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Review Article

The role of EGFR mutations in sensitivity of PD-1/PD-L1 blockade in non-small cell lung cancer

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Abstract: In non-small cell lung cancer (NSCLC), epidermal growth factor receptor (EGFR) is one of the most prevalent driver gene, whose expression and recurrent mutations are closely related to the prognosis of patients. EGFR tyrosine kinase inhibitors (EGFR-TKIs) are ones of the most used among the first line treatment of NSCLC, but their efficacy is significantly reduced due to the inevitable development of acquired EGFR-TKI resistance. Consequently, searching for innovative drugs to overcome this challenge is urgent. Immune checkpoint inhibitors such as antibodies against the programmed cell death protein-1 (PD-1) or its ligand (PD-L1), have exhibited remarkable potential in NSCLC therapy. While the response rates of PD-1/PD-L1 blockade in EGFR-mutated NSCLC patients remain controversial. To gain deeper insights, we first analyzed the different therapeutic effect of PD-1/PD-L1 blockade between EGFR wild-type and mutated NSCLC patients. Meanwhile, the factors and the mechanisms that affect therapeutic effect of PD-1/PD-L1 blockade were summarized, including PD-1/PD-L1 expression levels, the tumor microenvironment (TME), and the adoption of combination therapy strategies. Furthermore, we comprehensively evaluated the combinatorial therapeutic effect with established synergistic potential within these factors. Moreover, we further explored the potential of PD-1/PD-L1 as a predictive biomarker for EGFR mutations by conducting a systematic and multidimensional analysis, aiming to refine therapeutic decision-making and facilitate personalized treatment strategies for EGFR-mutated NSCLC. Additionally, we also discussed the novel strategies that could alleviate the EGFR-TKIs resistance in NSCLC base on PD-1/PD-L1 immune inhibitors, shedding light on challenges facing future research.

Keywords: PD-L1, EGFR, TME, tumor mutation burden, combination therapy

Introduction

Lung cancer, the foremost malignancy in the world, stands as the leading cause of cancer-related mortality worldwide, including non-small cell lung cancer (NSCLC, approximately 85%) and small cell lung cancer [1-4]. Epidermal growth factor receptor (EGFR), the most prevalent driver gene mutation observed in NSCLC. Consequently, EGFR tyrosine kinase inhibitors (EGFR-TKIs), exemplified by gefitinib, erlotinib, and osimertinib, are ones of the most used drugs among advanced EGFR-mutated NSCLC. However, the inevitable development of acquired EGFR-TKIs resistance within approximately a year results in developing anticancer compounds to overcome drug resistance [5, 6], including elemene [7-9], curcumin [10], baicalin [11, 12], erianin [13].

Tumor microenvironment (TME), especially the tumor immune microenvironment, plays a critical role in therapy resistance. As a famous transmembrane immune checkpoint protein, PD-L1 is not only expressed on the surface of tumor cells, immune cells, and other cells with-

