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## Research Article

# Progress in the Study on PD-L1 Inhibitor in the Treatment of EGFR-Mutant Non-Small Cell Lung Cancer

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## ARTICLE INFO

### Article history:

Received: 5 February, 2020

Accepted: 24 February, 2020

Published: 28 February, 2020

### Keywords:

Non-small cell lung cancer

Anti-PD-1/PD-L1 treatment

EGFR mutations

immunotherapy

## ABSTRACT

Immunotherapy has opened up a new area for human health and cancer treatment by enhancing the human immune system and removing in vivo tumor cells to suppress "tumor immune escape". Recent studies had demonstrated that the efficacy of immune checkpoint inhibitors in patients with epidermal growth factor receptor (EGFR) mutation non-small cell lung cancer (NSCLC) was unsatisfactory. The possible mechanisms mainly include low expression of programmed cell death protein ligand 1 (PD-L1), suppressive immune microenvironment and low tumor mutant burden. The series analysis of changes to immune microenvironment of patients with EGFR-mutant NSCLC, immune checkpoint inhibitors and researches progress of their combined application with TKI is expected to bring new hope to the treatment of patients with EGFR-mutant NSCLC. This paper major signaling pathways involved in the regulation of PD-L1 expression and the preclinical and clinical studies on the treatment with immune checkpoint inhibitors or combined with EGFR-TKIs in patients with EGFR-mutant NSCLC.

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## Introduction

The epidermal growth factor receptor (EGFR) gene is one of the most common driver genes in patients with non-small cell lung cancer (NSCLC) [1]. A subset of advanced NSCLC patients (15–55%) has EGFR driven mutations and benefits from treatment with EGFR TKIs [2–4]. EGFR TKIs are a first-line therapy for rapidly killing tumors such as those associated with NSCLC by blocking oncogenic receptor signaling. However, patients often inevitably develop drug resistance within 9–12 months after treatment [5]. Therefore, development of new treatments is needed urgently to deal with the occurrence of drug resistance. Recently, breakthroughs have been made in the treatment of lung cancer by programmed death-1 (PD-1) and its ligand PD-L1 inhibitors [6, 7]. However, the clinical and basic research of EGFR-mutant NSCLC is still in the exploratory stage, needing to optimize the efficacy, combination, sequence and dosage of immunotherapy and other treatments, to clarify the relationship between EGFR mutation, immune microenvironment and the efficacy of immunotherapy. This paper reviewed different signaling pathways involved in the regulation of PD-L1 expression of EGFR-mutant lung adenocarcinoma, compared and analyzed all preclinical and clinical studies on the feasibility of

treatment with immune checkpoint inhibitors (ICIs) or combined with EGFR-TKIs in patients with EGFR-mutant NSCLC.

## 1 PD-L1 Function and Treatment Status

PD-1 (CD279) is widely expressed in human and mouse T cells, B cells, natural killer cells, activated monocytes and dendritic cells, and mainly expressed on the surface of activated T and B cells. The recipients of PD-1 include PD-L1 (B7-H1, CD274) and PD-L2 (B7-DC, CD273) [8]. PD-L1 can be expressed in hematopoietic cells, including T cells, B cells, macrophages, dendritic cells (DCs), and mast cells, and can also be expressed in non-hematopoietic healthy tissue cells, including vascular endothelial cells, keratinocytes and islet cells. Moreover, PD-L1 can also be expressed in tumor cells and tumor stroma. When tumor cells and other types of cells were stimulated by interferon (IFN), the expression of PD-L1 on the cell surface was significantly up-regulated and bound to the co-stimulus factor CD80 to suppress the activation of immune signals [9].

