



## **ALK Positive Lung Cancer (UK)**

# **First-Line Treatment of ALK-Positive NSCLC: Lorlatinib Upfront or Alectinib First?**

### **1. Introduction**

Alectinib and Brigatinib, 2<sup>nd</sup> generation ALK inhibitors, have been used for 1<sup>st</sup> line treatment in the UK since 2018 and 2020, respectively. Although the side effects differ, Alectinib and Brigatinib are similarly effective. Alectinib has greater market penetration.

In 2022, Lorlatinib, a 3<sup>rd</sup> generation ALK inhibitor, was approved for 1<sup>st</sup> line use in Scotland and in 2025 in the rest of the UK. Lorlatinib has its own specific side effects.

At the date of this paper, October 2026, all three drugs are being prescribed for 1<sup>st</sup> line use.

Because survival with ALK-positive disease is now often measured in years rather than months, first-line choice involves a trade-off between depth and durability of control, tolerability over a long treatment horizon, and what remains available after progression.

This paper is for discussion between clinicians and informed patients. It is not for individual medical advice. It has been produced with the assistance of artificial intelligence.

### **2. Summary**

This paper focuses on the central question in the choice between the two most debated, Alectinib and Lorlatinib: should a fit patient start with the most potent, brain-penetrant agent (Lorlatinib), or begin with the better-tolerated agent (Alectinib) and keep Lorlatinib in reserve?

The case for Lorlatinib upfront is strong on disease-control endpoints. In the CROWN trial, 55% of patients were alive and progression-free at seven years, and median progression-free survival (PFS) has still not been reached after a median follow-up of about 83 months. Intracranial protection was exceptional. The case for caution is equally real: there is no randomised head-to-head trial against Alectinib, no overall survival (OS) advantage has been shown over Alectinib, and Lorlatinib carries a heavier burden of metabolic and neurocognitive side effects. This paper sets out the evidence for each position and closes with questions for discussion.

### **3. The evidence base**

Both drugs were tested against crizotinib, not against each other. Cross-trial comparisons are therefore indirect and should be read with caution.

|                     | Alectinib (ALEX)                                                   | Lorlatinib (CROWN)                                                                                   |
|---------------------|--------------------------------------------------------------------|------------------------------------------------------------------------------------------------------|
| Comparator          | Crizotinib                                                         | Crizotinib                                                                                           |
| Median PFS          | 34.8 months (investigator-assessed) vs 10.9                        | Not reached at 7 years (95% CI lower bound 64.3 months) vs 9.1                                       |
| PFS hazard ratio    | 0.43                                                               | 0.19                                                                                                 |
| Median follow-up    | about 4 years for PFS                                              | about 7 years (83 months)                                                                            |
| Overall survival    | Median 81.1 months vs 54.2; HR 0.78, not statistically significant | Immature at 7 years (123 deaths, below the 139 needed for the next planned analysis)                 |
| Intracranial effect | Strong CNS activity                                                | HR 0.06 for time to intracranial progression; no new intracranial progression events after 30 months |

The headline difference in PFS hazard ratios (0.43 vs 0.19) is striking, but trial populations, imaging schedules and assessment methods (investigator-assessed in ALEX, independent central review in CROWN) differ, so the two figures cannot be subtracted from one another.

## 4. The case for starting with Lorlatinib

### 4.1 Depth and durability of control

The seven-year update of CROWN, presented at ASCO 2026 and published in *Annals of Oncology*, shows the most durable disease control reported to date for a targeted therapy in advanced NSCLC. At a median follow-up of 83 months (data cut-off 31 October 2025), median investigator-assessed PFS with Lorlatinib was still not reached (hazard ratio 0.19), against 9.1 months with crizotinib. The seven-year PFS rate was 55% versus 3%, and 44% of Lorlatinib patients were still on treatment at cut-off. Only seven PFS events occurred between years five and seven. Patients who were progression-free at 24 months had a 79% probability of remaining so at seven years, which may be the most useful figure for a newly diagnosed patient: if the first two years go well, the plateau is likely to hold. For comparison, Alectinib's median PFS was 34.8 months in ALEX, and the Italian ATLAS real-world registry reported a median of 43.1 months for first-line Alectinib.

Three caveats apply. The seven-year analysis was post hoc and investigator-assessed, not based on the blinded central review used for the primary endpoint, and the trial was sponsored by Pfizer. Median PFS has still not been observed, so projections that it may reach 8 to 9 years or more are estimates, not data. And the comparator remains crizotinib.