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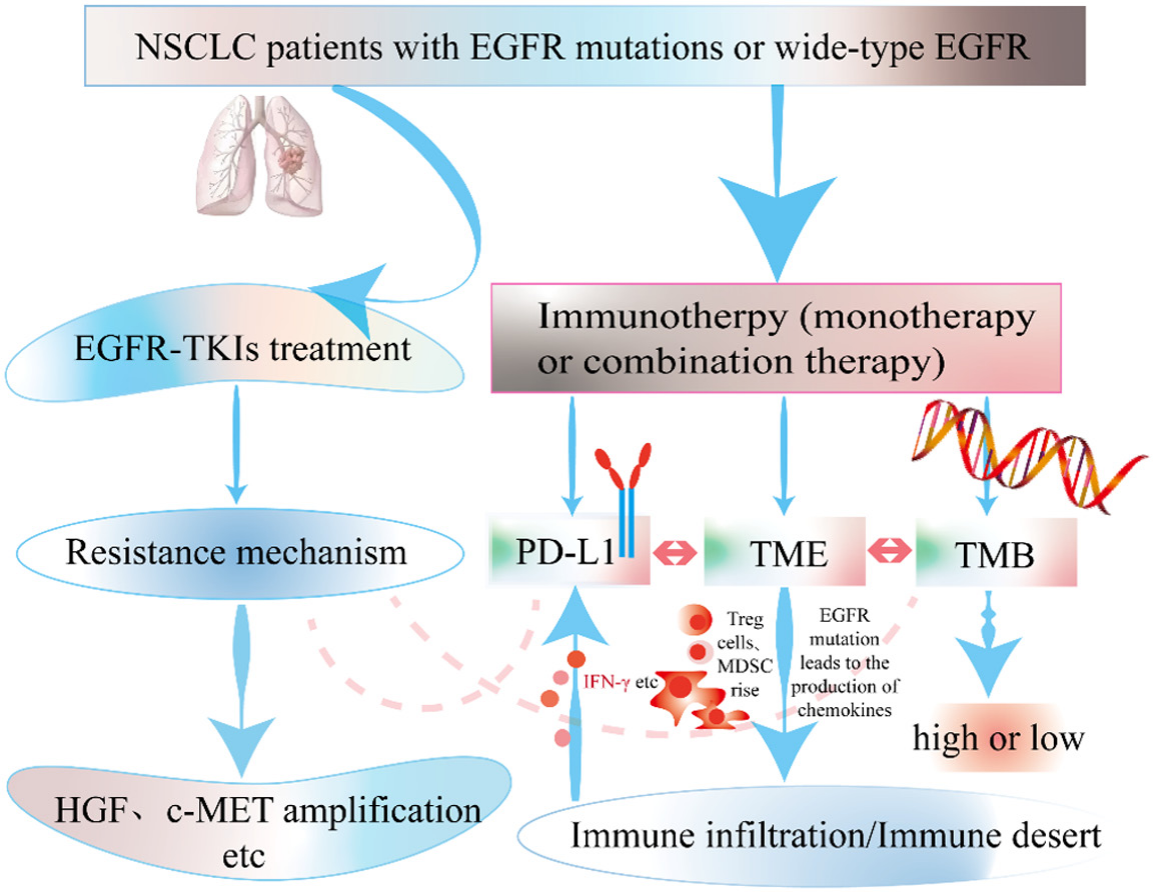

Figure 1. Comprehensive analysis of sensitivity differences in PD-L1 immunotherapy between patients with mutation EGFR and patients with wild-type EGFR. TME: tumor microenvironment, TMB: tumor mutation burden, HGF: hepatocyte growth factor.

in TME, but also can be released from tumor cells in the form of exosomes [14]. PD-L1 is involved in various bioprocess contributing to its multifaceted regulatory pathway, especially in diseases such as cancer. Over the past few years, immune checkpoint inhibitors (ICIs), represented by inhibitors of programmed death-1 (PD-1) and its ligand (PD-L1), have made breakthroughs in the treatment for lung cancer [15-17]. A pooled analysis of five randomized controlled trials has demonstrated that patients receiving anti-PD-1/PD-L1 monotherapy exhibit higher objective response rates (ORR) and 1-year overall survival (OS) compared to those in the first-line chemotherapy group, with a lower incidence of treatment-related adverse events. These findings collectively suggest that PD-1/PD-L1 blockade may present a more favorable therapeutic profile than conventional first-line chemotherapy in terms of both efficacy and safety for advanced NSCLC management [18].

However, the existing conclusions about the response of PD-1/PD-L1 blockade in advanced EGFR-mutated NSCLC are not consistent. For instance, some evidence has indicated that single-agent PD-1/PD-L1 blockade have low or no response in advanced EGFR-mutated NSCLC [19], while isolated cases have reported substantial benefits, underscoring the complexity of patients' responses [20]. Here, we have summarized the most advanced progresses and discussed the novel strategies on the response of PD-1/PD-L1 blockade in advanced EGFR-mutated NSCLC. In addition, our investigation explored the dual potential of PD-1/PD-L1 expression as a predictive biomarker for EGFR mutation status and precision therapeutic strategies tailored to EGFR-mutated NSCLC patients. This integrated approach emerges as a crucial research direction to explore the mechanisms of EGFR-TKIs resistance, particularly in patients with EGFR-TKIs resistance (**Figure 1**).

