Lung cancer, as the malignant tumor with the second incidence and the first mortality rate, is still a disease that poses a serious threat to human beings in the world (1,2). Among them, the incidence of non-small cell lung cancer (NSCLC), which accounts for the highest proportion, accounts for about 80% of the total number of lung cancers, and most patients are diagnosed with inoperable middle and advanced stage (1,3). Although the treatment of NSCLC has made some progress in the treatment of traditional malignant tumors, such as surgery, chemotherapy and radiotherapy in recent years, the 5-year survival rate is only 23% (4). With the promotion of next-generation sequencing and the arrival of precision medicine, targeted therapy for key genes and regulatory molecules has begun to play a pivotal role in the treatment of NSCLC. Epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) are the most frequently mutated targets in the treatment of NSCLC (5,6). Small-molecule tyrosine kinase inhibitors (TKIs) targeting EGFR and ALK targets show significant efficacy in NSCLC with EGFR and ALK genetic aberration (7,8). However, there will be a common problem in the application of TKIs, that is drug resistance. For NSCLC patients with EGFR and ALK genetic aberrations, it is a difficult problem to choose the treatment after TKIs resistance (9,10).

With the continuous progress of immunotherapy research, the application of immune checkpoint inhibitors (ICIs) targeting programmed death receptor 1 (PD-1) and its ligand (PD-L1) in advanced lung cancer, the 5-year survival rate has greatly improved (11). ICIs emerge as first or second line treatment option for NSCLC without driver mutation (12,13). However, previous studies have shown that the progression free survival (PFS) and survival rate of NSCLC patients with EGFR or ALK gene mutations were not significantly improved after ICIs treatment, indicating that EGFR and ALK genes may affect the expression of PD-1/PD-L1, change the tumor microenvironment, and have an impact on the efficacy of ICIs (14-17). For NSCLC patients with EGFR and ALK mutations, both immunotherapy and targeted therapy have potential problems, and the treatment effect is not very satisfactory. How to choose the follow-up treatment plan for these patients needs further study.
patients who progress or relapse after treatment with TKIs and first line chemotherapy regimens. This has always been an urgent problem in the professional field.

In the current issue of *Translational Lung Cancer Research*, Gao et al. offer us with a phase 1b/2, open-label, multicenter, multicohort study of application targeted therapy combined with immunotherapy for advanced NSCLC with EGFR or ALK gene mutation, these patients had disease progression or recurrence occurred after at least one platinum-based doublet chemotherapy (18). This study uses camrelizumab plus apatinib and shows moderate antitumor activity and acceptable safety. This may be the first study to report ICIs plus TKIs in pretreated patients with advanced EGFR+/ALK+ NSCLC provides a research direction for future treatment options for this kind of patients. Of course, this article also has certain shortcomings. As discussed in the article, the study is a single-arm, small-sample study. Although the objective response rate (ORR) is improved compared with previous studies, it still does not meet expectations.

The relationship between EGFR gene and PD-L1 is controversial. Some studies suggest that EGFR mutation positive may lead to immune escape by up-regulating PD-L1 expression (19,20), and other study results suggest that EGFR gene mutation is negatively correlated with PD-L1 expression and EGFR mutation will reduce the positive expression rate of PD-L1 (21). This study by Gao et al. suggests that TKIs combined with ICIs are still effective in patients with EGFR+/ALK+ NSCLC. Exon 19 deletion (19del) and exon 20 L858R point mutation are the two most common types of EGFR mutations (22), different types of mutations may have different responses to targeted therapy and immunity (18). In addition, EGFR mutations and ALK rearrangement co-mutations are generally considered to be rare types of genetic variation in NSCLC, and they are usually considered to be mutually exclusive. In recent years, the co-occurrence of EGFR and ALK gene mutations has also increased with the expansion of the coverage of genetic testing, especially when high-throughput sequencing begins to be used in clinical diagnosis and treatment. Due to the low incidence and insufficient number of samples, the molecular mechanism, biological behavior, clinicopathological characteristics of patients, and targeted treatment plans for the occurrence of EGFR and ALK double positivity still need to be further explored and a strong evidence-based basis is sought. Secondary biopsy after resistance to targeted therapy is very important for subsequent treatment selection. For patients with EGFR and ALK double-positive NSCLC, the choice of TKIs combined with ICIs after early treatment resistance will be a future research direction, and more research is needed to confirm. The signaling pathways and driving factors that play a role in the occurrence and development of malignant tumors provide targets for targeted therapy. Targeted drugs are becoming more and more diverse, and the rational selection of therapeutic strategies is particularly critical.

**Acknowledgments**

**Funding:** This work was supported by CAMS Innovation Fund for Medical Sciences (CIFMS) (No. 2021-I2M-1-061), CSCO-hengrui Cancer Research Fund (No. Y-HR2019-0239), CSCO-MSD Cancer Research Fund (No. Y-MSDZD2021-0213), and National Ten-thousand Talent Program.

**Footnote**

**Provenance and Peer Review:** This article was a standard submission to the journal. The article did not undergo external peer review.

**Conflicts of Interest:** All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-522/coif). The authors have no conflicts of interest to declare.

