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COMMENTARY

First Things First: Navigating *ALK*-Positive Metastatic Non-Small Cell Lung Cancer Treatment Options—A Podcast

Eric K. Singhi[1] · **Eric S. Nadler**[2]

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Abstract

The podcast discusses the available treatment options for patients with anaplastic lymphoma kinase (*ALK*)-positive metastatic non-small cell lung cancer (NSCLC) and focuses on the efficacy and safety of first-line treatments and sequencing strategies. Patients with *ALK*-positive NSCLC often need multiple lines of therapy owing to the development of resistance, disease progression, brain metastases, or adverse events. Several options are available for the treatment of *ALK*-positive NSCLC; therefore, it is important to make an informed decision on which treatment to use in the first line. The podcast also discusses the challenges in treatment sequencing due to high attrition rates from first-line to second-line therapy and the decline in treatment efficacy with each additional line. Real-world data indicate that many patients do not receive second-line therapy after discontinuing first-line treatment. The discussion emphasizes the importance of consideration of drug efficacy, safety outcomes, potential treatment resistance, and development of brain metastases when determining treatment strategies. Ultimately, it is essential to select the best treatment first and proactively manage any potential adverse events to ensure that patients can derive clinical benefit and safely remain on therapy.

The podcast and transcript can be viewed below the abstract of the online version of the manuscript. Alternatively, the podcast can be downloaded here: https://doi.org/10.6084/m9.figshare.30762473.

Key Points

Several first-line treatment options are currently available for patients with *ALK*-positive metastatic NSCLC.

The risk–benefit profile of each treatment option should be assessed and discussed with patients before starting treatment.

✉ Eric K. Singhi
EKSinghi@mdanderson.org

[1] The University of Texas MD Anderson Cancer Center, Houston, TX, USA

[2] Baylor University Medical Center, Dallas, TX, USA

Transcript

Eric Singhi, MD (ES): Thoracic and Head & Neck Medical Oncologist and Assistant Professor at The University of Texas MD Anderson Cancer Center

Eric Nadler, MD, MPP (EN): Medical Director of US Oncology Health Informatics and Internet Technology at Baylor University Medical Center

1 Introduction

ES: Hello, and welcome to the podcast. My name is Dr. Eric Singhi, and I am a Thoracic and Head & Neck Medical Oncologist and Assistant Professor at The University of Texas MD Anderson Cancer Center.

EN: Hello, my name is Eric Nadler, and I'm the Medical Director of Health Outcomes at Baylor University Medical Center and a head and neck and lung cancer doctor there as well.

In today's podcast, which is being hosted in the journal *Targeted Oncology*, we discuss the use of first-line treatments in patients with anaplastic lymphoma kinase–positive, or *ALK*-positive, metastatic non-small cell lung cancer (NSCLC). We will provide an overview of the guidelines for first-line treatment and discuss the clinical trials and evidence of efficacy and safety supporting these first-line

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treatment options, sequencing strategies, patient attrition from the first line to the second line, and the appropriate treatment based on the available data.

2 EN: Eric, can you provide us with an overview of ALK-positive NSCLC?

ES: Sure! So NSCLC, it accounts for approximately 85% of all lung cancers and is the leading cause of cancer deaths worldwide [1].

ALK-positive NSCLC represents 3–5% of all NSCLC cases [2–4] and is more common in younger patients and patients with no smoking history [5, 6].

ALK-positive NSCLC is characterized by a genetic rearrangement of the *ALK* gene, leading to the expression of fusion proteins that function as potent oncogenic drivers [7]. These gene arrangements also confer sensitivity to treatment with ALK tyrosine kinase inhibitors, or TKIs [4, 8].

Brain metastases in patients with *ALK*-positive NSCLC remain a key clinical challenge, with the baseline and cumulative incidences higher than with most other oncogenes [9–11]. So, in clinical studies, 26–42% of patients had brain metastases diagnosed at baseline [12–15]. Furthermore, brain metastases can develop after the initial diagnosis of *ALK*-positive NSCLC, with more than half of patients developing brain metastases over the course of their disease [11], and varying intracranial outcomes reported in clinical trials over different follow-up periods [12–15].

Brain metastases are associated with a poor prognosis; therefore, treatments to control intracranial disease and delay the onset of new brain metastases are important, and central nervous system, or CNS, response can influence treatment choices [16]. A real-world study published this year showed that brain metastases continue to impact Medicare patients, with incident brain metastases associated with a higher risk of mortality [17].