### 4.2 Protection of the brain

Brain metastases are a major source of morbidity in ALK-positive disease, and a substantial proportion of patients develop them over the course of their illness. In the seven-year CROWN analysis, the hazard ratio for time to intracranial progression versus crizotinib was 0.06, and about 92% of Lorlatinib-treated patients remained free of CNS progression. No new intracranial progression events occurred after the first 30 months on Lorlatinib. The authors note that Lorlatinib remains the only first-line ALK inhibitor with intracranial data of this duration.

Two cautions apply. First, the comparator was crizotinib, which penetrates the brain poorly; the gap against Alectinib, itself a CNS-active drug, is likely to be narrower. In the ATLAS registry, only 3.6% of patients on first-line Alectinib had the brain as a new site of progression. Second, the figure sometimes quoted as a “92% reduction in risk” is better described as follows: about 92% of Lorlatinib patients remained free of CNS progression at seven years, and the hazard ratio of 0.06 corresponds to a relative risk reduction of about 94%.

### **4.3 The sequencing argument**

A common instinct is to hold Lorlatinib in reserve. The counter-argument is that Lorlatinib performs far less durably when it is used after a second-generation inhibitor. Reported median PFS for Lorlatinib after prior Alectinib or other second-generation TKIs is mostly in the range of about 5.5 to 9 months (the phase 2 cohort reported 5.5 months; ATLAS reported 7.5 months with a median OS of 26.4 months from the start of second-line therapy). Some real-world series report much longer outcomes, but these are generally selected patients who had prolonged benefit from earlier treatment.

If Lorlatinib is started first, a high proportion of patients may remain on a single drug for many years; by contrast, Alectinib followed by Lorlatinib has a typical combined control time that appears shorter, although no randomised study has compared the two strategies. The argument is persuasive, but it rests on indirect comparison and on the assumption that long-term control with one drug is preferable to two drugs in sequence.

### **4.4 Side effects can often be managed**

Lorlatinib is associated with raised cholesterol and triglycerides, weight gain, oedema, peripheral neuropathy, and CNS effects such as mood change, cognitive slowing and sleep disturbance. In CROWN, high-grade adverse events were more frequent than with crizotinib, driven largely by laboratory abnormalities. Dose reduction is now routine practice. In the seven-year CROWN analysis, dose reductions did not appear to affect long-term PFS or intracranial outcomes, which supports dose modification instead of treatment discontinuation. Lipid-lowering therapy, weight monitoring and structured cognitive and mood check-ins are part of standard supportive care.

The seven-year analysis found no new safety signals. According to the sponsor's report, CNS effects led to permanent discontinuation in 2.1% of patients, temporary interruption in 10% and dose reduction in 8%.<sup>5</sup> The case for caution

### **5.1 No head-to-head data and no demonstrated survival advantage**

There is currently no randomised trial of Lorlatinib versus Alectinib. Longer PFS is an important endpoint, but not equivalent to longer survival. ALEX has reported an OS median of 81.1 months with Alectinib, and ALK-positive patients can live for many years across several lines of therapy. Whether upfront Lorlatinib improves OS compared with Alectinib followed by Lorlatinib is unknown, and it may be difficult to demonstrate given the effect of later-line treatment.

CROWN's own survival data are also not yet available. At the seven-year cut-off, 123 of 296 patients had died, short of the 139 deaths required for the protocol-specified interim OS analysis, so no survival comparison has been reported even against crizotinib. This is the main missing piece of evidence: the PFS plateau strongly suggests survival will be excellent, but that is an inference rather than a result.

## 5.2 Tolerability and quality of life over many years

The patients most likely to benefit from Lorlatinib's durability are young and fit, and the same patients will live with its side effects for the longest time. Cognitive and mood effects, although often mild and reversible, can affect work, relationships and driving. Alectinib is generally better tolerated in these domains, which matters if treatment is expected to last for a decade.

## 5.3 Option value after progression

Starting with Alectinib preserves Lorlatinib as a potent subsequent therapy, particularly for tumours that progress through ALK mutations. Starting with Lorlatinib leaves fewer targeted options after progression, typically chemotherapy, other TKIs with limited activity, or clinical trials, although biopsy at progression can sometimes guide further targeted treatment.