Table 1. Researchs and analysis on the therapeutic benefits of immunotherapy in NSCLC patients harboring EGFR mutations

Author	Study Design	Reasons
Tsuji K [25]	Durvalumab plus Chemoradiotherapy vs. Chemoradiotherapy	PD-L1 expression
Sangtian Liu [27]	anti-PD-1/PD-L1 plus EGFR-TKIs vs. EGFR-TKIs	Tumor microenvironment
Zhang [28]	Bevacizumab plus Sintilimab vs. EGFR-TKIs plus Chemoradiotherapy	Postive PD-L1 expression and/or Tumor microenvironment
Subudhi [62]	Pembrozulimab plus Ipilimumab vs. Pembrozulimab	$CD8^+$ T cells clonal expansion
Peng [45]	Before EGFR-TKIs resistance vs. After EGFR-TKIs resistance	EGFR-TKI resistance pathways
Chen Xie [55]	TCGA database	Tumor Mutation Burden and Tumor microenvironment

The impact of EGFR mutations on the sensitivity to PD-1/PD-L1 blockade

Currently, partial immunotherapy monotherapy has been approved as the primary therapeutic option for NSCLC patients. Studies on PD-1/PD-L1 blockade for the treatment of NSCLC are abundant, and the influence of EGFR mutations or wide-type on their therapeutic efficacy has garnered widespread attention. Accumulating evidence indicates that PD-1/PD-L1 blockade significantly improve clinical outcomes in NSCLC patients with elevated PD-L1 expression levels. However, the efficacy in patients with low PD-L1 expression remains uncertain [21], whilst the optimal therapeutic response can be observed in patients exhibiting PD-L1 positivity (≥50%) [22]. EGFR mutation also affects the response of PD-1/PD-L1 blockade in NSCLC patients. It has been reported that EGFR-mutated patients are less susceptible to PD-1/PD-L1 blockade compared to EGFR wild-type patients, and even when those with high PD-L1 expression [23]. Therefore, it can be reasonably inferred that EGFR-mutated NSCLC patients obtain less likely benefits from PD-1/PD-L1 blockade and exhibit a resistance to such treatments, comparing to those with EGFR wild-type. Conversely, it also has been reported that EGFR-mutated patients exhibit higher sensitivity to PD-L1 blockade [24]. Due to the contradictory results of related studies, we would further investigate the relationship between EGFR expression or EGFR mutations and PD-L1 blockade sensitivity in the following text, and briefly discuss their potential reasons for the differences in treatment efficiency, hoping to provide effective suggestions and guidance for the related studies and clinical applications of PD-1/PD-L1 blockade.

Related studies on high sensitivity of EGFR-mutated NSCLC patients to PD-1/PD-L1 blockade

Some studies have indicated that EGFR-mutated NSCLC patients exhibit high sensitivity to PD-L1 immunotherapy [24]. For instance, one multi-center retrospective study has been conducted to explore whether immunotherapy drugs are necessary in NSCLC patients after chemotherapy and radiotherapy. The results showed that among EGFR-mutated patients, those who received immunotherapy had a longer progression-free survival (PFS) compared to those who did not receive immunotherapy. Therefore, for these patients, immunotherapy is taken into account as a safe and effective treatment approach (**Table 1**) [25].

How about EGFR-TKI-resistant patients? The study conducted by Wei *et al.* has revealed that the combined therapeutic approach incorporating PD-L1 immune checkpoint inhibitors, bevacizumab, and platinum-based doublet chemotherapy in EGFR-TKI-resistant patients, exhibits superior survival outcomes and toxicity tolerance compared to traditional platinum-based doublet chemotherapy [26]. In addition, Liu *et al*. have performed research on advanced NSCLC patients who experienced treatment with EGFR-TKI resistance between 2016 and 2019 (**Table 1**) [27]. They have analyzed the alterations in the TME following immunotherapy. By comparing the clinical outcomes of immune checkpoint inhibitors combination therapy versus standard chemotherapy as second-line treatments, patients with shorter tyrosine kinase inhibitor-progression-free survival (TKI-PFS) have been demonstrated superior response to immunotherapy, accompanied by

distinct TME profiles between the two groups. Consequently, for patients featuring short TKI-PFS and absence of T790M mutation, the integration of chemotherapy with immunotherapy emerges as a promising second-line therapeutic alternative to traditional chemotherapy, with the underlying mechanisms still requiring further exploration [27].