Patients with *ALK*-positive NSCLC often need multiple lines of therapy due to development of resistance, disease progression, brain metastases, or adverse events [18]. Various options are available for the treatment of *ALK*-positive NSCLC; therefore, it is important to make an informed decision on which treatment to use in the first line.

3 ES: Eric, can you provide us with an overview of the current guidelines for first-line treatment in patients with ALK-positive metastatic NSCLC?

EN: Yes. Currently, six ALK TKIs are available for patients with *ALK*-positive metastatic NSCLC.

According to the National Comprehensive Cancer Network® (NCCN®) Clinical Practice Guidelines In Oncology (NCCN Guidelines®), second-generation ALK TKIs such as alectinib, brigatinib, and ensartinib and the third-generation ALK TKI lorlatinib are recommended as preferred first-line treatments for patients with *ALK*-positive metastatic NSCLC [13, 19].

The third-generation ALK TKI lorlatinib was designed with improved ability to cross the blood–brain barrier and to overcome *ALK* resistance mutations [20].

These next-generation ALK TKIs have demonstrated superior systemic and intracranial efficacy, including improved progression-free survival, or PFS, compared to crizotinib, a first-generation ALK TKI, in randomized clinical trials [12–15, 21]. These results are summarized in Supplementary Fig. 1 that accompanies this podcast.

Other ALK TKIs can be useful in certain circumstances [19]. When deciding upon a treatment, clinicians select an ALK TKI based on the balance of its clinical efficacy profile, including CNS activity, as well as its adverse event profile.

4 EN: Eric, can you tell us about the trials and their results that positioned the second-generation ALK TKIs as preferred agents in the current guidelines?

ES: Absolutely. So, several phase 3 studies have compared the second-generation ALK TKIs to first-generation crizotinib, and these include alectinib in the ALEX study [14, 22], brigatinib in the ALTA-1L study [12, 21], and ensartinib in the eXalt3 study [13]; these studies led to the US Food and Drug Administration, or FDA, approval of these ALK TKIs in the first-line setting [23–25].

The primary analysis from the ALEX trial showed significantly improved investigator-assessed PFS with alectinib compared with crizotinib, with a hazard ratio of 0.47 [14].

Time to CNS progression was significantly longer with alectinib than with crizotinib, with a hazard ratio of 0.16. The 12-month cumulative incidence rate was 9.4% with alectinib versus 41.4% with crizotinib.

In a follow-up analysis, at 37.8 months of median follow-up, median PFS was 34.8 months with alectinib, with a 4-year PFS rate of 44% [22].

In the final analysis of the ALEX study, after a median follow-up of 53.5 months with alectinib and 23.3 months with crizotinib, median overall survival was 81.1 months with alectinib compared with 54.2 months with crizotinib [26]. The 7-year overall survival rate was 48.6% with alectinib compared with 38.2% with crizotinib. However, the study was not powered to demonstrate any statistically significant difference in OS.

5 ES: Eric, can you review the key efficacy results from the other second-generation ALK TKIs?

EN: Of course. Let's start with the first interim analysis from the ALTA-1L trial, which showed superior PFS with brigatinib compared with crizotinib, and a hazard ratio of 0.49 by blinded independent central review [12].

In the follow-up analysis, at 40.4 months of median follow-up, the median PFS was 24.0 months with brigatinib, with a 4-year PFS rate of 36% [21].

The 4-year overall survival rate was 66% with brigatinib and the 4-year intracranial PFS rate was 46% in the intention-to-treat population [21].

In the eXalt3 trial, with a median follow-up of 23.8 months, a median PFS was 25.8 months with ensartinib in the intention-to-treat population [13].

At the time of the final analysis of overall survival, no statistical significant difference was observed between ensartinib and crizotinib [27].

6 EN: Eric, can you talk through the key efficacy results for the third-generation ALK TKI lorlatinib?

ES: Certainly. The interim analysis from the CROWN study demonstrated significantly longer PFS with lorlatinib than crizotinib, with a hazard ratio of 0.28 [15].

In subsequent 3- and 5-year follow-up analyses, lorlatinib continued to show superior efficacy in patients with *ALK*-positive metastatic NSCLC [28, 29].

As presented at ASCO 2024 by Dr. Ben Solomon, at a median follow-up of 60.2 months, median PFS was not reached with lorlatinib, with a 5-year PFS rate of 60%, which is unprecedented in the treatment of stage IV NSCLC.

