



# FGFR2-ERCI: A Subtype of FGFR2 Oncogenic Fusion Variant in Lung Adenocarcinoma and the Response to Anlotinib

Chen Hong <sup>\*</sup>, Jianping Wei<sup>\*</sup>, Tao Zhou, Xia Wang , Jing Cai

Department of Oncology, the Second Affiliated Hospital of Nanchang University, Nanchang, Jiangxi, 330006, People's Republic of China

<sup>\*</sup>These authors contributed equally to this work

Correspondence: Jing Cai, Department of Oncology, the Second Affiliated Hospital of Nanchang University, Nanchang, Jiangxi, 330006, People's Republic of China, Tel +86 15270905381, Email [cjdl879@163.com](mailto:cjdl879@163.com)

**Background:** Fibroblast growth factor receptor (FGFR) fusions in non-small cell lung cancer (NSCLC) are small genomic events. At present, there is no standard treatment strategy for patients with NSCLC carrying an FGFR fusion.

**Case Presentation:** We report the case of a 45-year-old female patient who was diagnosed with lung adenocarcinoma and underwent right upper lobectomy and postoperative adjuvant chemotherapy. After 13 months, the patient's lung lesions progressed. Next-generation sequencing of venous blood and lung tissues confirmed an FGFR2-ERCI fusion, and she received chemotherapy and immunotherapy. Two months later, the patient's lung lesions progressed again. Based on the target effect of anlotinib on FGFR, the patient was subsequently treated with anlotinib, and the progression-free survival interval exceeded 8.0 months.

**Conclusion:** These findings showed that patients with lung adenocarcinoma carrying an FGFR2-ERCI fusion gene may benefit from anlotinib. This case provided evidence to support the use of anlotinib in the treatment of NSCLC patients with FGFR fusion gene subtypes.