Additionally, a research report has detailed a case study of an advanced NSCLC patient carrying EGFR mutation, who was administered bevacizumab combined with sintilimab after failing in both chemotherapy and EGFR-targeted therapy. In this study, the patient has achieved a partial response (PR), with a PFS of 6 months. However, due to the small sample size, the findings require further validation through multi-center, large-scale clinical trials [28].

Related studies on the low sensitivity of EGFR-mutated NSCLC patients to PD-1/PD-L1 immunotherapy

In 2019, the Food and Drug Administration (FDA) has granted approval to pembrolizumab as a frontline monotherapy option for stage III/metastatic NSCLC individuals with PD-L1 ≥1% and no EGFR/ALK mutations, who are ineligible for surgery, radiation therapy, or chemotherapy [29]. A study investigating the administration of PD-1/PD-L1 immune checkpoint inhibitors in both EGFR-mutant and EGFR wild-type patients have revealed distinct outcomes. Notably, EGFR wild-type patients have exhibited significant benefits in terms of OS and PFS, whereas EGFR-mutant patients haven't derived OS benefit from PD-1/PD-L1 inhibitors and even have fared worse in PFS compared to docetaxel treatment [30]. Justin *et al.* have pinpointed 28 EGFR/ALK mutated NSCLC patients administered PD-1/PD-L1 inhibitors, contrasting them with 30 EGFR-wild-type and ALK-negative NSCLC patients receiving the same therapy during the identical timeframe [31]. Notably, EGFR-mutant/ALK$^+$ NSCLC patients show a lower response rate (3.6%) to PD-1/PD-L1 immune checkpoint inhibitors comparing with EGFR-wild/ALK-negative patients (23.3%), indicating reduced sensitivity.

Given the correlation between EGFR mutations and immune tolerance as well as low immunogenicity, Dong *et al.* have postulated that EGFR mutations could negatively forecast the success of PD-1 blockade immunotherapy among patients with NSCLC [32]. Hence, they have aggregated data from four randomized controlled trials (RCTs) involving 2752 patients, assessing the comparative effectiveness of PD-1/PD-L1 immune checkpoint inhibitors versus docetaxel in both EGFR-mutated and wild-type NSCLC cases. Patients with EGFR mutation haven't derived a survival benefit from PD-1/PD-L1 inhibitors in terms of OS and even have experienced worse in terms of PFS compared to docetaxel. In contrast, EGFR wild-type patients have displayed remarkable enhancements in both OS and PFS upon treatment with PD-1/PD-L1 inhibitors, as opposed to docetaxel. Furthermore, the study has revealed a negative link between EGFR mutation and PD-L1 expression, suggesting EGFR-mutated patients exhibit lower PD-L1 levels, potentially accounting for their suboptimal response to PD-1/PD-L1 inhibitors.

In summary, molecular targeted therapy remains the recommended treatment for patients with EGFR-mutated NSCLC, as immunotherapy drugs have shown limited efficacy in this population. However, it's worth noting that most studies have small sample sizes, lack control groups, and their analyses of efficacy and prognosis are relatively limited. Therefore, future large-scale clinical trials are essential to validate the present findings conclusively [33]. Additionally, other research has demonstrated that inhibiting ILT4 can enhance the effects of PD-L1 inhibitors in EGFR wild-type NSCLC, whereas no such therapeutic potentiation is observed in EGFR-mutated NSCLC [34].