The time to intracranial progression was longer with lorlatinib than with crizotinib, with a hazard ratio of 0.06. The probability of being free of intracranial progression was 92% with lorlatinib and 21% with crizotinib at 5 years [29]; brain scans were done every 8 weeks.

Overall survival follow-up is still ongoing; the results were immature at the time of the 5-year analysis.

7 EN: Now that we've discussed efficacy, let's talk about some of the safety data that have come from these clinical trials

EN: With alectinib, the most common adverse events were constipation in 37% of patients, anemia in 26%, and fatigue in 22% [22]. Grade 3–5 adverse events occurred in 52% of the patients treated with alectinib. Adverse events led to dose interruptions in 26% of patients, dose reductions in 20% of patients, and treatment discontinuation in 14% of patients, with reasons for discontinuation including increased alanine aminotransferase, increased aspartate aminotransferase, and pneumonitis [30].

With brigatinib, the most common adverse events were diarrhea in 58% of patients, increased blood creatine phosphokinase in 50%, and cough in 36% [21]. Myalgia was reported in 10% of patients treated with brigatinib versus 8% in patients treated with crizotinib. Grade 3 or 4 adverse events occurred in 70% of patients treated with brigatinib. Brigatinib was associated with the unique side effect of interstitial lung disease or pneumonitis, which occurred in 6% of patients and led to dose reductions in 1%. Adverse events led to dose interruptions in 72% of patients, dose reductions in 44% of patients, and treatment discontinuation in 13%.

With ensartinib, the most common treatment-emergent adverse events were rash in 71% of patients, increased alanine aminotransferase in 50%, and increased aspartate transaminase in 38% [13]. Grade 3 or 4 adverse events occurred in 50% of patients. Treatment-related adverse events led to dose reduction in 24% of patients and treatment discontinuation in 9%.

ES: With lorlatinib, the most common adverse events were hypercholesterolemia in 72% of patients, hypertriglyceridemia in 66%, and edema in 57% [29]. Grade 3 or 4 adverse events occurred in 77% of patients. Adverse events led to dose interruption in 62% of patients, dose reduction in 23%, and permanent discontinuation in 11%.

With lorlatinib, CNS adverse events, unique but important adverse events to be aware of, were reported in 42% of patients; the majority, or 86%, of these events were grade 1 or 2. CNS adverse events were further broken down into cognitive effects that occurred in 28% of patients, mood effects in 21%, speech effects in 6%, and psychotic effects in 5%.

Among the 149 patients treated with lorlatinib in the CROWN study, cognitive effects led to permanent discontinuation in 2 patients, and psychotic effects led to permanent discontinuation in 1 patient, indicating that most of the CNS adverse events can be managed. Overall, 60% of CNS adverse events resolved [31].

A post hoc analysis showed that lorlatinib dose reduction in the first 16 weeks of treatment did not impact median PFS or time to intracranial progression, indicating that dose reduction may be a strategy to mitigate toxicity without compromising efficacy [29].

Another CROWN post hoc analysis presented recently at ASCO 2025 showed us that dose reductions enabled patients to continue treatment on lorlatinib. The median duration of treatment after reduction was 42.2 months for the duration on a 75-mg dose (one dose reduction) and 20.7 months for the duration on a 50-mg dose (two dose reductions) [32].

8 ES: Eric, given the treatment options, what are the common sequencing patterns observed in clinical practice?

EN: The current NCCN Guidelines® indicate that following progression on second- or third-generation ALK TKIs, a different second- or third-generation ALK TKI can be used as subsequent therapy [19].

However, no prospective trials have compared these drugs sequentially, so data from clinical trials are limited.

Attrition rates are high from first-line to second-line therapy, and many patients do not receive a second-line therapy. A real-world study showed that among patients who discontinued first-line therapy, 44% did not receive a second-line therapy [33].

In addition, clinical trials have shown that treatment efficacy declines with each additional line of therapy [22, 29, 34, 35], suggesting that efficacy in the first line does not translate to the second line.

Therefore, patients may be most likely to derive the greatest clinical benefit from the most effective ALK TKIs in the first-line setting [33].

After 5 years of follow-up in the CROWN study, in a small cohort of 38 patients treated with lorlatinib who had at least 1 subsequent systemic anticancer therapy, the most common subsequent systemic therapy was alectinib or chemotherapy [36].

