# Treatment Strategy of Lung Adenocarcinoma with Concomitant EGFR Mutation and ALK Rearrangement

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**Research**

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## Abstract

# Background

The incidence of synchronous mutations of Epidermal growth factor receptor (EGFR) and anaplastic large-cell lymphoma kinase (ALK) rearrangements in non-small cell lung cancer (NSCLC) was low. Now clinical experience is still insufficient. Simultaneously the treatment of brain metastasis hemorrhage in the acute phase with lung cancer is still controversial. We described the clinical treatment strategy of a patient with synchronous mutations of EGFR and ALK.

# Methods

The patient was a 55-year-old man with a mass in the right lower lobe. Pathological examination confirmed adenocarcinoma, tissue molecular examination showed EGFR exon 19 deletion, and ALK rearrangement. The patient received pemetrexed combined with cisplatin chemotherapy, gefitinib targeted therapy, clotriminib targeted therapy, albumin paclitaxel combined with nedaplatin and anlotinib therapy, and seretinib therapy. In the course of treatment, the patients had sudden tumor emergency, extensive hemorrhage and edema of brain metastasis, paralysis occurred in the patients. Subsequently, targeted therapy with ceritinib was given. After 1 month, lung tumors, brain metastases, and cerebral hemorrhage were all significantly improved.

# Results

The tumor was well controlled. Progression-free survival (PFS)1 was 4 months, PFS2 was 3 months, PFS3 was 5 months, PFS4 was 5 months, and PFS5 was 9 months. At present, the patient still maintains partial response (PR) status.

# Conclusions

Patients with simultaneous mutations choose the correct treatment strategy, which can significantly benefit the patients' PFS and quality of life. Especially for patients with acute hemorrhage of brain metastases, oral ceritinib may be an effective choice.

## Background

In non-small cell lung cancer (NSCLC), the coexistence of Epidermal growth factor receptor (EGFR) mutations and anaplastic large-cell lymphoma kinase (ALK) rearrangements is very rare [1, 2]. A few studies had been conducted on EGFR mutation and ALK rearrangement to explore the best treatment for these patients [3, 4]. The incidence of brain metastasis in lung cancer is about 50% [5]. When there was symptomatic brain metastasis in the course of anti-tumor treatment, we often choosed brain

radiotherapy. Here, we reported a patient who diagnosed as stage IV of lung adenocarcinoma, with EGFR mutation and ALK rearrangement. The treatment process of brain metastasis tumor rupture and hemorrhage provided some reference for clinical treatment.

# Methods

A 55-year-old smoking man presented to our respiratory with cough and hemoptysis in April 2019. Physical examination revealed low right lower lung breath sounds and laboratory test results prompts CEA 4.58 ng/ml. The chest Computer tomography (CT) scan revealed a 9.2 cm × 9.8 cm solid nodule in the right lower lung and scattered metastatic nodules in both lungs (Fig. 1A). Bronchoscopy showed that new organisms in the lumen of the right lower lobe blocked the lumen. The clinical stage was stage IVA ($cT_4N_3M_{1b}$). The results of bronchoscopy biopsy and immunohistochemistry showed adenocarcinoma (Fig. 2). The patient refused genetic testing. First line chemotherapy, pemetrexed and cisplatin (pemetrexed 500 mg / $m^2$ and cisplatin 75 mg / $m^2$) were started on April 17, 2019. After 4 cycles, the re-examination showed that the lesion was progressive disease (PD), gastrointestinal reaction III ° during chemotherapy. Genetic testing of lung cancer tissues showed that EGFR exon 19 deletion (Fig. 3A) and ALK-Exon-20 were fusions (Fig. 3C). The patient was treated with gefitinib, 250 mg one a day, from July 17, 2019. After 12 weeks of treatment, patient's condition was PD, and the tumor size increased to 9.8 cm × 11.4 cm (Fig. 1B). The patient had a small amount of hemoptysis. Subsequently, the patient was orally given clozatinib 250 mg bid. The chest CT was reexamined after 3 months treatment, and partial response (PR) was evaluated (Fig. 1C). On April 24, 2020, the patient's condition was PD (Fig. 1D, Fig. 4A, 4B), there were new and multiple transfers in the brain. The blood panoramic gene test showed that EGFR and ALK were negative. From May 15, 2020, we started six cycles of triple line albumin paclitaxel, nedaplatin and anlotinib chemotherapy, during which we reexamined the condition of stable disease (SD). On October 27, 2020, the patient began to had a headache, and then developed weakness of the right limbs. MRI and CT examination of the head showed that there were massive high-density shadows at the junction of the left occipital lobe and frontoparietal lobe, with a large range of 3.2 cm × 3.0 cm, swelling and bleeding of surrounding tissues (Fig. 1E,Fig. 4C, 4D, 4E, 4F). The patient's condition progressed rapidly, bleeding, right hemiplegia, aphasia, poor mental state. The neurologist's consultation opinion was to strengthen dehydration treatment. After active dehydration symptomatic treatment, a short-term review of brain Magnetic Resonance Imaging (MRI) showed that the brain lesions continued to increase, and the improvement of brain edema was not obvious. Seretinib targeted therapy (450 mg QD) was started on November 19, 2020. One week after oral administration, the muscle strength of the right lower limb recovered to grade 3 and aphasia improved. One month later, the pulmonary and cranial lesions were partial response (PR). The latest reexamination showed that the right limb muscle strength of the patient recovered, the language communication was normal, the quality of life was significantly improved, and the mood was happy.

