Letter to the Editor

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

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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

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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.

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