Preclinical studies have revealed that blocking the interaction between PD-L1 and PD-1 can down-regulate the expression of inhibitory factor

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IL-10, increase the number of effector T cells and enhance the activity of tumor-specific T cells [10-12]. After PD-L1 binds to PD-1 and CD 80 on the surface of T cells, on the one hand, the activated PD-1 phosphorylates the SHP-2 tyrosine site, which prevents lymphocyte-specific LCK (lymphocyte-specific protein tyrosine kinase) mediated ZAP70 (zeta-chain-associated protein kinase) phosphorylation, antagonizes TCR recognition system in T cells, and blocks T cell effects; On the other hand, PD-1 inhibits CD 38-induced PI3 K activation and downstream AKT and mTOR activation which inhibits the Ras pathway and the PI3K/AKT/mTOR signaling pathway, thereby inhibits T cell proliferation and cytotoxicity and changes the metabolism of T cells which may explain that tumor cells expressing PD-L1 escape immune surveillance of NK cells and T cells [13-16]. Different from PD-L1, in the tumor microenvironment where PD-L1 expression is induced by inflammatory factors, PD-L2 can induce T cell depletion by combining with PD-1, thus inhibiting the anti-tumor effect of T cells [17].

PD-L1 plays an important role in maintaining central and peripheral immune tolerance through combination with the PD-1/PD-L1 pathway formed by the PD-1 receptor [18]. Firstly, PD-L1 is highly expressed in thymus and dendritic cells, and interactional PD-L1/PD-1 prevents proliferation and differentiation of naive T cells, and PD-L1 also interacts with CD80, thus producing a negative regulating effect on activated T cells [19, 20]. Secondly, PD-1/PD-L1 also participates in the physiological mechanism of immunodepletion, i.e., induces apoptosis of effector T cells in the continuous presence of antigen and inhibits the replication and maturation of T cells to prevent tissue destruction in chronic infections [21]. Furthermore, PD-L1 is involved in the regulation of anti-tumor immune reaction, PD-1 is generally found to be up-regulated persistently in tumor-infiltrating lymphocytes, and malignant tumor cells will use PD-L1 expression to escape its destruction caused by the immune system [22].

In 2015, the Food and Drug Administration (FDA) approved the first ICIs PD-1 antibody, Nivolumab, for the treatment of advanced NSCLC, marking that ICIs are the third largest treatment for advanced NSCLC following the chemotherapy and targeted therapy. By expressing an immunosuppressive signal such as PD-L1 and binding to the receptor PD-1, tumor cells inhibit the cellular activity of cytotoxic lymphocyte (CTL) and induce the apoptosis of T cells to eventually escape immunological surveillance. Currently, clinically used ICIs mainly bind to the immunosuppressive molecule PD-L1 on the surface of tumor cells competitively, thereby blocking signal transduction with the receptor PD-1 on the surface of immune cells, and re-activating T cells to play the role of immune surveillance [23-25]. In four Stage III clinical studies, PD-1 inhibitors (Nivolumab and Pembrolizumab) and PD-L1 inhibitors (Atezolizumab and Durvalumab) were used as second-line therapeutic regimen for patients with NSCLC after failure as platinum chemotherapy first-line treatment. The results showed that both PD-1 and PD-L1 inhibitors had more significant clinical effects than the docetaxel regimen [26-28].

KEYNOTE-021 evaluated combinations of platinum-doublet chemotherapy with the anti-programmed death 1 monoclonal antibody pembrolizumab [29]. Patients with previously untreated, advanced NSCLC without EGFR/ALK aberrations were randomized to pembrolizumab 2 or 10 mg/kg Q3W plus carboplatin area under the

serum concentration- time curve (AUC) 6 mg/mL/min plus paclitaxel 200 mg/m<sup>2</sup> (cohort A, any histology), carboplatin AUC 6 mg/mL/min plus paclitaxel 200 mg/m<sup>2</sup> plus bevacizumab 15 mg/kg (cohort B, non-squamous), or carboplatin AUC 5 mg/mL/min plus pemetrexed 500 mg/m<sup>2</sup> (cohort C, non-squamous) for 4 cycles followed by maintenance pembrolizumab (cohort A), pembrolizumab plus bevacizumab (cohort B), or pembrolizumab plus pemetrexed (cohort C). Response was assessed by blinded independent central review. Overall, 74 patients were randomized; median follow-up was 21.4, 16.4, and 17.4 months in cohorts A, B, and C, respectively.