**Keywords:** FGFR fusion, lung adenocarcinoma, anlotinib, ERC1, NGS

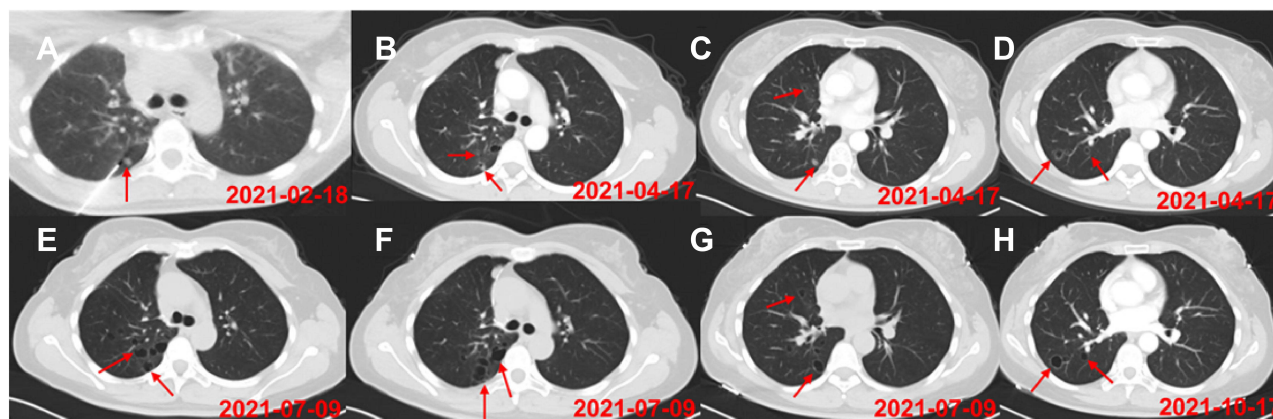
## Introduction

Lung cancer is a malignant tumor that has the highest incidence and fatality rates in China and worldwide, and is the leading cause of cancer-related deaths globally.<sup>1,2</sup> Targeted therapy has been added to treatment strategies for advanced non-small cell lung cancer (NSCLC). In addition, the toxic side effects and drug resistance of traditional therapies such as chemotherapy have also promoted the development of targeted therapy. Targeted therapy has greatly improved the survival and prognosis of lung cancer. However, only a small number of patients treated with the targeted drugs currently in use can benefit. Thus, there is still a great need for new targets to increase treatment options and improve prognosis in advanced NSCLC. Fibroblast growth factor receptor (FGFR) belongs to the tyrosine kinase family, which consists of four subtypes, FGFR1, FGFR2, FGFR3, and FGFR4. FGFR has been found in many solid tumors. Abnormalities in the FGFR signaling pathway may drive tumorigenesis, and FGFR has become a potential therapeutic target for malignancies.<sup>3</sup> When FGF and FGFRs interact with one another, they can activate and amplify the signal pathway, and transmit the signal to the downstream mediators Ras/Raf/MEK and PI3K-AKT.<sup>4</sup> FGFR malformations include point mutations, amplifications, and gene rearrangements that result in fusion proteins.<sup>5</sup> As one member of the tyrosine receptor kinase family, FGFR2 is also involved in the occurrence and development of tumors, and FGFR2 gene fusions are emerging targets for targeted therapy in solid tumors, which are most common in cholangiocarcinoma.<sup>6,7</sup> The most common fusion partner of FGFR2 is the BICC Family RNA Binding Protein.<sup>8,9</sup> One study found that the FGFR fusion rate in NSCLC was 0.20% (52/26054), with a FGFR2 fusion rate of 0.04% (10/26054) following Comprehensive Genomic Profiling of 26054 NSCLC patient specimens, this study also found co-occurrence of FGFR3 or FGFR4 fusions with mutations in epidermal growth factor receptor and MNG HOS Transforming gene (MET) in

NSCLC, but co-occurrence of other mutated genes with FGFR2 fusions has not been reported in NSCLC currently.<sup>10</sup> The potential oncogenic mechanism of FGFR fusions includes activation of the FGFR kinase domain leading to abnormal activation of downstream signaling pathways,<sup>11–13</sup> fusion protein mislocalization to mitotic spindle poles, which causes genomic instability and transcriptional dysregulation,<sup>9,11</sup> and gene fusions with strong promoters or loss of genomic regulatory elements leading to overexpression of the fusion protein.<sup>9,13,14</sup> FGFR fusion partners have been reported in many solid tumors, but are rare in NSCLC, especially lung adenocarcinoma with FGFR2 and ERCC1 fusion.<sup>10</sup> ERCC1 has been shown to be a fusion partner of several genes, such as RET and Rearrangements in the anaplastic lymphoma kinase gene (ALK),<sup>15–17</sup> but no fusion of ERCC1 with the FGFR family other than FGFR2 has been reported. Herein, we report the first case of right upper lobe invasive adenocarcinoma harboring the FGFR2-ERCC1 fusion which was sensitive to anlotinib therapy.