# Results

Reexamination on July 12, 2021 showed that the patient's condition continued to be PR at present, the large range of lung lesion was 1.0 cm × 2.0 cm and the largest brain lesion was 1.8 cm × 1.2 cm (Fig. 1G, Fig. 4G, 4F). The current survival time of the patient is 26 months. Oral seretinib is still effective (Fig. 5).

# Discussion

Here we report the case presented with lung adenocarcinoma with brain metastases. The results of molecular profiling showed that EGFR gene mutation and echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase (EML4-ALK) rearrangement were positive. The patient received chemotherapy, EGFR-tyrosine kinase inhibitor (TKI) treatment, the curative effect was SD, the patient continued hemoptysis during the course of the disease, and the symptoms did not improve. After 5 months of oral administration, the hemoptysis stopped after one week of oral administration. During the period, the curative effect was evaluated as PR, but the maintenance time was short. After 5 months, the patient's condition was obviously PD, and the treatment time of clotriminib was shorter than the average PFS. Considering that it was related to the double mutation of the patient, there may be interaction between the two. Previous reports said that EGFR mutation was more common in well differentiated adenocarcinoma, while ALK rearrangement was often found in typical poorly differentiated adenocarcinoma [6]. The effect and duration of oral EGFR-TKI in this patient were poor, and the duration of oral kezotinib was short. The gene detection method of patient tissue was the first-generation amplification refractory mutation system-polymerase chain reaction (ARMS-PCR) method, which did not showed mutation abundance. Therefore, for patients with double mutations, EGFR-TKI treatment was first selected based on the high incidence of common mutations when selecting targeted drugs. No mutation of EGFR and ALK was detected after blood gene test. After chemotherapy combined with anlotinib anti-tumor therapy, the patient's condition was PD, and brain metastases ruptured and hemorrhage occurred. The patient developed hemiplegia, speech disorder, and a wide range of cerebral hemorrhage. At this time, the treatment was in trouble. During the period of acute brain metastasis hemorrhage, there are still controversies whether brain radiotherapy or surgical treatment. A study evaluating the effectiveness and safety of whole brain radiotherapy (WBRT) used alone or in combination with other therapies in adults with newly diagnosed multiple brain metastases, the results showed that the choice of multiple brains for NSCLC with metastases, compared with radiotherapy, only the best supportive treatment may had no difference in overall survival (OS). The combination of radiosensitizers, chemotherapy or molecular targeted drugs with WBRT is still in the experimental stage [7]. At present, there is no unified treatment for the acute stage of brain metastases rupture and hemorrhage. We treated the patients with dehydration symptomatically and took seretinib orally. The symptoms and cerebral hemorrhage foci of the patients were significantly improved, and the curative effect was evaluated after one month. At present, it is still in PR, and the patient has moved freely. This case suggests that there is still a certain difference in the consistency between tissue gene test and blood gene test. There are many clinical cases in which blood gene test and oral targeted drugs are still effective. If conditions permit, we should try our best to send for tissue genetic testing. Secondly, in the acute stage of rupture and hemorrhage of brain metastases, there is a greater risk in both brain radiotherapy and surgery. For patients with positive driving genes in the past