In another randomized controlled Stage III clinical study (OKA), compared with the docetaxel group, the Atezolizumab group significantly prolonged the OS of patients with advanced NSCLC who suffered first-line treatment failure (13.9 months vs. 9.6 months), and the efficacy of Atezolizumab group was related to the expression level of PD-L1; PD-L1 high expression (the PD-L1 positive expression tumor cells > 50% or immune cells >10%) group benefited the most, the median OS of patients reached 20.5 months; PD-L1 non-expression or negative (PD-L1 positive expression tumor cells <1% or immune cells <1%) group benefited the least, and Atezolizumab group still showed a significant survival advantage [7]. In addition, the expression status of PD-L1 did not affect the efficacy of Atezolizumab in the second-line treatment of squamous cell carcinoma and adenocarcinoma. Based on the results of the above randomized clinical studies, FDA has approved the application of Pembrolizumab, Nivolumab, Atezolizumab, and Durvalumab in second-line treatment of advanced NSCLC.

## II Relationship between EGFR and PD-L1

It is believed that the tumor proportion score (TPS) of PD-L1 in about 20%-30% of NSCLC is >50%, and its expression leads to changes in tumor immune microenvironment, facilitating the invasiveness and immune escape of tumor cells [30]. The EGFR mutation rate in Asian populations (47%) is more common than that in non-Asian populations (13%-15%), mainly because of 19 exon deletions (del746\_A750) or 21 exon point mutations (L858R) [31]. Currently, with regard to the increased or decreased expression level of PD-L1 in EGFR-mutant lung cancer, the results of different studies are inconsistent and even contradictory.

Azuma *et al.* firstly reported the relationship between EGFR mutation and PD-L1 expression in surgically resected specimens [30]. The positive rate of EGFR mutation was significantly higher than that of wild-type PD-L1, with the odds ratio (OR) of 25.4. Subsequent studies have also indicated that the expression level of PD-L1 in EGFR-mutant lung cancer is obviously increased as compared with EGFR wild type [32, 33]. However, Ji M *et al.* found that the expression level of PD-L1 in EGFR-mutant lung cancer decreased, and combined analysis of 3,959 patients in 18 studies showed that EGFR mutation caused a significant decrease in PD-L1 expression, the OR was 0.59 compared with EGFR wild type (95%CI: 0.39-0.92, P < 0.02), and TCGA data analysis indicated the inverse relationship between EGFR mutations and PD-L1 expression [34-36].

EGFR-mutant lung cancer is rarely associated with strong positive PD-L1 expression, and the incidence of PD-L1 expression ≥50% is 0.5%-

9.9% [37]. PD-L1 expression was independent of EGFR mutation type, and there was no significant difference in PD-L1 expression between 19 exon deletion and L858R point mutation [38]. The expression levels of PD-L1 in different drug resistance mechanisms were different, and the expression level of T790M resistant mutant PD-L1 was decreased [39]. Comparison of T790M mutation negative and positive indicated the similarity in the ratio of PD-L expression  $\geq 1\%$ , but the ratio of PD-L expression  $\geq 10\%$  and  $\geq 50\%$  was increased significantly. PD-L1 can still not be used as a predictive marker of immunotherapy of EGFR-mutant NSCLC, and despite of high PD-L1 expression, the immunotherapy is not satisfactory. Keynote001 study shows that PD-L1 expression of Pembrolizumab in treatment of EGFR mutation and wild type  $\geq 50\%$  NSCLC, objective response rate (ORR) was 20% and 40%, respectively, and the median overall survival (OS) was 6.5 months and 15.7 months, respectively [40].

The relationship between EGFR mutation and regulation of PD-L1 expression is still controversial. However, in vitro experiments and large center studies suggest that EGFR mutation leads to an abnormal increase in PD-L1 expression in NSCLC. Azuma et al. found that high expression of PD-L1 was closely related to EGFR mutations and affects the survival prognosis of patients with NSCLC [31]. The correlation between PD-L1 TPS  $\geq 50\%$  and EGFR mutations were also confirmed in multiple studies [37, 41, 42]. However, other study showed that PD-L1 was highly expressed in EGFR wild-type lung cancer tissues, and there was no significant correlation between its expression and EGFR mutations [38]. There is a complex network of signal transduction pathways between the initial injury of cancer cells caused by drug therapy and their final death. Therefore, as an important oncogene and drug target of NSCLC, it is particularly important to better understand that EGFR mutations directly or indirectly regulate PD-L1 expression through different correlation signaling pathways and participate in tumor immune escape.