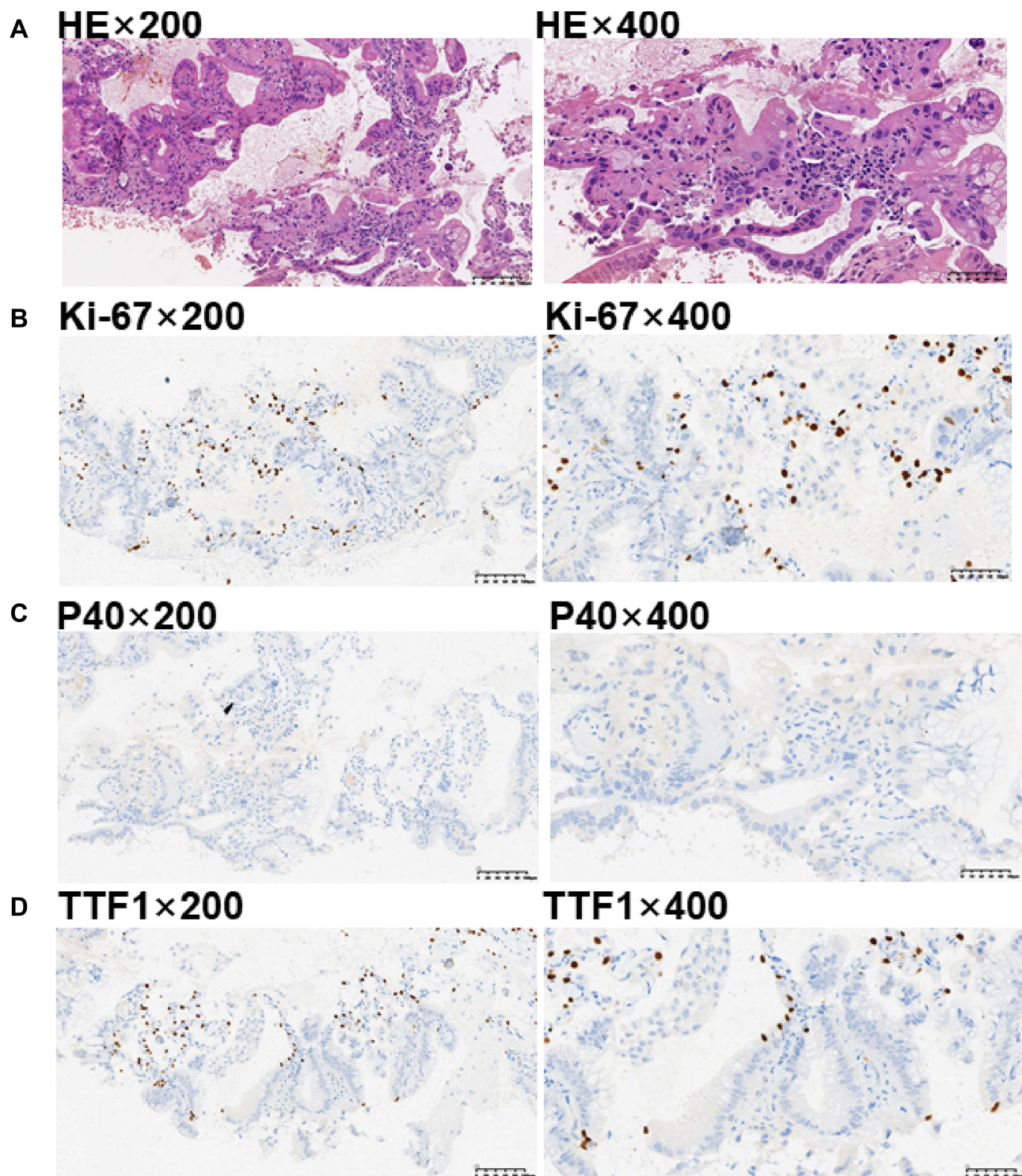
## Case Presentation

A 45-year-old woman presented to Jiangxi Chest Hospital due to intermittent coughing and hemoptysis. Chest computed tomography (CT) showed a right upper lung space-occupying lesion (3.5 cm x 3.7 cm). On December 18, 2019, the patient underwent thoracoscopic right upper lobectomy with lymph node dissection under general anesthesia. The patient was diagnosed with invasive adenocarcinoma of the right upper lobe, of which 60% was alveolar adenocarcinoma and 40% was mucinous adenocarcinoma. Postoperatively, the patient was given pemetrexed 500 mg/m<sup>2</sup> combined with carboplatin AUC5 chemotherapy for four cycles. After that, the patient attended the hospital regularly for review. On January 30, 2021, the patient underwent CT re-examination which showed that compared with the chest CT on October 27, 2020, the original right lung nodules had increased in size and number. The patient underwent CT-guided percutaneous lung biopsy for diagnosis confirmation (Figure 1A). Hematoxylin and eosin staining confirmed typical lung adenocarcinoma morphology (Figure 2A), and immunohistochemistry showed that cancer cells were focally positive for Ki-67 (Figure 2B), negative for P40 (Figure 2C), and approximately 5% positive for TTF-1 (Figure 2D). The patient then underwent gene mutation examination, and next-generation-sequencing (NGS) analysis of venous blood and lung tissue. FGFR2-ERCC1 fusion was detected only in tumor tissue DNA, and its mutant DNA fragment/total DNA fragment was 98/1629, the mutation abundance was 6.02% (Figure 3A and B). No mutations were detected in epidermal growth factor receptor, ALK, round spermatid injection, BRAF, mesenchymal-epithelial transition factor, RET, erb-b2 receptor tyrosine kinase 2, KRAS, neurotrophic TRK1, and neurotrophic TRK3. From March 8, 2021, the patient was given two cycles of chemotherapy combined with immunotherapy consisting of liposomal paclitaxel 150 mg/m<sup>2</sup> and carboplatin (AUC5) combined with camrelizumab 200 mg. On April 17, 2021, the patient's chest plain CT scan and enhancement showed multiple nodules in the right lung, a nodule in the upper lobe of the left lung and multiple cavities, which were possible metastatic tumors. Compared with the chest CT on January 30, 2021, some of the nodules and cavities had increased (Figure 1B–D). The patient refused chemotherapy, and received anlotinib based on its targeted effect on FGFR. Since then, the patient has been regularly re-examined and her condition has been stable (Figure 1E–H). In this case, the patient