In a US real-world evidence study that looked at sequencing patterns in patients treated with second-generation ALK TKIs prior to lorlatinib's FDA approval, the most frequent treatment sequence was alectinib followed by lorlatinib [33]. The FDA approved lorlatinib for *ALK*-positive NSCLC in the first line in March of 2021.

It is important to note that patients may eventually develop resistance to ALK TKIs [18]. Depending on the specific ALK TKI, resistance may be due to on-target alterations in *ALK* (for example, mutations or gene amplification), *ALK*-independent resistance mechanisms (for example, the activation of a bypass signaling pathway), or progression in the CNS due to inadequate CNS penetration [18].

Therapy sequencing should thus consider the efficacy and safety outcomes with each drug, the possibility of drug resistance, and the health of the patient. Decisions should be made based on shared decision-making by the patient and the physician.

9 EN: Eric, what are some considerations when selecting the appropriate first-line treatment?

ES: When considering treatment options for our patients with *ALK*-positive NSCLC, we must remember that these patients are typically younger and active, often caring for young families, and are working; therefore, delaying development of brain metastases and controlling active metastases is significant for them. In oncology, using the best treatment first should be prioritized because second-line treatment is not guaranteed. If the patient does not tolerate the first-line treatment, then other options can be considered.

Given that the clinical trials compared a second- or third-generation ALK TKI against crizotinib, head-to-head clinical comparative data for these next-generation ALK TKIs are lacking, resulting in difficulty comparing the efficacy and safety of these drugs and making a selection [12–15, 21, 22, 28, 29, 37].

Comparisons between these trials should be made with caution as the methods and patient populations differed. Notably, diagnostic methods varied, with fluorescence in situ hybridization used in ALTA-1L and eXalt3 and immunohistochemical assays in ALTA-1L, ALEX, and CROWN [12–15, 38].

Full disease characterization is important when selecting first-line treatment as the *EML4:ALK* variant or presence of co-mutation may impact treatment response [29, 30, 38].

In a 5-year matching-adjusted indirect comparison, despite the small sample sizes, lorlatinib demonstrated a numerical benefit over alectinib in patients with baseline brain metastases. The safety profile was similar between lorlatinib and alectinib in terms of adverse events leading to treatment changes; however, rates of grade ≥ 3 adverse events were higher with lorlatinib [39].

Selecting the optimal treatment requires an analysis of the available evidence, with attention to systemic and intracranial efficacy, as well as patient factors and preferences [40]. Each of the ALK TKIs has their own reported adverse event profile that needs to be considered. However, the studies show that some of these events can be managed with dose reduction or interruption [13, 14, 21, 29, 41].

We mentioned earlier that brain metastases are highly prevalent among patients with *ALK*-positive NSCLC at baseline [5, 6, 11, 15, 42]. Some ALK TKIs have shown intracranial activity, as discussed earlier [13, 21, 22, 29], and should be considered as options to delay development of brain metastases or for patients with baseline brain metastases.

Ultimately, the risk–benefit profile of each treatment option should be assessed and discussed with patients, taking into consideration disease- and patient-related factors (for example, extent of disease or tumor burden, performance status, and comorbidities).

10 ES: As we conclude our discussion, we should mention some of the future directions in treating patients with ALK-positive metastatic NSCLC

EN: Therapies in development for *ALK*-positive NSCLC include fourth-generation ALK TKIs [43].

Fourth-generation, or double mutant active, ALK TKIs, such as TPX-0131 and NVL-655, are being developed to overcome the emergence of double *ALK* mutations, with sequential use of single mutant active second- and third-generation ALK TKIs [43–45].

The phase 1/2 ALKOVE-1 study is assessing NVL-655 in patients with previously treated metastatic *ALK*-positive NSCLC and other solid tumors [46]. If approved, this may provide a treatment option after progression on second- and third-generation ALK TKIs.

Another study, the phase 3 ALKAZAR study, is assessing NVL-655 compared with alectinib in treatment-naive patients with *ALK*-positive NSCLC [47].

We also look forward to the continued CROWN data on lorlatinib and await the eventual time at which median PFS and overall survival are reached, as this will provide a more complete understanding of the long-term benefit of this ALK TKI.

Thank you for listening to both Eric and Eric.