### III EGFR Mutations Regulating the Relevant Signaling Pathway of PD-L1 Expression of Lung Adenocarcinoma

#### i PI3K / AKT / mTOR Signaling Pathway

EGFR in NSCLC can activate PI3K/AKT/mTOR signaling pathway, can increase cell proliferation, metabolism and survival, and play a key role in the formation of lung cancer. In EGFR-mutant NSCLC cells, the PD-L1 expression decreases significantly with time when PI3K, AKT and mTOR expressions are simultaneously down-regulated [43, 44]. The use of EGFR-TKIs in EGFR mutation-sensitive cells also leads to a decrease in PD-L1 expression. After down-regulation of PI3K expression, AKT also experienced a decrease in phosphorylation levels and ultimately caused a decrease in PD-L1 expression [45]. The AKT/mTOR signaling pathway can be activated in EGFR-mutant lung adenocarcinoma, and mTOR can regulate PD-L1 expression independently. The above has confirmed that the PI3K/AKT/mTOR signaling pathway regulates the PD-L1 expression in EGFR-mutant NSCLC. However, one study showed that AKT phosphorylation was activated after EGFR mutation, and no change in PD-L1 expression occurred after inhibition of AKT phosphorylation, but the possible mechanism remained unclear [46].

#### ii MAPK Signaling Pathway

The MEK/ERK pathway in MAPK is normally activated by amplification or mutation of tyrosine kinase receptor of tumor abnormal upstream signal. Evidence suggests that MEK/ERK cross-regulates the PD-L1 expression through the inflammatory signaling pathway [47]. The MEK-ERK signaling pathway was also found to regulate PD-L1 expression in EGFR-mutant NSCLC cells, and activation of the ERK1/2 pathway significantly up-regulated PD-L1 expression [46, 48]. However, some studies found that inhibition of ERK in EGFR-mutant cells, the regulation of PD-L1 expression by MAPK signaling pathway did not appear [43]. This indicates that the MAPK signaling pathway is not a direct pathway for direct regulation of EGFR-mutant NSCLC.

#### iii JAK/STAT Signaling Pathway

JAK/STAT is a classical signaling pathway for tumorigenesis, development and formation. In the EGFR-mutant TKIs-sensitive/resistant cell lines, decrease in PD-L1 expression was found after inhibition of JAK/STAT3 [43]. However, when EGFR-TKIs were used to regulate PD-L1 expression, PD-L1 expression was decreased only after dephosphorylation of STAT3, but no change in PD-L1 expression was found after direct silencing of STAT3 [45]. In EGF-induced EGFR and STAT3 phosphorylated and activated cells, STAT3 and JAK2 were inhibited and silenced, respectively, and PD-L1 showed a significant decrease in mRNA level and protein level, suggesting that JAK/STAT3 pathway plays an important role [49].

#### iv NF- $\kappa$ B Signaling Pathway

NF- $\kappa$ B, a family of transcription factors, can be activated by cytokines produced by tumor mutant oncogenes and the inflammatory microenvironment. Studies found that subunit RELA (p65) of NF- $\kappa$ B can bind with the promoter of PD-L1 in NSCLC cells and regulate the transcription of PD-L1 in the form of the RELA-MUC1-C complex [50]. NF- $\kappa$ B, as an important downstream pathway of EGFR activation, regulates tumor cell proliferation and chemoresistance. The expression in EGFR-mutant cell lines was higher than EGFR wild type and was positively correlated with PD-L1 expression. After NF- $\kappa$ B was silenced in EGFR-mutant cell lines, PD-L1 expression was found to be attenuated with the silencing of subunit RELA (p65) of NF- $\kappa$ B, demonstrating again that the rise of PD-L1 expression in EGFR-mutant NSCLC requires the participation of NF- $\kappa$ B [51].