or at present, oral targeted drug therapy can be considered, especially seretinib. Previous clinical studies had proved that seretinib had a significant effect on lung adenocarcinoma patients with ALK rearrangement positive and brain metastasis. In ASCEND-8 study, the median PFS was not reached in the 450 mg seretinib group after more than 25 months of follow-up. In ASCEND-4 study, 60% of patients with brain metastasis had symptoms, but the intracranial complete remission rate (CR) was 20.4%. In patients without previous radiotherapy, the intracranial CR rate was as high as 25% [8, 9]. For the difficulties and controversies in clinical treatment, we need to accumulate more cases to confirm. At the same time, we need to further study the mechanism of curative effect.

# Conclusion

We report a case of advanced lung adenocarcinoma with simultaneous EGFR mutation combined with ALK mutation. The treatment has been impressive, especially the rupture and bleeding of brain metastases. Therefore, oral ceritinib may be an effective choice for patients with acute hemorrhage of brain metastases.

# Abbreviations

NSCLC
non-small cell lung cancer; EGFR:Epidermal growth factor receptor; ALK:Anaplastic lymphoma kinase; EML4-ALK:echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase;PR:partial response SD stable disease; PD:progressive disease; PFS progression-free survival; OS:overall survival; CT:computed tomography; MRI:magnetic resonance imaging; WBRT whole brain radiotherapy NGS:next generation sequencing; TKI:tyrosine kinase inhibitor; ARMS-PCR:amplification refractory mutation system-polymerase chain reaction.

# Declarations

### Ethics approval and consent to participate

This study was approved by the Ethics Clerk Association of the Thoracic Department of the Brain Hospital Affiliated to Nanjing Medical University. All aspects of the study are in line with the guidelines of the Declaration of Helsinki. In this study, patient participated voluntarily, and all patient data were strictly confidential. Because it is a retrospective study, the Ethics Committee of the Thoracic Department of the Brain Hospital Affiliated to Nanjing Medical University has specifically approved it without written consent.

### Consent for publication

Not applicable.

### Availability of data and material

All the data generated or analyzed for the purposes of this study are included in the published article. All data are available by contacting correspondence authors.

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### Competing interests

CHX , JZand LL were involved in the design of these trials, in the interpretation of the data and in writing the manuscript. WL was involved in analysing the data.


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### Authors' contributions

LL drafted the manuscript and performed the statistical analysis. JZ carried out the immunoassays and the molecular genetic studies. CHX participated in the design of the study and conceived of the study. WL participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.