**Ethical Statement:** The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

**Open Access Statement:** This is an Open Access article distributed in accordance with the Creative Commons Attribution-NonCommercial-NoDerivs 4.0 International License (CC BY-NC-ND 4.0), which permits the non-commercial replication and distribution of the article with the strict proviso that no changes or edits are made and the original work is properly cited (including links to both the formal publication through the relevant DOI and the license). See: https://creativecommons.org/licenses/by-nc-nd/4.0/.

**References**

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin 2020;70:7-30.
2. Ferlay J, Colombet M, Soerjomataram I, et al. Cancer statistics for the year 2020: An overview. Int J Cancer 2021. [Epub ahead of print]. doi: 10.1002/ijc.33588.
3. Zarogoulidis K, Zarogoulidis P, Darwiche K, et al. Treatment of non-small cell lung cancer (NSCLC). J Thorac Dis 2013;5 Suppl 4:S389-96.
4. Miller KD, Nogueira L, Mariotto AB, et al. Cancer treatment and survivorship statistics, 2019. CA Cancer J Clin 2019;69:363-85.
5. Soda M, Choi YL, Enomoto M, et al. Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer. Nature 2007;448:561-6.
6. Gerlinger M. Targeted drugs ramp up cancer mutability. Science 2019;366:1452-3.
7. Miyachi E, Inoue A, Kobayashi K, et al. Efficacy of chemotherapy after first-line gefitinib therapy in EGFR mutation-positive advanced non-small cell lung cancer data from a randomized Phase III study comparing gefitinib with carboplatin plus paclitaxel (NEJ002). Jpn J Clin Oncol 2015;45:670-6.
8. Mitsudomi T, Morita S, Yatabe Y, et al. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. Lancet Oncol 2010;11:121-8.
9. Infinarino NR, Park JH, Krytska K, et al. The ALK/ROS1 Inhibitor PF-06463922 Overcomes Primary Resistance to Crizotinib in ALK-Driven Neuroblastoma. Cancer Discov 2016;6:96-107.
10. Tuck ER, Danielson LS, Innocenti P, et al. Tackling Crizotinib Resistance: The Pathway from Drug Discovery to the Pediatric Clinic. Cancer Res 2015;75:2770-4.
11. Subbiah V, Velcheti V, Tuch BB, et al. Selective RET kinase inhibition for patients with RET-altered cancers. Ann Oncol 2018;29:1869-76.
12. Zhou C, Wu YL, Chen G, et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. Lancet Oncol 2011;12:735-42.
13. Wu YL, Zhang L, Kim DW, et al. Phase Ib/II Study of Capmatinib (INC280) Plus Gefitinib After Failure of Epidermal Growth Factor Receptor (EGFR) Inhibitor Therapy in Patients With EGFR-Mutated, MET Factor-Dysregulated Non-Small-Cell Lung Cancer. J Clin Oncol 2018;36:3101-9. Erratum in: J Clin Oncol 2019;37:261.
14. Ayati A, Moghimi S, Salarinejad S, et al. A review on progression of epidermal growth factor receptor (EGFR) inhibitors as an efficient approach in cancer targeted therapy. Bioorg Chem 2020;99:103811.
15. Hu X, Han B, Gu A, et al. A single-arm, multicenter, safety-monitoring, phase IV study of icotinib in treating advanced non-small cell lung cancer (NSCLC). Lung Cancer 2014;86:207-12.
16. Hirsch FR, Bunn PA Jr. EGFR testing in lung cancer is ready for prime time. Lancet Oncol 2009;10:432-3.
17. Champiat S, Dercle L, Ammari S, et al. Hyperprogressive Disease Is a New Pattern of Progression in Cancer Patients Treated by Anti-PD-1/PD-L1. Clin Cancer Res 2017;23:1920-8.
18. Gao G, Ni J, Wang Y, et al. Efficacy and safety of camrelizumab plus apatinib in previously treated patients with advanced non-small cell lung cancer harboring EGFR or ALK genetic aberration. Transl Lung Cancer Res 2022;11:964-74.
19. Marzec M, Zhang Q, Goradia A, et al. Oncogenic kinase NPM/ALK induces through STAT3 expression of immunosuppressive protein CD274 (PD-L1, B7-H1). Proc Natl Acad Sci U S A 2008;105:20852-7.
20. Ota K, Azuma K, Kawahara A, et al. Induction of PD-L1 Expression by the EML4-ALK Oncoprotein and Downstream Signaling Pathways in Non-Small Cell Lung Cancer. Clin Cancer Res 2015;21:4014-21.
21. Akbay EA, Koyama S, Carretero J, et al. Activation of the PD-1 pathway contributes to immune escape in EGFR-driven lung tumors. Cancer Discov 2013;3:1355-63.
22. Sangodkar J, Dhawan NS, Melville H, et al. Targeting the FOXO1/KLF6 axis regulates EGFR signaling and treatment response. J Clin Invest 2012;122:2637-51.

Cite this article as: Yang X, Zhu C, Zhao H. Immune checkpoint inhibitors combined with tyrosine kinase inhibitors is the treatment option of previously treated advanced non-small cell lung cancer harboring EGFR or ALK genetic aberration. Transl Lung Cancer Res 2022;11(10):2164-2166. doi: 10.21037/tlcr-22-522