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# A Case Report of Locally Advanced Non-Small Cell Lung Cancer Treated with Lorlatinib to Achieve R0 Resection

**Kun Yan and Guiping Yu***

Department of Cardiothoracic Surgery, The Affiliated Jiangyin Hospital of Southeast University Medical College, Jiangyin, Jiangsu Province, 214400, China

***Corresponding author:**

Guiping Yu,
Department of Cardiothoracic Surgery, The Affiliated Jiangyin Hospital of Southeast University Medical College, Jiangyin, Jiangsu Province, 214400, China

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## 1. Abstract

Anaplastic Lymphoma Kinase-Tyrosine Kinase Inhibitors (ALK-TKIs) are highly effective in treating ALK-positive patients with advanced non-small cell lung cancer (NSCLC). However, ALK-TKI neoadjuvant therapy in ALK-positive NSCLC has not been fully explored to date. In this case, the treatment of a patient initially diagnosed with stage IIB (T2bN1M0) lung adenocarcinoma has been described. This patient harbor an ALK mutationt and was treated with lorlatinib for three cycles. Consequently, the mass and mediastinal lymph nodes shrank significantly, compared with the previous findings. Following the surgery, the patient continued lorlatinib adjuvant treatment; a subsequent review did not show any recurrence or metastasis. Therefore, our results suggest that lorlatinib neoadjuvant therapy is a viable option for ALK-positive NSCLC patients.

## 2. Introduction

Since some IIB non-small cell lung cancer (NSCLC) patients cannot be treated by radical surgery at the time of initial diagnosis, neoadjuvant therapy plus surgery becomes an alternate treatment option. Neoadjuvant chemotherapy is a common therapeutic intervention in certain cases requiring neoadjuvant therapy. Nonetheless, the 5-year progression-free survival (PFS) with neoadjuvant chemotherapy alone is approximately 5-6% [1]. Clinical trials like NeoADAURA [2] have revealed that neoadjuvant targeted therapies display better clinical outcomes for Epidermal Growth Factor Receptor（EGFR） mutation patients, compared to neoadjuvant chemotherapy. Accounting for 3-7% of all NSCLC cases, the anaplastic lymphoma kinase (ALK) fusion gene is the third most common tumor driver gene in NSCLC [3,4]. However, the efficacy and safety of neoadjuvant therapy for ALK-positive locally advanced NSCLC cases remain ambiguous due to the lack of relevant randomized controlled trials. A third-generation ALK-TKI, lorlatinib effectively penetrates the blood-brain barrier and displays elevated levels within the central nervous system (CNS)[5]. Moreover, lorlatinib exerts a strong anti-tumor effect in advanced NSCLC cases after first- or second-generation ALK-TKI resistance [6,7]. The CROWN [8,9] trial has established that lorlatinib significantly prolongs disease-free survival (DFS) in ALK-positive NSCLC patients compared to crizotinib. Here, we report the case of a patient with an ALK fusion variant and initially staged as stage IIB (T2aN1M0). However, the patient was downgraded to stage IA after lorlatinib neoadjuvant treatment and achieving R0 resection by surgery. Thus, we aimed to use our findings to highlight lorlatinib's potential as a neoadjuvant treatment for NSCLC patients.

## 3. Case Data

A 48-year-old female with no smoking history or other illnesses was admitted to the hospital on 30 November 2023 with the complaint of "coughing up sputum for more than a month". The patient had no blood-filled sputum or hemoptysis, chest pain or tightness, shortness of breath, fever, night sweats, or general malaise. The