### IV Yes-Associated Protein 1 (YAP1)

YAP1, an effector on the Hippo pathway, is an oncogene in many cancers. As a co-transcription factor, it forms a complex with TEAD and is featured by DNA-binding domain and regulation of multiple genes in cell proliferation, apoptosis inhibition and epithelial-mesenchymal transition [2]. By means of chromatin immunoprecipitation (ChIP), YAP/TEAD was found to bind in the PD-L1 promoter region, and thus YAP regulates its expression by increasing the transcription of PD-L1 [52]. Furthermore, YAP expression is involved in tumor progression in a hypoxic environment, and in EGFR-mutant NSCLC, PD-L1 is affected through an apoptotic pathway to regulate the drug resistance of EGFR-TKI [53, 54]. Bridging integrator 1, BIN1, is a MYC aptamer protein

with cancer inhibition properties [55]. Both in vitro and in vivo experiments demonstrated that over-expression of BIN1 can inactivate the EGFR/MAPK signaling pathway and inhibit and regulate PD-L1-mediated immune escape [56].

## V Tumor Mutational Burden (TMB)

Recently, TMB has also been assessed in NSCLC and appears to be a promising predictive biomarker of the efficacy of ICIs [57]. As TMB increases, tumor immunogenicity is enhanced. Unlike the greater difference of PD-L1 expression level, the TMB value of EGFR-mutant lung cancer was lower. Offin *et al.* reported that the median TMB value decreased significantly compared with wild type, 3.77 mutation/megabase (Mu/Mb) vs. 6.12 Mu/Mb ( $P < 0.01$ ) [58]. EGFR-TKIs treatment resulted in changes in TMB, and TMB was significantly elevated after EGFR-TKIs resistance compared with pre-treatment, 3.42 Mu/Mb vs. 6.56 Mu/Mb ( $P = 0.008$ ). TMB increase after EGFR-TKIs resistance provides a theoretical basis for late-line immunotherapy.

Low TMB before treatment may be related to secondary T790M resistance mutations, and the drug resistance mutation baseline with or without TMB shows a downward trend, 3.77 Mu/Mb vs. 4.77 Mu/Mb ( $P = 0.057$ ). Patients with low TMB are more prone to T790M mutation after drug resistance. 4TMB can predict the efficacy of EGFR-TKIs. Blakely *et al.* used cfDNA to analyze mutation burden, and TMB increased significantly in patients with ineffective EGFR-TKIs treatment; with median TMB as threshold, the treatment interruption time of median to EGFR-TKIs in the low TMB group and high TMB group was 17 months and 10 months, respectively ( $HR = 0.56$ ,  $P = 0.006$ ) [59]. TMB was a prognostic factor for EGFR-mutant lung cancer. The median OS of the low TMB subgroup and high TMB subgroup was 41 months and 29 months, respectively ( $HR = 0.52$ ,  $P = 0.03$ ) [58].

## VI Immunotherapy of Patients with EGFR-Mutant NSCLC

### i Efficacy of Immunotherapy vs. Chemotherapy and TKI Treatment

As mentioned above, EGFR-mutant gene can affect the efficacy response of NSCLC immune checkpoint inhibitors. Based on the immune status such as low PD-L1 expression and low TMB caused by above-mentioned EGFR-mutant genes, recent clinical trials have revealed that such patients are unable to benefit from immunotherapy or even worse efficacy is obtained. Keynote-001, as Stage I clinical trial, found that pembrolizumab was used for treatment of EGFR-mutant NSCLC. The objective response rate (ORR) of PD-L1 positive (TPS  $\geq 50\%$ ) and (TPS 1% - 49%) patients was 20% and 8.7%, respectively, but the ORR was 0% when PD-L1 was negative (TPS  $< 1\%$ ) [60].