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# Figures

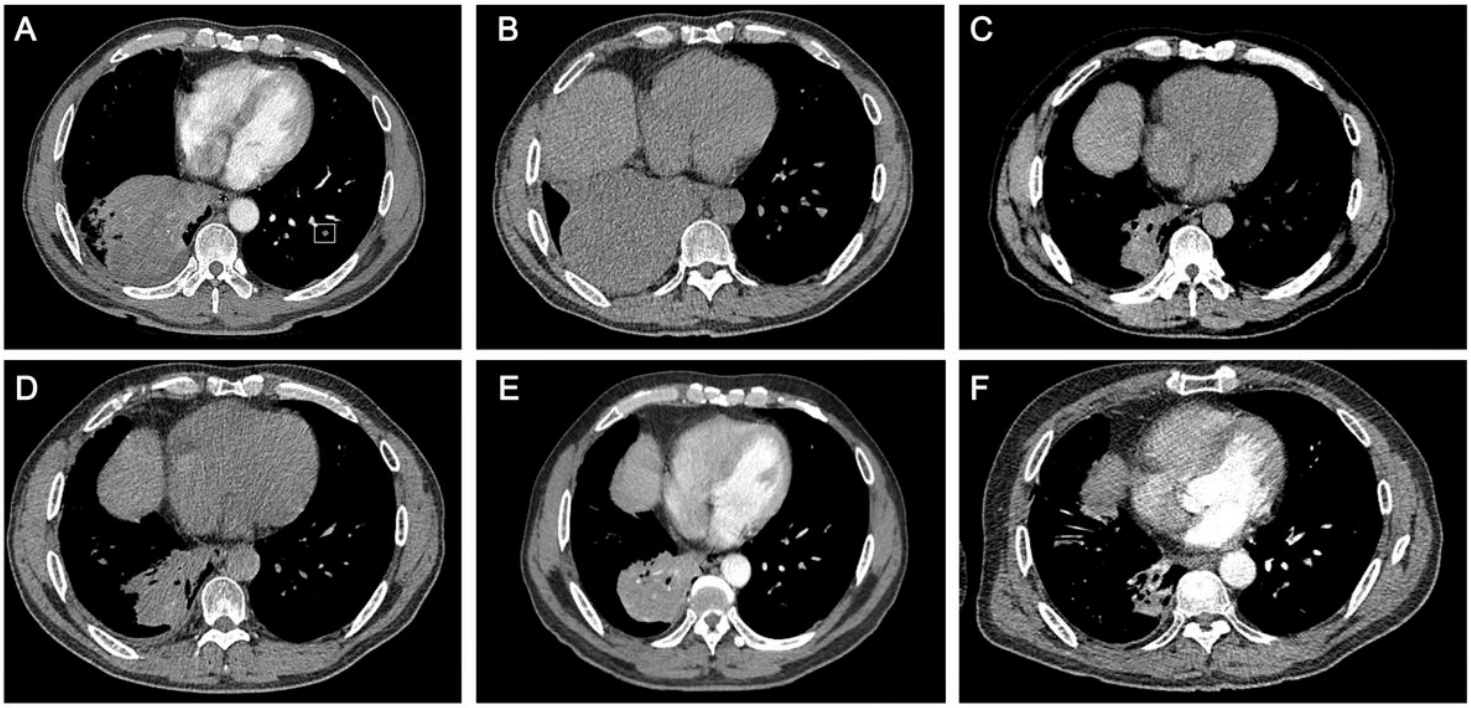
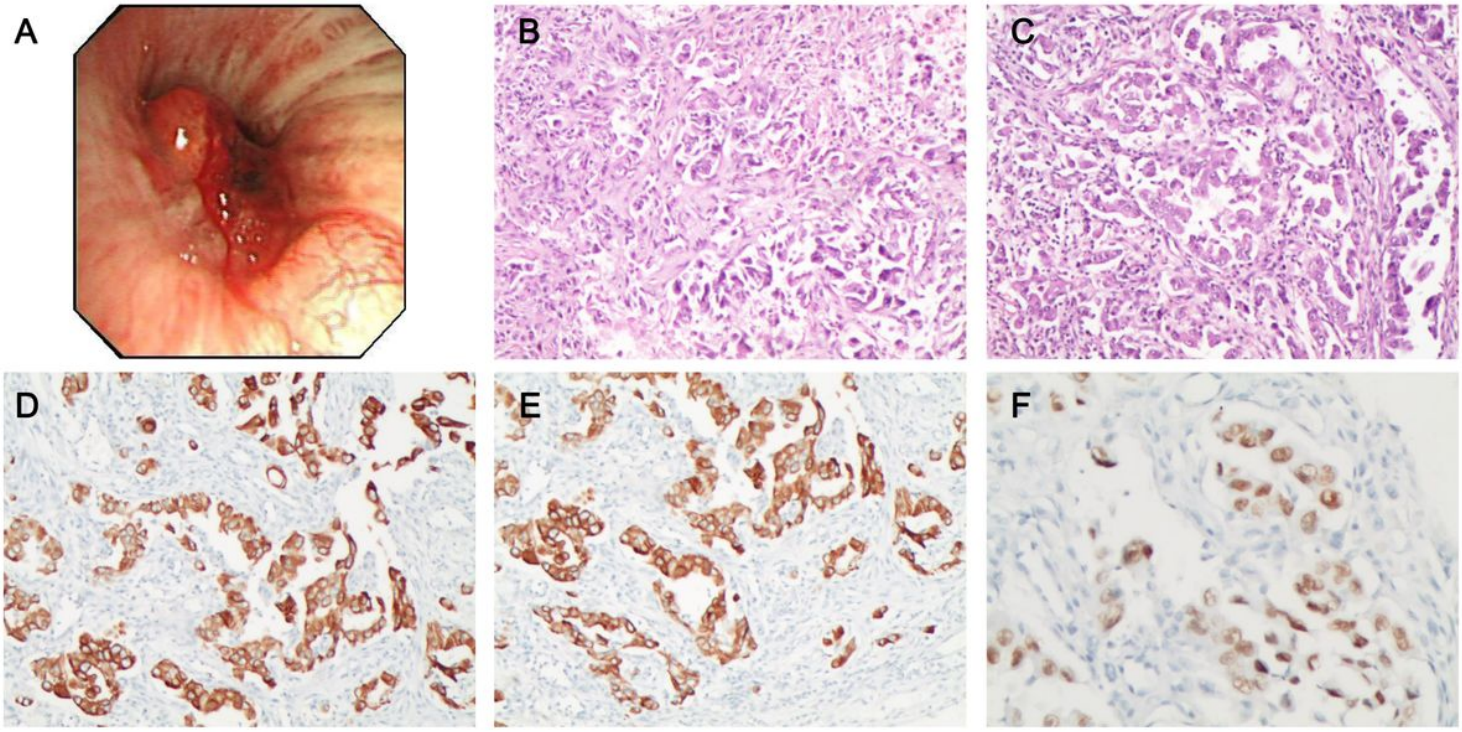