tumor marker carbohydrate antigen 72-4 (CA72-4) was 7.4ng/ml-1. Enhanced CT of the chest displayed a soft tissue density mass shadow in the right lung's lower lobe with uneven enhancement, measuring approximately 4.2 cm × 3.7 cm × 3.3 cm (Figure 1A), enlarged R10 hilar lymph node, and constricted upper lobe's bronchial opening (Figure 1C). Tracheoscopy revealed a fish-like neoplasm at the right secondary lung eminence, obstructing an extensive area of the right upper lobe of the lung lumen. Due to the inability of the scope to traverse the area, alveolar lavage and neoplasm brushing were administered for neoplasm examination. Pathological examination of lavage detected a small number of heterogeneous cells (Figure 2A), and neo-biological brushing showed the presence of heterogeneous cells, favoring NSCLC. (Figure 2B). However, cranial MRI findings were unremarkable. In PET-CT findings, the mass in the right lung's lower lobe and enlarged hilar lymph nodes were considered a malignant tumor and lymph node metastases, respectively. Following a CT-guided puncture biopsy, the pathological diagnosis was poorly differentiated lung adenocarcinoma (Figure 2C). Immunohistochemistry (IHC) showed the presence of thyroid transcription factor-1 (TTF-1, Figure 2D). A genetic testing of the puncture specimens revealed mutations in the ALK gene EML4-ALK and ALK-IGR fusions, respectively (Table 1). Thus, her lung malignancy was staged as cT2bN1M0, stage IIB. After a multidisciplinary team (MDT) discussion, the patient was scheduled for lorlatinib neoadjuvant targeted therapy for 3-6 months. The patient received oral lorlatinib 100 mg-d-1 from 12 December 2023 to 10 March 2024 (3 cycles of 28 days each). However, the patient complained of mild sleep disturbances without any discomfort during the treatment period. On 10 March 2024, the patient underwent a follow-up intensive chest CT, which showed that the mass in the right lung's lower lobe was significantly diminished, with a cross-sectional size of approximately 1.6 cm × 1.1 cm (Figure 1B). The right hilar lymph nodes were significantly reduced, and the stenosis of the lumen of the right lung's upper lobe improved, compared with the earlier findings (Figure 1D). All the tumor markers were normalized in the follow-up examination. After a re-discussion by MDT, the patient's tumor shrunk after targeted therapy, and Pathological Partial Response (PPR) assessed its efficacy, with the chance of radical surgical treatment. The patient underwent general anesthesia thoracoscopic lower lobectomy of the right lung+lymph node dissection+pleural adhesion release on 15 March 2024 after excluding surgical contraindications. The postoperative routine pathological assessment showed invasive adenocarcinoma (Figure 2E). The tumor was approximately 1.6 cm × 1.5c m × 1.1 cm, solid, hard, with no involvement of lung membranes or bronchi, nerves (-), Vascular tumor thrombus (+), and STAS (-); no cancer metastases were seen in the lymph nodes. The pathological staging was ypT1bN0M0, stage I A. IHC results showed positive expressions of TTF-1, CK7, NapsinA, Ki-67 (10% positive), and P53 (partially positive). Postoperative genetic testing of tumor tissues also showed ALK mutation. The patient's postoperative recovery was smooth. Considering the postoperative pathology suggestive of the vasculature (+) and a discussion by MDT, it was recommended that the patient should continue to take lorlatinib 100 mg-d-1 orally from 24 March 2024 to prevent any reoccurrence. However, at the time of writing, the patient had only experienced one episode of grade 2 diarrhea, which resolved with symptomatic treatment. All tumor markers were reviewed three months postoperatively and showed no deviations. An additional plain chest CT showed no recurrence or metastasis (Figure 3).

**Table 1**: The CT-guided pathological evaluation results displaying lung occupancy puncture before treatment.

| Gene | Sample | Detection result | The results of interpretation |
|---|---|---|---|
| | Tumor tissue | EML4-ALK fusion | mutation |
| ALK | | | |
| | Tumor tissue | ALK-IGR fusion | mutation |
| BRAF | Tumor tissue | - | mutation |
| EGFR | Tumor tissue | - | mutation |
| KARS | Tumor tissue | - | mutation |
| MET | Tumor tissue | - | mutation |
| ROS1 | Tumor tissue | - | mutation |

Note: Tumor cell content: 60%; test date: 09/12/2023.