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References

1. Ali A, Goffin JR, Arnold A, Ellis PM. Survival of patients with non-small-cell lung cancer after a diagnosis of brain metastases. Curr Oncol. 2013;20(4):e300–6. https://doi.org/10.3747/co.20.1481.
2. Gainor JF, Varghese AM, Ou SH, et al. ALK rearrangements are mutually exclusive with mutations in EGFR or KRAS: an analysis of 1,683 patients with non-small cell lung cancer. Clin Cancer Res. 2013;19(15):4273–81. https://doi.org/10.1158/1078-0432.Ccr-13-0318.
3. Wong DW, Leung EL, So KK, et al. The EML4-ALK fusion gene is involved in various histologic types of lung cancers from nonsmokers with wild-type EGFR and KRAS. Cancer. 2009;115(8):1723–33. https://doi.org/10.1002/cncr.24181.
4. Koivunen JP, Mermel C, Zejnullahu K, et al. EML4-ALK fusion gene and efficacy of an ALK kinase inhibitor in lung cancer. Clin Cancer Res. 2008;14(13):4275–83. https://doi.org/10.1158/1078-0432.Ccr-08-0168.
5. Doebele RC, Lu X, Sumey C, et al. Oncogene status predicts patterns of metastatic spread in treatment-naive nonsmall cell lung cancer. Cancer. 2012;118(18):4502–11. https://doi.org/10.1002/cncr.27409.
6. Kang HJ, Lim HJ, Park JS, et al. Comparison of clinical characteristics between patients with ALK-positive and EGFR-positive lung adenocarcinoma. Respir Med. 2014;108(2):388–94. https://doi.org/10.1016/j.rmed.2013.11.020.
7. Yoda S, Lin JJ, Lawrence MS, et al. Sequential ALK inhibitors can select for lorlatinib-resistant compound ALK mutations in ALK-positive lung cancer. Cancer Discov. 2018;8(6):714–29. https://doi.org/10.1158/2159-8290.Cd-17-1256.
8. Planchard D, Popat S, Kerr K, et al. Metastatic non-small cell lung cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2018;29(suppl 4):iv192–237. https://doi.org/10.1093/annonc/mdy275.
9. Drilon A, Lin JJ, Filleron T, et al. Frequency of brain metastases and multikinase inhibitor outcomes in patients with RET-rearranged lung cancers. J Thorac Oncol. 2018;13(10):1595–601. https://doi.org/10.1016/j.jtho.2018.07.004.
10. Gillespie CS, Mustafa MA, Richardson GE, et al. Genomic alterations and the incidence of brain metastases in advanced and metastatic NSCLC: a systematic review and meta-analysis. J Thorac Oncol. 2023;18(12):1703–13. https://doi.org/10.1016/j.jtho.2023.06.017.
11. Rangachari D, Yamaguchi N, VanderLaan PA, et al. Brain metastases in patients with EGFR-mutated or ALK-rearranged non-small-cell lung cancers. Lung Cancer. 2015;88(1):108–11. https://doi.org/10.1016/j.lungcan.2015.01.020.
12. Camidge DR, Kim HR, Ahn MJ, et al. Brigatinib versus crizotinib in ALK-positive non-small-cell lung cancer. N Engl J Med. 2018;379(21):2027–39. https://doi.org/10.1056/NEJMoa1810171.
13. Horn L, Wang Z, Wu G, et al. Ensartinib vs crizotinib for patients with anaplastic lymphoma kinase-positive non-small cell lung cancer: a randomized clinical trial. JAMA Oncol. 2021;7(11):1617–25. https://doi.org/10.1001/jamaoncol.2021.3523.
14. Peters S, Camidge DR, Shaw AT, et al. Alectinib versus crizotinib in untreated ALK-positive non-small-cell lung cancer. N Engl J Med. 2017;377(9):829–38. https://doi.org/10.1056/NEJMoa1704795.