**Figure 1**

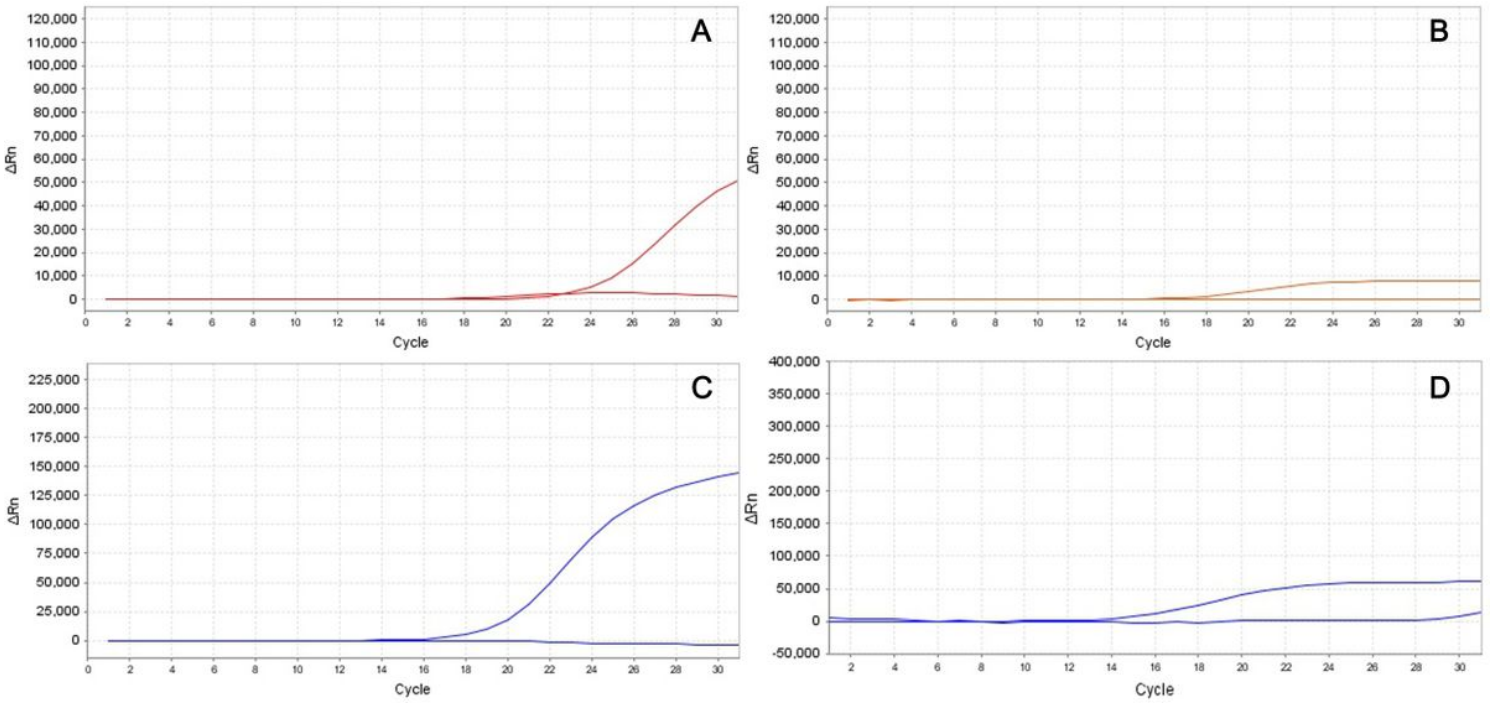
The dynamic evolution of the patient's primary lung tumor (A–F) after treatment. (A) The baseline chest computed tomography (CT) scan (April 17, 2019) showing a 9.2 × 9.8 cm mass in the right lower lung