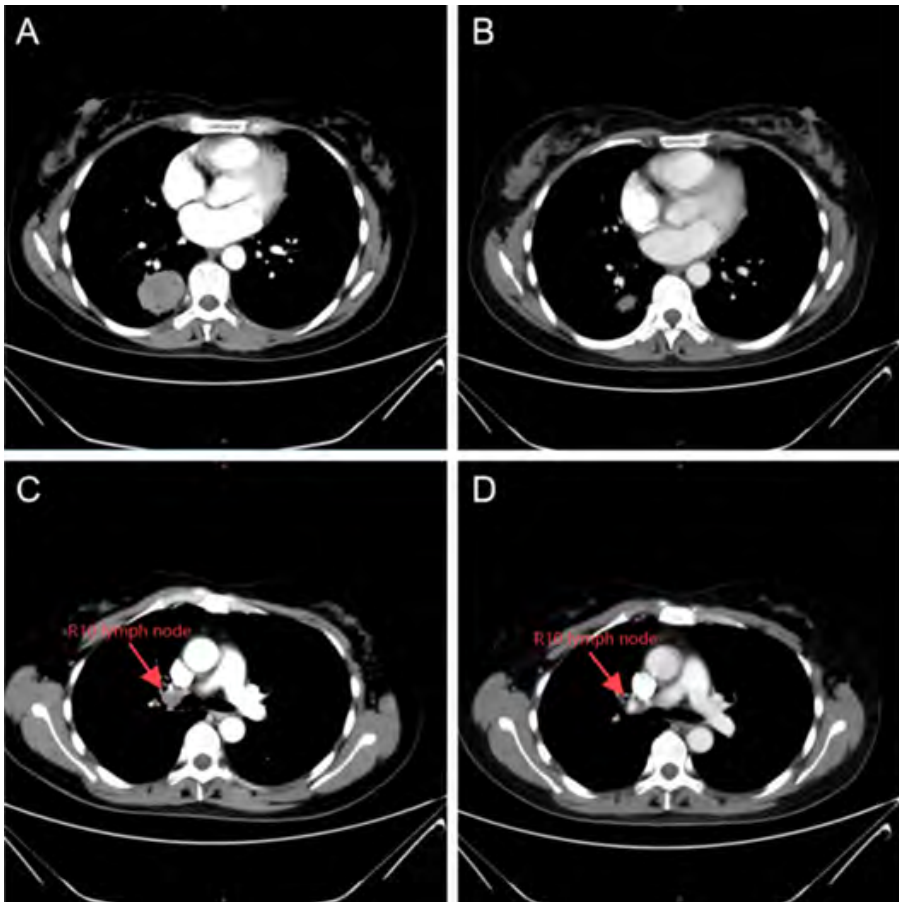


**Figure 1**: Changes in mass and hilar lymph nodes before and after lorlatinib treatment characterized by (A) Enhanced CT before lorlatinib treatment (30 November 2023) indicated a mass in the right lung's lower lobe, measuring approximately 4.2 cm × 3.7 cm × 3.3 cm; (B) Enhanced CT scan post-lorlatinib administration (10 March 2024) indicated a significantly smaller right lung's lower lobe mass, with a cross-sectional size of approximately 1.6 cm × 1.1 cm; (C) Enhanced CT before lorlatinib treatment (30 November 2023) indicated an enlarged R10 hilar lymph node, compressing the ductal opening of the right lung's upper lobe; (D) Enhanced CT post-lorlatinib (10 March 2024) revealed that the R10 hilar lymph node decreased in size when compared with the previous finding, and the luminal narrowing of the right lung's upper lobe was resolved.