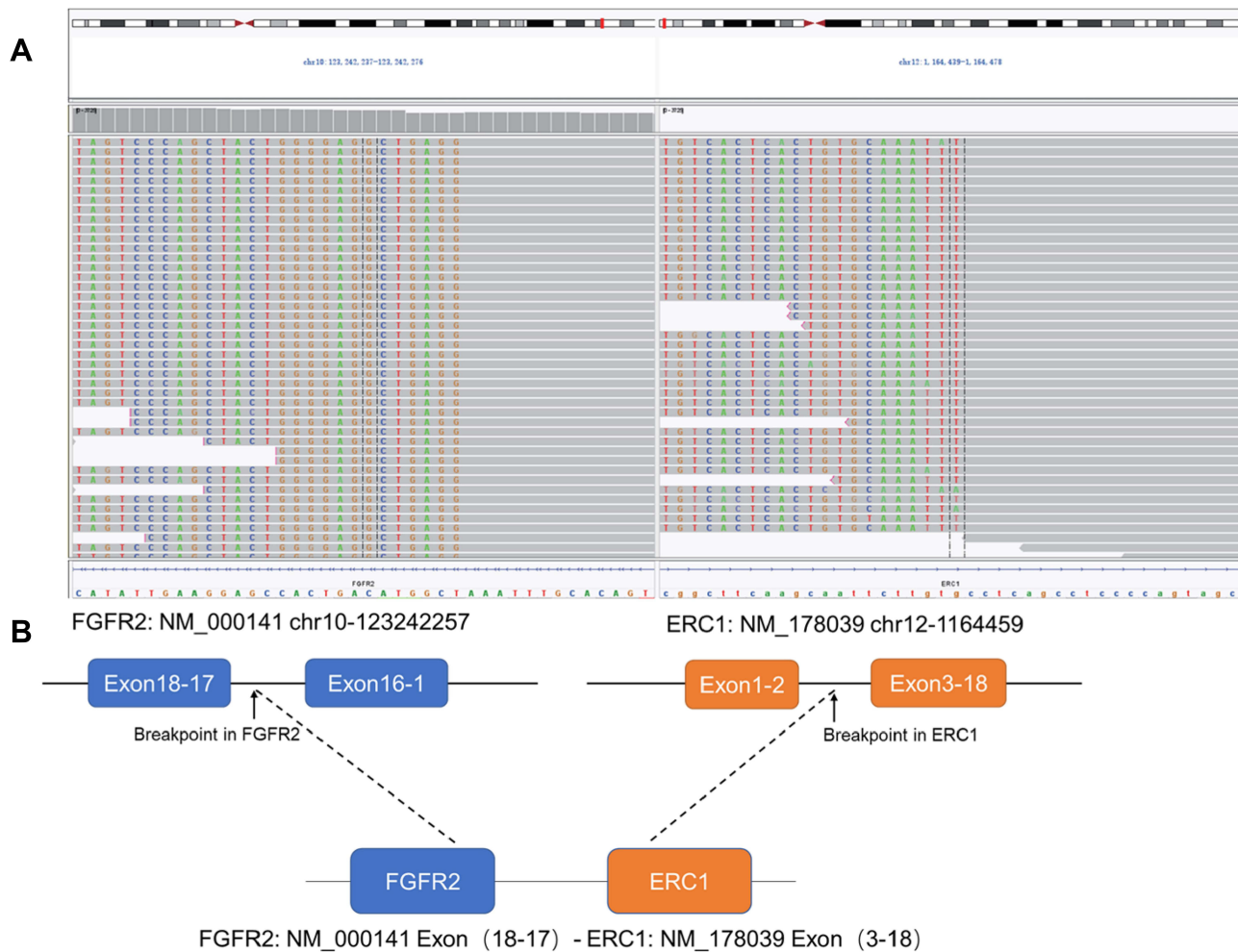
**Figure 1** CT shows (A) the puncture position. (B–D) new lung cavities and metastases before treatment with anlotinib. (E–H) stabilization of lung lesions after anlotinib treatment. The red arrows in the figure indicate changes in lesions before and after treatment.





**Figure 2** Pathological analysis of percutaneous lung biopsy. **(A)** HE staining confirmed typical lung adenocarcinoma morphology, immunohistochemistry showed that **(B)** Ki-67 was approximately 5% positive, **(C)** P40 negative, and **(D)** TTF-1 focally positive.

was insensitive to either chemotherapy or immunotherapy, and she had a progression-free survival (PFS) of more than 8.0 months after treatment with anlotinib. The timeline of the clinical diagnosis and treatment of this patient is summarized in [Figure S1](#).



**Figure 3** Next-generation sequencing analysis showed an FGFR2-ERC1 fusion mutation following blood analysis and lung tissue biopsy. **(A)** Integrative Genomics Viewer snapshot of the FGFR2-ERC1 fusion; **(B)** a schematic map of the FGFR2-ERC1 fusion protein domain structure.