and scattered metastatic nodules in both lungs. (B) Chest CT scan after 7 months of PP and gefitinib treatment (November 19, 2019).The lesion of the primary lung tumor was obviously bigger (from 9.2 × 9.8 cm to 9.8 cm × 11.4 cm). (C) Chest CT scan after 3 months of crizotinib treatment (February 21, 2020). The primary tumor was decreased (from 9.2 × 9.8 cm to 3.0 cm × 3.2 cm). (D) Chest CT scan after 5 months of crizotinib treatment (April 24, 2020). The lesion of the primary lung tumor was bigger compared with on February 21, 2020 (from 3.0 × 3.2 cm to 4.9 cm × 5.8 cm). (E) Chest CT scan after 5 months of TN and anlotinib treatment (October 10, 2020). The lesion of the primary lung tumor was bigger compared with on April 24, 2020 (from 4.9 × 5.8 cm to 6.0 cm × 7.1 cm). (F) Chest CT scan after 6 months of seretinib treatment (July 12, 2021). The lesion of the primary lung tumor was smaller compared with on October 10, 2020 (from 6.0 × 7.1 cm to 1.0 cm × 2.0 cm).



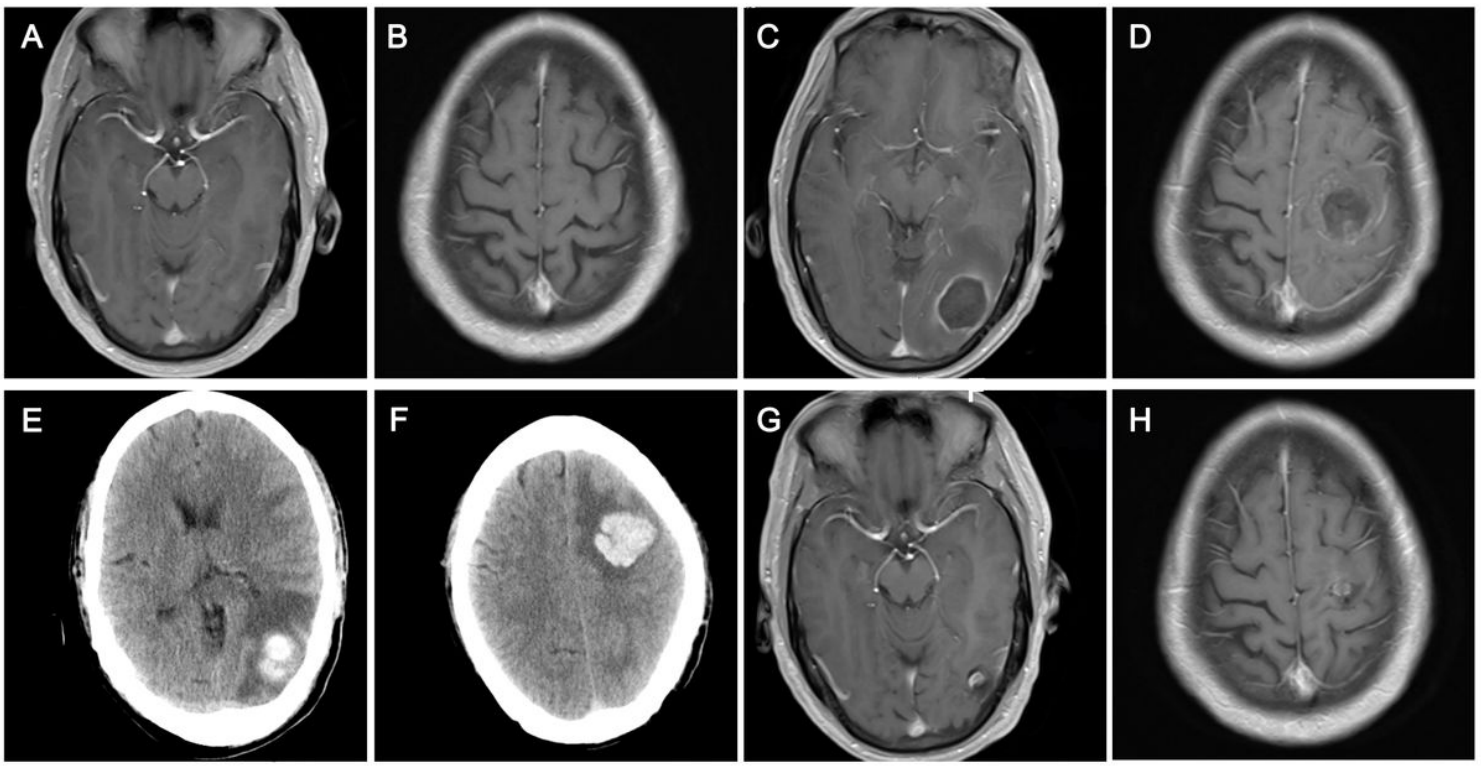

## Figure 2

Bronchoscopy and histopathological findings. (A) A new organism in the lumen of the right lower lobe blocked the lumen of the bronchus. (B and C) Histopathological findings of tissue biopsy. The tumor can be seen in the formation of glandular cavities, and some are arranged in tubular or adenoid structures. HE staining, original magnification 100. (D and E) Immunohistochemical staining positive for CK7, original magnification 100. (F) Immunohistochemical staining positive for TTF-1, original magnification 100. HE: Hematoxylin and eosin.