The CAURAL trial is a multiphase III trial in which osimertinib is combined with durvalumab. Both EGFR-TKI-sensitizing- and EGFR T790M mutation-positive advanced patients were included in the study, though the results did not show a benefit for the combination arms with regard to ORR (64% vs 80%), duration of response (DOR) (17.5 months vs 21.4 months) or disease control rate (DCR) (93% vs 100%), which was even lower than that of the osimertinib monotherapy treatment group [61]. In the CheckMate057 trial and KEYNOTE010 trial, in terms

of the efficacy, second-line PD-1/PD-L1 inhibitors were compared with docetaxel in the treatment of NSCLC, and the results showed that patients with EGFR mutations failed to benefit from PD-1/PD-L1 inhibitors at overall survival (OS), they were even worse than docetaxel in progression free survival (PFS), whereas EGFR wild-type patients displayed significant benefit on OS and PFS [27, 28]. A retrospective analysis published recently, including 28 patients with advanced adenocarcinoma of lung treated with PD-1 PD-L1 / inhibitors, showed that the objective response rate (ORR) of patients with EGFR mutations was only 5% [62].

However, ATLANTIC studies showed that the patients with PD-L1 expression more than 25%, with EGFR+/ALK+, may also benefit from immunotherapy [63]. In the study, the 444 patients with local advanced inoperable Stage III NSCLC were treated with PD-L1 inhibitor (durvalumab), and the results showed that compared to placebo, durvalumab could prolong the PFS of patients by more than 11 months. Surprisingly, for the NSCLC group with positive EGFR+/ALK+ and PD-L1 expression, the response rate of the third-line treatment with durvalumab was 12.2% (9/74), and its safety was consistent with other PD-1/PD-L1 inhibitors. The study also showed that after 21 months of treatment with durvalumab, in the patients with more than 25% of PD-L1 expression, 56%(5/9) of the previous responders remained progression-free, while in patients with PD-L1 expression less than 25%, the disease progressed after PR was obtained.

This suggests that depending on the PD-L1 expression, a suitable population who may benefit before immunotherapy is selected as a predictive marker of immunotherapy in patients with EGFR mutations, but further exploration is needed to confirm the PD-L1 threshold and combined application with other markers. According to the NCCN guidelines, EGFR-mutated NSCLC is not effective in immunotherapy, and it is not recommended for EGFR-mutated NSCLC to receive immunotherapy. However, according to the results of the phase II ATLANTIC study, immunotherapy can be used as one of the third line and posterior line treatment options for NSCLC patients with EGFR mutation with high expression of PD-L1.

There are contradictions in the results of studies on the therapeutic effects of immune checkpoint inhibitors in patients with EGFR-mutant NSCLC. It may be related to the following factors: the first one is the heterogeneity of PD-L1 detection technique and sample source; the second one is the expression of PD-L1 on TIL (tumor infiltrating lymphocyte) cell except tumor cells; last but not least, the immune status of tumor patients with TKI drug was changed dynamically during and after drug resistance [64- 66]. The expression level of PD-L1 and TIL infiltration of EGFR-mutated NSCLC patients changed dynamically before and after the use of TKI resistance, and some showed significant increase of PD-L1 and/or TIL infiltration, which could explain the better efficacy of second-line immunotherapy after drug resistance in some patients. Although most studies still believe that the treatment of EGFR-mutated patients with NSCLC with immune checkpoints is not effective, based on the emergence of some effective cases, it is still worth considering such problems as the efficacy of immune checkpoint inhibitors for patients with EGFR mutations, and whether with the help of the possible predictive marker PD-L1, more patients can be helped to benefit.



## ii Immune Checkpoint Inhibitor Combined with TKI Treatment

In terms of drug combination, the Checkmate-012 study evaluated the safety and tolerability of nivolumab in combination with chemotherapy or erlotinib or ipilimumab or as a monotherapy in the treatment of patients with NSCLC. As part of the study, in the nivolumab plus erlotinib treatment group, 21 patients were enrolled and treated by drug combination until occurrence of disease progression or intolerable toxic reaction, with an ORR of 19%, 24-week progressive free survival (PFS) rate of 51% and 18-month OS rate of 64%. Of the 20 patients treated with EGFR-TKI, 3 patients achieved partial remission (PR), with the median remission time of 60.1 months, and 1 patient treated initially with EGFR-TKI achieved PR and continued to receive 72.3 months of treatment at the time of literature report [67].