## Discussion and Conclusions

The receptor tyrosine kinase (RTK) superfamily consists of 20 structurally conserved subfamily cell surface receptors, all of which play a key role in regulating cell differentiation, proliferation, survival, metabolism, and migration.<sup>18</sup> FGFRs belong to the highly conserved single-transmembrane tyrosine receptor family, which consist of extracellular ligand binding domains and cytoplasmic conservative tyrosine kinase.<sup>19</sup> The FGFR family includes receptors FGFR1–4 that are individually encoded but highly homologous to vascular endothelial growth factor receptors, platelet-derived growth factor receptors and other tyrosine kinase receptors.<sup>20,21</sup> An abnormal FGFR signaling pathway has become an important cause of many tumors. FGF, FGFR and heparan sulfate proteoglycan form a 2:2:2 ternary complex, which causes dimerization of receptors and transphosphorylation of kinases, which then activates the PI3K-AKT, RAS-MEK-ERK, PLC- $\gamma$ , and JAK-STAT3 signaling pathways.<sup>19,22</sup> Most fusion partners contain dimers that dimerize non-ligand receptors, leading to proliferation of cancer cells, metastasis, and angiogenesis.<sup>23,24</sup>

At present, the detection methods for FGFR fusion in clinical diagnosis include fluorescence in situ hybridization, immunohistochemistry, reverse transcription-polymerase chain reaction, and NGS approaches.<sup>25</sup> NGS significantly increases the clinical detection level of FGFR gene fusion and has the advantages of low cost and easy to obtain, Although the frequency of FGFR in human malignant tumors is low, with the accumulation of sample size, targeted drugs for FGFR are still promising, which also provides hope for the treatment of patients with NSCLC carrying a FGFR fusion gene.

Anlotinib acts as a multi-target inhibitor of the small molecule RTK, and inhibits angiogenesis induced by Vascular Endothelial Growth Factor (VEGF)/Platelet-Derived Growth Factor -BB/FGF-2 by blocking tyrosine kinase phosphorylation and its downstream signaling pathways.<sup>26</sup> A preclinical model showed that anlotinib combines with the ATP-binding pocket of Vascular endothelial growth factor receptor-2 (VEGFR2) tyrosine kinase and exhibits a high degree of selectivity and inhibition ( $IC_{50} < 1$  nmol/L) of VEGFR2.<sup>27</sup> Blocking the VEGF pathway alone will result in continued activation of the bypass, leading to tumor revascularization and regeneration.<sup>28</sup> Anlotinib inhibits tumor growth by comprehensively inhibiting the angiogenic pathway, thereby reducing bypass activation and inhibiting revascularization. On the other hand, it can also control tumor cell proliferation and metastasis by inhibiting targets such as c-Kit, Ret, FGFR, and c-Met.<sup>29</sup> Anlotinib also reshapes the tumor microenvironment and combines with other treatment modalities to increase the effectiveness. Anlotinib increases infiltration of T cells, NK cells and APC cells, and the combination of anlotinib and immunotherapy has a synergistic effect.<sup>30,31</sup> In addition, anlotinib has been shown to have synergistic effects with chemotherapy and targeted therapies.<sup>32,33</sup> Adverse effects of anlotinib monotherapy have been shown to be manageable in previous studies.<sup>34–36</sup> Based on the ALTER0303 study, anlotinib has been approved as an NSCLC standard third-line treatment indication.<sup>37</sup>

In a retrospective analysis, a case of cholangiocarcinoma with an FGFR2-ERC1 fusion was mentioned. In addition, two patients with glioblastoma multiforme carrying the FGFR-TACC3 fusion gene achieved partial remission after receiving anlotinib.<sup>38</sup> A multicenter, double-blind, randomized Phase III clinical trial showed that patients with advanced NSCLC treated with anlotinib as a third-line or further treatment had better overall survival (OS), PFS, and objective response rates.<sup>37</sup> A Phase I study validated the controlled toxicity and antitumor potential of anlotinib, and preclinical results have shown that anlotinib significantly inactivates FGFR1–4, especially FGFR2.<sup>36</sup> Although Phase III clinical trials have demonstrated that anlotinib significantly improved OS and PFS in patients with NSCLC,<sup>37</sup> resistance was inevitable in the later stages of malignancy treatment. In this case, the patient was insensitive to chemotherapy as well as immunotherapy, and anlotinib was a third-line treatment. In the case of resistance to anlotinib or disease progression, additional local radiotherapy may be considered. Furthermore, based on the synergistic effects that anlotinib may have with other treatment options, we may try anlotinib in combination with chemotherapy or immunotherapy. There are currently studies exploring the mechanisms of resistance to anlotinib, for example, miR-136-5p confers resistance to anlotinib in NSCLC cells by targeting PPP2R2A,<sup>39</sup> TFAP2A plays an important role in anlotinib resistance by promoting tumor-induced angiogenesis,<sup>40</sup> CXCL2 is involved in the development of anlotinib resistance in human lung cancer cells.<sup>41</sup> Nevertheless, the mechanism of anlotinib resistance is still unclear, and further exploration is needed to clarify the optimal treatment strategy and drug selection for patients after anlotinib resistance.