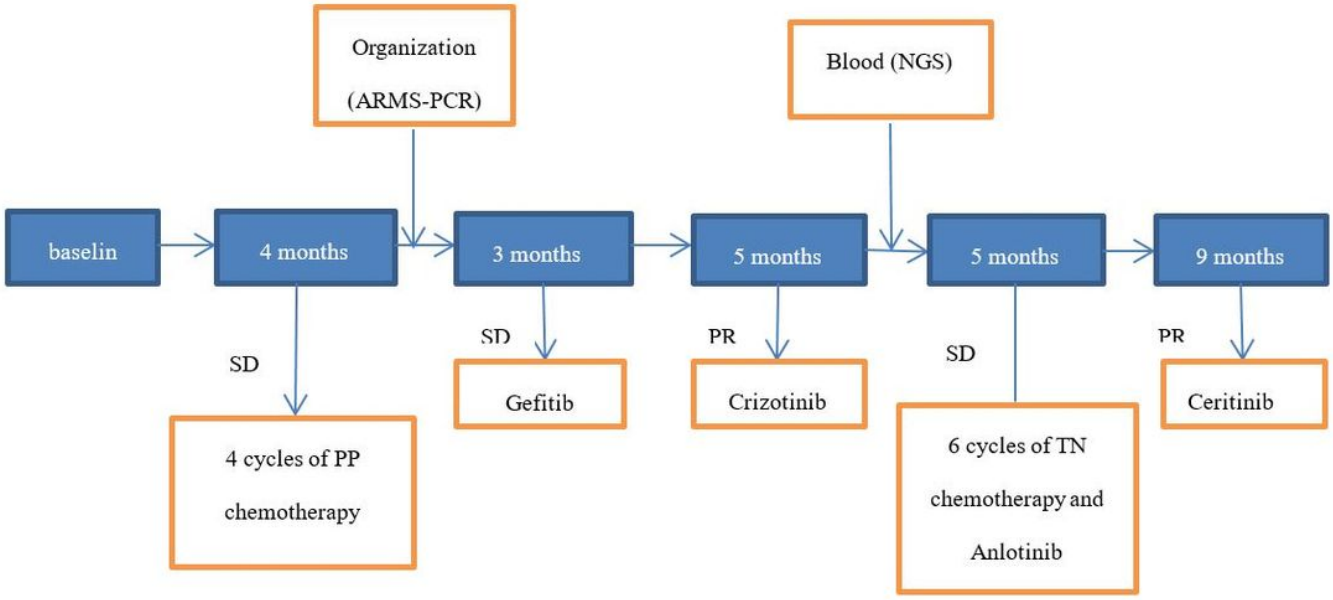

## Figure 3

First-generation sequencing (ARMS-PCR) findings of testing of the primary lung tumor tissue samples. (A) EGFR 19del site test positive. (B) EGFR G719X, T790M, S768I, 20ins, L858R, L861Q site detection did not detect mutations. (C) EML4-ALK fusion gene Exon-13, 6, 20 positive mutation.(D) No mutations were detected in the remaining sites of ALK and ROS1. EGFR, epidermal growth factor receptor gene; ROS1,c-ros oncogene 1 receptor kinase gene; EML4, echinoderm microtubule associated protein like 4 gene; ALK, anaplastic lymphoma kinase receptor tyrosine kinase gene .



## Figure 4

The dynamic evolution of the patient's brain metastases tumor (A–H) after treatment. (A) Head MRI showed a 12mm left temporal lobe lesion (April 24, 2020). (B) Head MRI showed no metastases on the top of the left forehead (April 24, 2020). (C) Head MRI scan after 5 months of TN and anlotinib treatment (October 10, 2020). The lesion of the left temporal lobe lesion was bigger compared with on April 24, 2020 (from diameter 12mm to 2.1 cm × 1.8cm). (D) Head MRI scan after 5 months of TN and anlotinib treatment (October 10, 2020). The lesion of the top of the left forehead was new compared with on April 24, 2020 (1.2 cm × 1.0 cm). (E) Head MRI scan showed acute brain metastasis rupture and hemorrhage (November 2, 2020). The lesion of the left temporal lobe lesion was bigger compared with October 10, 2020 (from 2.1 cm × 1.8 cm to 3.2 cm × 3.0 cm). (F) Head MRI scan showed acute brain metastasis rupture and hemorrhage (November 2, 2020). The lesion of the top of the left forehead was bigger compared with October 10, 2020 (from 1.2 cm × 1.0 cm to 2.5 cm × 3.0 cm). (G) Head MRI scan after 9 months of seretinib treatment (July 12, 2021). The lesion of the left temporal lobe lesion was bigger compared with on November 2, 2020 (from 3.2 cm × 3.0 cm to 1.8 cm × 1.2 cm). (H) Head MRI scan after 9 months of seretinib treatment (July 12, 2021). The lesion of the top of the left forehead was new compared with on November 2, 2020 (from 1.2 cm × 1.0 cm to 0.6 cm × 0.4 cm).




## Figure 5

The clinical course of the diagnosis and treatment of the patient. On April 17, 2019, the patient's chest CT scan suggested a right lung tumor and scattered lung metastases; On April 22, 2019, he started 4 cycles of PP chemotherapy treatment. On August 20, 2019, Tissue genetic testing suggested EGFR 19del and EML4-ALK rearrangements; On August 24, 2019, he started gefitib treatment ; On November 19, 2019, he started crizotinib treatment. On April 24, 2020, blood gene test negative for driver gene. He switched to nidaplatin plus paclitaxel chemotherapy and anlotinib for six cycles. On November 19, 2020, he started

seretinib. on July 12, 2021, chest CT indicated PR of the lesion. PR, partial response; PD, progressive disease; SD, stable disease.