## 5.4 TP53 and other high-risk features

TP53 co-mutation is a recognised adverse prognostic marker. In a Japanese cohort of 90 patients treated with Alectinib, median PFS was 11.7 months with a TP53 mutation, compared with a median not reached for TP53 wild-type tumours. This is sometimes used to argue for Lorlatinib in TP53-mutant disease. However, TP53 mutation also appears to worsen outcomes on Lorlatinib (in the German early-access programme, median PFS was 3.7 versus 10.8 months), although those were heavily pretreated patients. In CROWN, the seven-year PFS benefit with Lorlatinib was consistent across all prespecified subgroups, and biomarker analyses including TP53 are emerging. TP53-specific outcomes from the seven-year publication were not available for this paper and should be checked before this argument is relied on. Any such subgroup figure would come from a trial against crizotinib, so it could suggest, but not prove, that Lorlatinib upfront blunts the TP53 penalty seen with Alectinib. Baseline molecular profiling is an area where more data are needed.

## 6. The fourth generation: what is, and is not, available

Next-generation agents such as neladalkib (NVL-655) are designed to be ALK-selective, brain-penetrant and active against compound resistance mutations that can arise after Lorlatinib, while sparing TRK to reduce neurological side effects. Pivotal data from the ALKOVE-1 trial support a new drug application for TKI-pretreated patients; the FDA has granted it priority review, with a decision date reported as 27 November 2026. A randomised phase 3 trial in the first-line setting has begun but has no results.

This matters for the sequencing debate in two ways. A credible post-Lorlatinib option reduces the force of the argument that starting with Lorlatinib leaves nothing in reserve. But it is not yet approved, would initially be approved only for pretreated patients, and access will vary between health systems. A treatment plan should not rely on a drug that has not yet been approved or reimbursed.

## 7. Why might guidelines and protocols lag?

The gap between the strongest efficacy signal and routine practice is often framed as institutional inertia. Several more substantive reasons deserve to be weighed.

- **Evidence structure.** No head-to-head comparison with Alectinib, and no demonstrated OS benefit.
- **Familiarity.** Alectinib has a longer record of use, a predictable safety profile and substantial real-world data.
- **Tolerability.** Clinicians may prefer to avoid metabolic and neurocognitive toxicity unless the benefit is clear for the individual patient.

- **Access and cost.** Funding bodies often require evidence of OS or quality-adjusted benefit, and reimbursement of Lorlatinib as first-line therapy differs by country.
- **Time.** Guidelines and local protocols are updated on review cycles that may trail new data by a year or more. Readers should check the current version of their national or institutional guideline, since several now list Lorlatinib as a first-line option alongside Alectinib and brigatinib.

## 8. Which patients might favour which approach?

| Considerations favouring upfront Lorlatinib                                                                                     | Considerations favouring Alectinib first                                                              |
|---------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|
| Brain metastases at diagnosis, especially multiple or leptomeningeal disease                                                    | Pre-existing psychiatric or cognitive vulnerability                                                   |
| Young, fit patient prioritising the longest possible first-line control                                                         | Significant cardiovascular risk or uncontrolled dyslipidaemia                                         |
| High-risk molecular features (for example TP53 co-mutation or EML4-ALK variant 3), while recognising the limits of the evidence | Strong preference for a milder start with fewer short-term side effects                               |
| Access to monitoring and supportive care for lipids, weight and mood                                                            | Concern about limited options after progression, or limited access to Lorlatinib and later-line drugs |

## 9. Questions for discussion

1. Is a PFS difference versus a common comparator (crizotinib) sufficient to justify upfront Lorlatinib in the absence of a head-to-head trial or an OS benefit?
2. How should the burden of long-term cognitive, mood and metabolic effects be weighed against reduced risk of brain progression?
3. Does the approach of a fourth-generation inhibitor change the value of preserving Lorlatinib for later, or does it strengthen the case for using the strongest agent first?
4. Should tumour biology (TP53, EML4-ALK variant) drive the choice of first-line drug, and what evidence would be needed?
5. How should health systems that fund treatment decide when emerging evidence is strong enough to change the standard of care?
6. What does shared decision-making look like when two reasonable options offer different trade-offs between time and quality of life?

## 10. Conclusion

Lorlatinib offers the deepest and most durable disease control yet seen in ALK-positive NSCLC (55% of patients progression-free at seven years in CROWN), with exceptional protection against brain progression, and for fit patients with high-risk features it is a compelling first-line choice. Alectinib remains a legitimate, well-evidenced alternative with a milder side-effect profile and an OS median exceeding six years in ALEX, and starting with it does not rule out Lorlatinib later. The honest summary is that the strongest evidence favours Lorlatinib for disease control, while evidence of net benefit on survival and quality of life over a lifetime has yet to be gathered, and CROWN's own survival analysis is still awaited. The decision is best made with the patient, with early molecular profiling, baseline brain imaging, and a clear plan for monitoring and dose adjustment.

## Key sources

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October 2026

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