Therefore, in patients with advanced FGFR mutations, anlotinib can be added to the treatment strategy. In addition, there are several drugs that have been or are being developed to suppress FGFR/FGF signaling,<sup>36</sup> and some FGFR small molecule inhibitors, such as erdafitinib and pemigatinib, have been approved by the Food and Drug Administration for the treatment of malignant tumors such as urothelial carcinoma and cholangiocarcinoma.<sup>42</sup> At present, FGFR inhibitors for NSCLC are still in clinical trials, but it is already starting to pay off.<sup>43</sup> With regard to the FGFR gene, only when we explore its molecular mechanism and biological effects, can we really develop targeted drugs with high specificity and sensitivity. With the advent of the era of molecular targeted therapy, an increasing number of targets have been identified. We continue to research and develop targeted drugs with higher specificity and fewer side effects.

In summary, this is the first case report of a woman with lung adenocarcinoma carrying the FGFR2-ERC1 fusion gene that was sensitive to anlotinib therapy, suggesting the critical role of targeted therapy for advanced patients with FGFR mutations. Targeted therapy for FGFR mutations in patients with NSCLC is still under development, especially for lung squamous cell carcinoma. It is necessary to further explore the biological characteristics and molecular mechanism in order to find the best treatment mode for patients with this subtype of lung cancer. With the advent of the era of precision oncology, targeted therapy plays an important role in the treatment of malignant tumors. The safety and efficacy of anlotinib, and whether it can be combined with chemotherapy and immunotherapy in the overall treatment strategy, require further examination.



## Abbreviations

FGFR, Fibroblast Growth Factor Receptor; NSCLC, non-small cell lung cancer; MET, MNNG HOS Transforming gene; ALK, Rearrangements in the anaplastic lymphoma kinase gene; CT, computed tomography; AUC, area under the curve; NGS, next-generation-sequencing; PFS, progression-free survival; RTK, The receptor tyrosine kinase; VEGF, Vascular Endothelial Growth Factor; VEGFR2, Vascular endothelial growth factor receptor-2; IC50, Half maximal (50%) inhibitory concentration; OS, overall survival.

## Data Sharing Statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

## Ethics Approval and Consent to Participate

Written informed consent was obtained from the patient for publication of this case report and accompanying images. This is a retrospective case report and institutional approval was not needed.

## Acknowledgments

We owe thanks to the patient and her family.

## Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agreed to be accountable for all aspects of the work.

## Funding

This work was supported by the National Natural Science Foundation [grant number 82060547] and Jiangxi Provincial Natural Science Foundation [grant number 20212BAB206051].

## Disclosure

The authors report no conflicts of interest in this work.