15. Shaw AT, Bauer TM, de Marinis F, et al. First-line lorlatinib or crizotinib in advanced *ALK*-positive lung cancer. N Engl J Med. 2020;383(21):2018–29. https://doi.org/10.1056/NEJMoa2027187.
16. Zhao B, Han Y, Wang Y, et al. A Bayesian network meta-analysis regarding the comparative efficacy of therapeutics for ALK-positive, brain metastatic non-small cell lung cancer. Pharmacol Res. 2021;174:105931. https://doi.org/10.1016/j.phrs.2021.105931.
17. Uprety D, Abrahami D, Marcum ZA, et al. Brain metastases and mortality in patients with ALK + metastatic non-small cell lung cancer treated with second-generation ALK tyrosine kinase inhibitors as first-line targeted therapies: an observational cohort study. Lung Cancer. 2025;201:108436. https://doi.org/10.1016/j.lungcan.2025.108436.
18. Arnaoutakis K, Wan Y, Elliott J, et al. Real-world treatment patterns and outcomes across three lines of therapy in patients with ALK+ NSCLC. Adv Ther. 2024;41(8):3217–31. https://doi.org/10.1007/s12325-024-02899-6.
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20. Johnson TW, Richardson PF, Bailey S, et al. Discovery of (10R)-7-amino-12-fluoro-2,10,16-trimethyl-15-oxo-10,15,16,17-tetrahydro-2H-8,4-(metheno)pyrazolo[4,3-h][2,5,11]-benzoxadiazacyclotetradecine-3-carbonitrile (PF-06463922), a macrocyclic inhibitor of anaplastic lymphoma kinase (ALK) and c-ros oncogene 1 (ROS1) with preclinical brain exposure and broad-spectrum potency against ALK-resistant mutations. J Med Chem. 2014;57(11):4720–44. https://doi.org/10.1021/jm500261q.
21. Camidge DR, Kim HR, Ahn MJ, et al. Brigatinib versus crizotinib in ALK inhibitor-naive advanced ALK-positive NSCLC: final results of phase 3 ALTA-1L trial. J Thorac Oncol. 2021;16(12):2091–108. https://doi.org/10.1016/j.jtho.2021.07.035.
22. Mok T, Camidge DR, Gadgeel SM, et al. Updated overall survival and final progression-free survival data for patients with treatment-naive advanced ALK-positive non-small-cell lung cancer in the ALEX study. Ann Oncol. 2020;31(8):1056–64. https://doi.org/10.1016/j.annonc.2020.04.478.
23. Alectinib approved for (ALK) positive metastatic non-small cell lung cancer (NSCLC). [press release]. November 6 2017.
24. FDA approves brigatinib for ALK-positive metastatic NSCLC. [press release]. May 22 2020.
25. FDA approves ensartinib for ALK-positive locally advanced or metastatic non-small cell lung cancer [press release]. December 18 2024.
26. Peters S, Camidge R, Dziadziuszko R, et al. Alectinib versus crizotinib in previously untreated ALK-positive advanced non-small cell lung cancer: final overall survival analysis of the phase III ALEX study. Ann Oncol. 2026;37(1):92–103. https://doi.org/10.1016/j.annonc.2025.09.018.
27. Ensacove (ensartinib). Package insert. Xcovery Holdings, Inc; 2024.
28. Solomon BJ, Bauer TM, Mok TSK, et al. Efficacy and safety of first-line lorlatinib versus crizotinib in patients with advanced, ALK-positive non-small-cell lung cancer: updated analysis of data from the phase 3, randomised, open-label CROWN study. Lancet Respir Med. 2023;11(4):354–66. https://doi.org/10.1016/s2213-2600(22)00437-4.
29. 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. 2024;42(29):3400–9. https://doi.org/10.1200/jco.24.00581.
30. Camidge DR, Dziadziuszko R, Peters S, et al. Updated efficacy and safety data and impact of the EML4-ALK fusion variant on the efficacy of alectinib in untreated ALK-positive advanced non-small cell lung cancer in the global phase III ALEX study. J Thorac Oncol. 2019;14(7):1233–43. https://doi.org/10.1016/j.jtho.2019.03.007.
31. Liu G, Solomon BJ, Mazieres J, Kim D-W, Cortinovis D, Inoue T, et al. Kinetics and management of adverse events associated with lorlatinib after 5 years of follow-up in the CROWN study. Oncologist. 2025;30(10):oyaf287. https://doi.org/10.1093/oncolo/oyaf287.