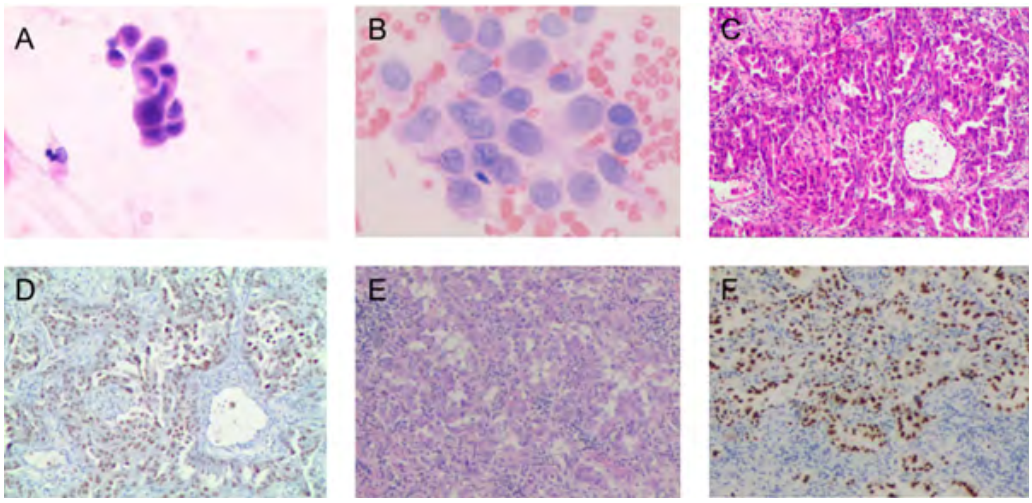


**Figure 2**: Bronchoscopic smears as well as puncture biopsies, postoperative pathology sections stained with hematoxylin-eosin, and immunohistochemical assays. (A) Smear of patient's alveolar lavage fluid; (B) Bronchial brushings smear; (C) Hematoxylin-eosin-stained image of lung biopsy specimen; (D) Immunohistochemical image showing TTF-1 positivity in lung biopsy specimen; (E) Hematoxylin-eosin-stained section of postoperative resected lung tissues, and (F) Immunohistochemical image showing TTF-1 positivity in postoperative resected lung tissues.

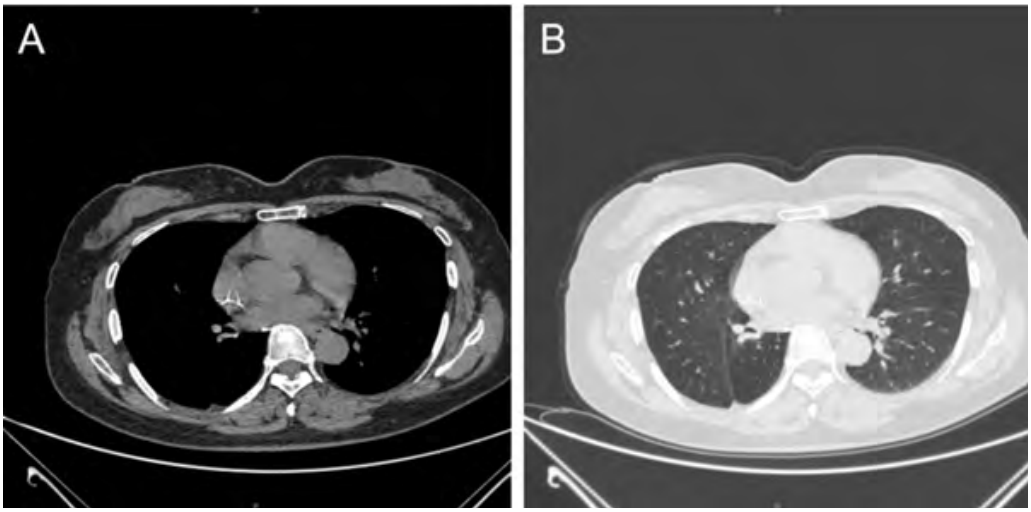


**Figure 3**: A 3-month postoperative follow-up chest CT.
Note: A postoperative review (22 June 2024) of the mediastinal (A) and lung windows (B) showed no tumor recurrence.