## References

1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2021;71(3):209–249.
2. Fitzmaurice C, Dicker D, Pain A, et al. The global burden of cancer 2013. *JAMA Oncol.* 2015;1(4):505–527.
3. Theelen WS, Mittempergher L, Willems SM, et al. FGFR<sub>1, 2</sub> and <sub>3</sub> protein overexpression and molecular aberrations of FGFR<sub>3</sub> in early stage non-small cell lung cancer. *J Pathol Clin Res.* 2016;2(4):223–233.
4. Katoh M, Nakagama H. FGF receptors: cancer biology and therapeutics. *Med Res Rev.* 2014;34(2):280–300.
5. Roskoski R. The role of fibroblast growth factor receptor (FGFR) protein-tyrosine kinase inhibitors in the treatment of cancers including those of the urinary bladder. *Pharmacol Res.* 2020;151:104567.
6. Alqahtani SA, Colombo M. Systemic therapy for advanced cholangiocarcinoma: new options on the horizon. *Hepatoma Res.* 2020;1(10):45–59.
7. Lowery MA, Ptashkin R, Jordan E, et al. Comprehensive molecular profiling of intrahepatic and extrahepatic cholangiocarcinomas: potential targets for intervention. *Clin Cancer Res.* 2018;24(17):4154–4161.
8. Scheiter A, Keil F, Lüke F, et al. Identification and in-depth analysis of the novel FGFR<sub>2</sub>-NDC80 fusion in a cholangiocarcinoma patient: implication for therapy. *Curr Oncol.* 2021;28(2):1161–1169.
9. Touat M, Ileana E, Postel-Vinay S, André F, Soria JC. Targeting FGFR signaling in cancer. *Clin Cancer Res.* 2015;21(12):2684–2694.
10. Qin A, Johnson A, Ross JS, et al. Detection of known and novel FGFR fusions in non-small cell lung cancer by comprehensive genomic profiling. *J Thorac Oncol.* 2019;14(1):54–62.
11. Singh D, Chan JM, Zoppoli P, et al. Transforming fusions of FGFR and TACC genes in human glioblastoma. *Science.* 2012;337(6099):1231–1235.
12. Williams SV, Hurst CD, Knowles MA. Oncogenic FGFR<sub>3</sub> gene fusions in bladder cancer. *Hum Mol Genet.* 2013;22(4):795–803.
13. Wu YM, Su FY, Kalyana-Sundaram S, et al. Identification of targetable FGFR gene fusions in diverse cancers. *Cancer Discov.* 2013;3(6):636–647.
14. Parker BC, Annala MJ, Cogdell DE, et al. The tumorigenic FGFR<sub>3</sub>-TACC<sub>3</sub> gene fusion escapes miR-99a regulation in glioblastoma. *J Clin Invest.* 2013;123(2):855–865.