The Ib trail TATTON study evaluated the efficacy of osimertinib combined with durvalumab in the treatment of EGFR-mutant NSCLC. The study divided the patients into the TKI initial treatment group (dose-expanded therapy) and the drug resistance group (dose escalation therapy) [68]. The results showed that of the 21 patients treated with TKI, 12 patients achieved PR and 9 patients achieved stable disease (SD); of the 10 patients treated initially with TKI, 8 patients achieved PR and 2 achieved SD. Gettinger *et al.* evaluated the efficacy and safety of nivolumab combined with Erlotinib in the treatment of patients with EGFR-mutant advanced NSCLC treated initially with chemotherapy and also divided the patients into TKI initial treatment group (1 case) and post-treatment drug resistance group (20 cases) [69]. The results showed that the patients had an ORR of 19% (4/21), the median duration of response (DOR) was not reached, the 24-week PFS was 51%, and the 1-year overall survival rate was 73%. Wherein, 1 patient treated initially with TKI reached PR, with the DOR greater than 72.3 weeks; of the 20 patients in the Erlotinib-resistant patient group, 15% (3/20) reached PR, and 45% (9/20) had the best effect response of SD.

The KEYNOTE-021 study was conducted to test the efficacy of combination pembrolizumab with erlotinib in EGFR-mutant advanced NSCLC patients [70]. The combination treatment enhanced the median PFS (19.5 months) benefit along with ORR (41.7%) compared with that of patients taking first-generation EGFR-TKIs (11.0 months) or osimertinib (19.2 months). Many researchers still do not recommend the use of TKI targeting drugs in combination with immune checkpoint inhibitors in patients with EGFR mutations, considering it to be far less effective than first line TKI targeting agents, and may lead to outbreak progression.

In addition, adverse events (AE) were within acceptable limits and no treatment-related pneumonia was found. Grade 3-4 treatment-related AE was 23.8% (5/24) and 19% (4/21) of patients discontinued treatment due to AE. Many investigators still do not recommend the combined use of TKI-targeted drugs and immune checkpoint inhibitors in patients with EGFR mutations, thinking that they are much less than first line TKI-targeted drugs in effective rate and may lead to the outbreak. However, the superposition of toxic effects is an important issue should not be overlooked. One study evaluated the safety of Erlotinib combined with atezolizumab and the results showed that the most common Grade 3-4 AEs were fever and alanine transaminase (ALT) elevation [71]. No pneumonia and Grade 2 AE occurred in this study.

The TATTON study [61] showed that 38% (13/34) of patients treated with Osimertinib and Durvalumab developed interstitial lung disease [the frequency of occurrence was much higher than single-drug Osimertinib (2.9%) or Durvalumab (2%)], with 15% (5/34) being Grade 3-4. 59% of patients discontinued treatment due to the AE. One study summarized the data of a total of 20,000 patients with EGFR-mutant NSCLC, showing that the incidence of interstitial lung diseases accounts for 4.8% of all population; 4.59% of 5,777 patients treated with EGFR inhibitor; 6.4% of 5,178 patients treated with PD-1 inhibitor; however, as high as 25.7% of patients receiving EGFR-TKI and PD-1 inhibitors [72]. As can be seen, the risk of interstitial lung disease arising from the drug combination increased by 5.09 times. Therefore, the experimental investigators believe that patients with EGFR-mutant advanced NSCLC should try to choose anti-angiogenic drugs such as targeted drugs, chemoradiotherapy and bevacizumab. PD-1 inhibitor or drug combination is not a suitable choice.

## Conclusion

In summary, improvement of the survival of patients with advanced NSCLC has been an urgent problem in thoracic neoplasms. Currently, EGFR-TKIs remain the first choice for treatment of EGFR-mutant NSCLC. The related research on EGFR mutation and PD-L1 expression is still in its initial stage, and many unknown factors need to be resolved. It is believed that the deepening of relevant research will provide a theoretical basis for PD-1/PD-L1 inhibitors in multi-modal immune-targeted therapy strategies for single-drug or combination with EGFR-TKIs in patients with EGFR-mutant NSCLC to improve the treatment and prognosis of future NSCLC.

## Funding

None.

## Competing Interests

None.

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