caucasian patients (39% and 42%, respectively), suggesting generalizability across different ethnic groups. The median age was 59 years in both arms, indicating that the benefits extend to a broad adult population. The trial also included patients with varying numbers of prior metastases, further reflecting real-world heterogeneity.

Lorlatinib's mechanism of action involves potent inhibition of ALK and ROS1 kinases, including those with common

resistance mutations (e.g., G1202R) that emerge after treatment with first- and second-generation ALK TKIs. Its chemical structure allows for high permeability across the blood-brain barrier, explaining its superior intracranial activity. This targeted approach to overcoming resistance and improving CNS penetration represents a significant advancement in the management of ALK-positive NSCLC. The drug's ability to maintain disease control for such an extended period, particularly in the brain, fundamentally alters the treatment paradigm for these patients.

The CROWN trial's long-term follow-up data, presented at subsequent medical conferences, consistently reinforced the initial findings. The sustained PFS benefit, with a hazard ratio remaining stable over time, solidified lorlatinib's position as a highly effective first-line agent. The safety profile also remained consistent, with no new unexpected signals emerging with longer exposure. This extended data provides clinicians with greater confidence in the long-term management of patients on lorlatinib. The question now becomes how to sequence therapies after lorlatinib, and what novel agents will address resistance mechanisms that eventually emerge even with this potent TKI.

CLINICAL IMPLICATIONS

Lorlatinib's CROWN trial data fundamentally reshapes the initial treatment strategy for ALK-positive advanced NSCLC. The sheer magnitude of the progression-free survival benefit, coupled with its unparalleled intracranial efficacy, makes a compelling case for its use over crizotinib as a first-line agent. Clinicians must now consider lorlatinib as the benchmark for initial therapy, particularly for patients presenting with or at high risk for brain metastases.

The observed metabolic adverse events, specifically hypercholesterolemia and hypertriglyceridemia, require proactive management. This means regular lipid panel monitoring and, in many cases, initiating lipid-lowering therapy. Ignoring these side effects risks trading one disease burden for another, a trade-off no patient should have to make if preventable.

For the pharmaceutical industry, these results set a high bar for future ALK inhibitors. Any new agent entering this space will need to demonstrate not only superior or non-inferior systemic efficacy but also comparable or better CNS penetration and a more favorable safety profile. The era of incremental improvements in ALK inhibition is over; durable, comprehensive disease control is now the expectation.

The long-term overall survival data remains an open question, but the substantial and sustained PFS benefit, especially with such robust intracranial control, suggests a strong likelihood of improved survival. Patients with ALK-positive NSCLC can now expect a significantly longer period without disease progression, offering a better quality of life and more time before needing subsequent lines of therapy.

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