15. Tertre MCD, Marques M, Tremblay L, Bouchard N, Agulnik J. Analysis of the genomic landscape in ALK+ NSCLC patients identifies novel aberrations associated with clinical outcomes. *Mol Cancer Ther.* 2019;18(9):1628–1636.
16. Ma J, Wang B, Meng E, Meng X. Case report: identification of ERC1-RET fusion in a patient with pancreatic ductal adenocarcinoma. *Gland Surg.* 2021;10(9):2874–2879.
17. Shi M, Wang W, Zhang J, et al. Identification of RET fusions in a Chinese multicancer retrospective analysis by next-generation sequencing. *Cancer Sci.* 2022;113(1):308–318.
18. Wintheiser G, Silberstein P. *Physiology, Tyrosine Kinase Receptors*. Treasure Island (FL): StatPearls Publishing; 2021. Available from: <https://www.statpearls.com/articlelibrary/viewarticle/30723/>. Accessed June 2, 2022.
19. Chen LF, Zhang YM, Yin L, et al. Fibroblast growth factor receptor fusions in cancer: opportunities and challenges. *J Exp Clin Cancer Res.* 2021;40(1):345.
20. Dai SY, Zhou Z, Chen ZC, Xu GY, Chen YH. Fibroblast Growth Factor Receptors (FGFRs): structures and small molecule inhibitors. *Cells.* 2019;8(6):614.
21. Hubbard SR, Till JH. Protein tyrosine kinase structure and function. *Annu Rev Biochem.* 2000;69(1):373–398.
22. Wesche J, Haglund K, Haugsten EM. Fibroblast growth factors and their receptors in cancer. *Biochem J.* 2011;437(2):199–213.
23. Babina IS, Turner NC. Advances and challenges in targeting FGFR signalling in cancer. *Nat Rev Cancer.* 2017;17(5):318–332.
24. Parker BC, Engels M, Annala M, Zhang W. Emergence of FGFR family gene fusions as therapeutic targets in a wide spectrum of solid tumours. *J Pathol.* 2014;232(1):4–15.
25. De Luca A, Esposito Abate R, Rachiglio AM, et al. FGFR fusions in cancer: from diagnostic approaches to therapeutic intervention. *Int J Mol Sci.* 2020;21(18):6856.
26. Lin B, Song X, Yang D, Bai D, Yao Y, Lu N. Anlotinib inhibits angiogenesis via suppressing the activation of VEGFR<sub>2</sub>, PDGFR $\beta$  and FGFR<sub>1</sub>. *Gene.* 2018;654:77–86.
27. Xie C, Wan X, Quan H, et al. Preclinical characterization of anlotinib, a highly potent and selective vascular endothelial growth factor receptor-2 inhibitor. *Cancer Sci.* 2018;109(4):1207–1219. doi:10.1111/cas.13536
28. Casanovas O, Hicklin DJ, Bergers G, Hanahan D. Drug resistance by evasion of antiangiogenic targeting of VEGF signaling in late-stage pancreatic islet tumors. *Cancer Cell.* 2005;8(4):299–309. doi:10.1016/j.ccr.2005.09.005
29. Shen GS, Zheng FC, Ren DF, et al. Anlotinib: a novel multi-targeting tyrosine kinase inhibitor in clinical development. *J Hematol Oncol.* 2018;11(1):120.
30. Yang Y, Li L, Jiang Z, Wang B, Pan Z. Anlotinib optimizes anti-tumor innate immunity to potentiate the therapeutic effect of PD-1 blockade in lung cancer. *Cancer Immunol Immunother.* 2020;69(12):2523–2532. doi:10.1007/s00262-020-02641-5
31. Wang Y, Zhang Q, Miao L, Zhou Y. Nivolumab in combination with anlotinib achieved remarkable efficacy in a patient with driver-negative lung squamous cell carcinoma and PS of 4. *Ann Palliat Med.* 2020;9(6):4384–4388.
32. Xiong Q, Qin B, Xin L, et al. Real-World Efficacy and Safety of Anlotinib With and Without Immunotherapy in Advanced Non-Small Cell Lung Cancer. Original Research. *Front Oncol.* 2021;2021:11. doi:10.3389/fonc.2021.659380
33. Wang HY, Chu JF, Zhao Y, et al. A Trial of the Safety and Efficacy of Chemotherapy Plus Anlotinib vs Chemotherapy Alone as Second- or Third-Line Salvage Treatment for Advanced Non-Small Cell Lung Cancer. *Cancer Manag Res.* 2020;12:3827–3834. doi:10.2147/cmar.S249678
34. Shao L, Wang W, Song Z, Zhang Y. The efficacy and safety of anlotinib treatment for advanced lung cancer. *Onco Targets Ther.* 2019;12:6549–6554. doi:10.2147/ott.S205674
35. Jiang HT, Li W, Zhang B, Gong Q, Qie HL. Efficacy and Safety of Anlotinib Monotherapy as Third-Line Therapy for Elderly Patients with Non-Small Cell Lung Cancer: a Real-World Exploratory Study. *Int J Gen Med.* 2021;14:7625–7637. doi:10.2147/ijgm.S334436
36. Sun Y, Niu W, Du F, et al. Safety, pharmacokinetics, and antitumor properties of anlotinib, an oral multi-target tyrosine kinase inhibitor, in patients with advanced refractory solid tumors. *J Hematol Oncol.* 2016;9(1):105. doi:10.1186/s13045-016-0332-8
37. Cheng Y, Han B, Li K, et al. Effect of anlotinib as a third- or further-line therapy in advanced non-small cell lung cancer patients with different histologic types: subgroup analysis in the ALTER0303 trial. *Cancer Med.* 2020;9(8):2621–2630. doi:10.1002/cam4.2913
38. Gu WQ, Yang J, Wang Y, et al. Comprehensive identification of FGFR<sub>1-4</sub> alterations in 5 557 Chinese patients with solid tumors by next-generation sequencing. *Am J Cancer Res.* 2021;11(8):3893–3906.
39. Gu G, Hu C, Hui K, Zhang H, Jiang X. Exosomal miR-136-5p derived from anlotinib-resistant NSCLC cells confers anlotinib resistance in non-small cell lung cancer through targeting PPP2R2A. *Int J Nanomedicine.* 2021;16:6329–6343.
40. Zhang L, Lu J, Liu R, et al. Chromatin accessibility analysis reveals that TFAP2A promotes angiogenesis in acquired resistance to anlotinib in lung cancer cells. *Acta Pharmacol Sin.* 2020;41(10):1357–1365.
41. Lu J, Xu W, Qian J, et al. Transcriptome profiling analysis reveals that CXCL2 is involved in anlotinib resistance in human lung cancer cells. *BMC Med Genomics.* 2019;12(S2):38.
42. Chandana SR, Babiker HM, Mahadevan D. Clinical complexity of utilizing FGFR inhibitors in cancer therapeutics. *Expert Opin Investig Drugs.* 2020;29(12):1413–1429.
43. Katoh M. Fibroblast growth factor receptors as treatment targets in clinical oncology. *Nat Rev Clin Oncol.* 2019;16(2):105–122.

## OncoTargets and Therapy

Dovepress

### Publish your work in this journal

OncoTargets and Therapy is an international, peer-reviewed, open access journal focusing on the pathological basis of all cancers, potential targets for therapy and treatment protocols employed to improve the management of cancer patients. The journal also focuses on the impact of management programs and new therapeutic agents and protocols on patient perspectives such as quality of life, adherence and satisfaction. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <https://www.dovepress.com/oncotargets-and-therapy-journal>