## 4. Discussion

Neoadjuvant therapy plus surgery might be an excellent treatment strategy for NSCLC patients with locally advanced stages and potential surgical opportunities. This therapeutic strategy increases the probability of radical resection by reducing the tumor stage, thereby enhancing the patient's postoperative quality of life and survival [10,11]. Currently, neoadjuvant therapy relies on chemotherapy, which limits its overall efficacy and induces severe side effects during chemotherapy. These adverse effects include tissue damage and necrosis, as well as abnormal bronchial and vascular changes, resulting in difficult surgical interventions and increasing postoperative complications. Using neoadjuvant targeted agents clinically has revolutionized the situation for patients with positive tumor driver genes. A majority of neoadjuvant targeted therapy studies have focused on EGFR-mutated NSCLCs; however, limited studies are available on the efficacy of ALK-TKI in ALK-positive NSCLCs[12]. Hence, these limited cases suggest the potential of neoadjuvant ALK-TKI therapy in achieving pathological partial remission or even pathological complete remission, but these cases have focussed on other ALK-TKIs (Alectinib, Ensartinib or Ceritinib) [13,14]. Lorlatinib, as a third-generation ALK-TKI, is structurally optimized and displays broad-spectrum and highly potent activities against various ALK kinase domain-resistant mutations that might have appeared during treatment with the first two ALK-TKI generation drugs. Lorlatinib's unique structure reduces P-glycoprotein-mediated efflux, resulting in an enhanced ability to penetrate the blood-brain barrier. In the CROWN study [9], lorlatinib demonstrated a high intracranial response rate (58% complete response rate) in baseline brain metastasis patients. Additionally, lorlatinib significantly curtailed CNS progression, prevented brain metastases, and significantly prolonged PFS. However, the median progression-free survival (mPFS) of the patients followed up in the CROWN trial, remained unmet, exceeding 60 months in most recent phase III results, and with a 5-year PFS rate of 60%. Our patient had a large tumor with enlarged hilar lymph nodes and airway compression. This made achieving R0 resection difficult, and the tumor was potentially resectable after neoadjuvant therapy as per the MDT discussion. Since the genetic testing suggested ALK gene positivity, neoadjuvant therapy was directly administered orally with the third-generation ALK-TKI lorlatinib as the patient refused chemotherapy. Consequently, the malignant mass and hilar lymph nodes shrank significantly after three treatment cycles. Following another MDT discussion, the patient had a possibility of R0 resection, then underwent video-assisted thoracoscopic surgery for right lower lobectomy and systematic lymph node dissection were performed, and the patient was discharged from the hospital after safe extubation four days postoperatively. After lorlatinib neoadjuvant treatment, the patient's tumor stage was downgraded from stage IIB to stage IA, and the efficacy was assessed as Pathological Partial Response (PPR). The surgical treatment achieved R0 tumor resection, and the patient was considered Vascular tumor thrombus (+) postoperatively. Furthermore, lorlatinib was again recommended to prevent tumor reoccurrence. The optimal duration of postoperative lorlatinib adjuvant therapy remains controversial. In the CTONG1104[15] and EVAN [16] clinical trials, the patients received adjuvant therapy with gefitinib or erlotinib for approximately two years postoperatively. In the ADAURA [17] study, patients received osimertinib adjuvant therapy for three years postoperatively. In all these trials, DFS was significantly prolonged in patients treated with TKI. Thus, the duration of postoperative adjuvant TKI therapy can be extended from 1 to 2 years to prolong patients' DFS.

## 5. Summary

The preoperative lorlatinib neoadjuvant treatment, in this case, achieved a good therapeutic effect and provided a valid reference for using neoadjuvant treatment options for locally ad-

vanced unresectable ALK-mutated NSCLC patients. The ALNEO (NCT05015010) and NAUTIKA1 (NCT04302025) trials are the two ongoing studies on neoadjuvant therapies for ALK-positive mutations. It is anticipated that the results of these trials will stimulate additional explorations of neoadjuvant therapy for ALK-positive mutations. The CROWN Phase III results indicated that lorlatinib could be effective in patients with ALK-positive NSCLCs with or without baseline brain metastases; however, the potential for lorlatinib in neoadjuvant therapy has not been fully explored to date. There are still many unanswered questions regarding the use of preoperative lorlatinib neoadjuvant therapy in ALK-sensitive mutant NSCLC patients, like the preoperative neoadjuvant therapy duration, postoperative adjuvant therapy regimen and duration, and whether the targeted drug administration might increase the difficulty and risk of surgical resection. Hence, additional evidence-based studies are required to validate whether lorlatinib can replace neoadjuvant chemotherapy and radiotherapy in ALK-mutated lung cancer patients.

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