32. Liu G, Nadal E, Baijal S, et al. Impact of lorlatinib dose modifications on adverse event outcomes in the phase 3 CROWN study. J Clin Oncol. 2025;43(suppl 16):Abstract 8590. https://doi.org/10.1200/JCO.2025.43.16_suppl.8590
33. Bauman JR, Liu G, Preeshagul I, et al. Real-world treatment sequencing and effectiveness of second- and third-generation ALK tyrosine kinase inhibitors for ALK-positive advanced non-small cell lung cancer. Lung Cancer. 2024;195:107919. https://doi.org/10.1016/j.lungcan.2024.107919.
34. Novello S, Mazieres J, Oh IJ, et al. Alectinib versus chemotherapy in crizotinib-pretreated anaplastic lymphoma kinase (ALK)-positive non-small-cell lung cancer: results from the phase III ALUR study. Ann Oncol. 2018;29(6):1409–16. https://doi.org/10.1093/annonc/mdy121.
35. Solomon BJ, Besse B, Bauer TM, et al. Lorlatinib in patients with ALK-positive non-small-cell lung cancer: results from a global phase 2 study. Lancet Oncol. 2018;19(12):1654–67. https://doi.org/10.1016/S1470-2045(18)30649-1.
36. Mok T, Solomon BJ, Campelo MRG, et al. MA06.07 patterns of progression with lorlatinib and insights into subsequent anticancer therapy efficacy in advanced ALK+ NSCLC. J Thorac Oncol. 2024;19(10):S75. https://doi.org/10.1016/j.jtho.2024.09.134.
37. Nakagawa K, Hida T, Nokihara H, et al. Final progression-free survival results from the J-ALEX study of alectinib versus crizotinib in ALK-positive non-small-cell lung cancer. Lung Cancer. 2020;139:195–9. https://doi.org/10.1016/j.lungcan.2019.11.025.
38. Urbanska EM, Koffeldt PR, Grauslund M, Melchior LC, Sørensen JB, Santoni-Rugiu E. Refining criteria for choosing the first-line treatment for real-world patients with advanced ALK-rearranged NSCLC. Int J Mol Sci. 2025. https://doi.org/10.3390/ijms26135969.
39. Mazieres J, Bauer T, Abrahami D, et al. 94P: Long-term efficacy of lorlatinib vs alectinib in patients with and without brain/central nervous system metastases: matching-adjusted indirect comparisons. J Thorac Oncol. 2025;20(3):S67–8. https://doi.org/10.1016/S1556-0864(25)00289-8.
40. Chazan G, Solomon BJ. Optimal first-line treatment for metastatic ALK+ non-small cell lung cancer—a narrative review. Transl Lung Cancer Res. 2023;12(2):369–78. https://doi.org/10.21037/tlcr-22-656.
41. Reed M, Rosales AS, Chioda MD, Parker L, Devgan G, Kettle J. Consensus recommendations for management and counseling of adverse events associated with lorlatinib: a guide for healthcare practitioners. Adv Ther. 2020;37(6):3019–30. https://doi.org/10.1007/s12325-020-01365-3.
42. Johung KL, Yeh N, Desai NB, et al. Extended survival and prognostic factors for patients with ALK-rearranged non-small-cell lung cancer and brain metastasis. J Clin Oncol. 2016;34(2):123–9. https://doi.org/10.1200/jco.2015.62.0138.
43. Ou SI, Nagasaka M, Brazel D, Hou Y, Zhu VW. Will the clinical development of 4th-generation "double mutant active" ALK TKIs (TPX-0131 and NVL-655) change the future treatment paradigm of ALK+ NSCLC? Transl Oncol. 2021;14(11):101191. https://doi.org/10.1016/j.tranon.2021.101191.
44. Murray BW, Zhai D, Deng W, et al. TPX-0131, a potent CNS-penetrant, next-generation inhibitor of wild-type ALK and ALK-resistant mutations. Mol Cancer Ther. 2021;20(9):1499–507. https://doi.org/10.1158/1535-7163.Mct-21-0221.

45. Lin JJ, Horan JC, Tangpeerachaikul A, et al. NVL-655 is a selective and brain-penetrant inhibitor of diverse ALK-mutant oncoproteins, including lorlatinib-resistant compound mutations. Cancer Discov. 2024;14(12):2367–86. https://doi.org/10.1158/2159-8290.Cd-24-0231.
46. ClinicalTrials.gov. A study of NVL-655 in patients with advanced NSCLC and other solid tumors harboring ALK rearrangement or activating ALK mutation (ALKOVE-1). https://clinicaltrials.gov/study/NCT05384626. Accessed 20 March 2025.
47. ClinicalTrials.gov. Neladalkib (NVL-655) for TKI-naive patients with advanced ALK-positive NSCLC (ALKAZAR). https://www.clinicaltrials.gov/study/NCT06765109. Accessed 7 April 2025.