Factors influencing the sensitivity of PD-1/PD-L1 immunotherapy

Previous studies have showed that there is significant inconsistency between the sensitivity of PD-L1 immunotherapy and EGFR mutations in cancer cells. Despite high PD-L1 expression, the therapeutic effect of PD-L1 immunotherapy in patients with EGFR mutations remains suboptimal, suggesting that in addition to PD-L1 expression, there are other factors that can contribute to its therapeutic effect. Specifically, PD-L1 expression levels, TME, and TMB may play critical roles in determining the responsiveness of EGFR-mutated NSCLC patients to PD-1/PD-L1 inhibitors. Through further investigation of relevant research, we have distilled the following reasons (**Figure 1**).

The level of PD-1/PD-L1 expression affects the therapeutic efficacy of its immune checkpoint inhibitors

The expression of PD-L1 in tumor cells serves as a critical factor in the establishment of immune suppression and the induction of tumor immune evasion, with high levels of expression generally correlating with a higher therapeutic response (**Figure 2**). Research has demonstrated that EGFR mutations are capable of inducing PD-L1 expression in EGFR-mutated NSCLC cells via the IL-6/JAK/STAT3 signaling pathway, whereas EGFR-TKIs can inhibit the expression of PD-L1 (**Figure 2**) [35]. In a clinical study involving 25 EGFR mutation-positive NSCLC patients, it has observed that EGFR mutation-positive but T790M-negative NSCLC patients are more likely to benefit from nivolumab treatment following EGFR-TKIs therapy compared to T790M-positive patients [36]. The researchers hypothesize that the observed efficacy may stem from elevated PD-L1 expression in T790M-negative NSCLC patients. Echoing this, the Keynote-024 trial have demonstrated superior outcomes with immunotherapy among patients displaying PD-L1 levels exceeding 50%. Furthermore, pembrolizumab, currently the only immune checkpoint inhibitor approved for first-line treatment of advanced NSCLC, is recommended by guidelines such as CSCO/NCCN/ESMO for monotherapy use exclusively for patients with PD-L1 expression >50% [37]. Therefore, monitoring changes in PD-L1 expression levels holds significant scientific importance in studying the relationship between PD-L1 immunotherapy sensitivity and EGFR mutations or wide-type.

As mentioned, most studies suggest that EGFR wild-type NSCLC patients tend to have higher levels of PD-L1 expression compared to EGFR mutant patients. ATLANTIC: an open-label, single-arm, phase 2 study has conducted across 139 research centers in Asia, Europe, and North America, and divided 444 patients into three cohorts: EGFR/ALK-positive, EGFR-negative, and ALK-negative, and administered durvalumab to each cohort. This study has found that EGFR/ALK-positive patients had a lower benefit compared to negative counterparts, and that patients with elevated PD-L1 expression in their tumors demonstrated a higher rate of positive response [38]. Therefore, we believe that the varying directions of previous studies and the different therapeutic approaches employed have led to changes in PD-L1 expression levels, resulting in inconsistent PD-L1 immunotherapy sensitivity.

EGFR-TKIs and EGFR mutation affect the therapeutic efficacy of immune checkpoint inhibitors

Indeed, numerous studies have shown that EGFR-TKIs can downregulate PD-L1 in EGFR-mutated NSCLC, while acquired resistance can promote immune evasion in lung cancer by upregulating PD-L1 expression. Currently, the T790M mutation in EGFR is a well-characterized contributor to resistance against second-generation EGFR-TKIs [39]. However, contrasting findings indicate that PD-L1-negative tumor patients exhibit a higher frequency of T790M mutations and longer PFS after EGFR-TKI treatment [40]. Moreover, compared to T790M-negative NSCLC patients, those with T790M-positive tumors tend to have lower PD-L1 expression levels [41]. We believed that these conflicting viewpoints might stem from various factors. At present, the relationship between tumor PD-L1 expression and EGFR signaling pathway-dependent cell proliferation is still unclear. In addition to EGFR mutations, multiple oncogenes regulate tumor PD-L1 expression, contributing to the diverse outcomes observed in current research. EGFR-TKIs may modulate downstream signaling pathways directly, such as the Mitogen-Activated Protein Kinase (MAPK) and Phosphoinositide 3-Kinase/Protein Kinase B/Mammalian Target of Rapamycin (PI3K/AKT/mTOR) pathways, to exert their effects. Alternatively, in the context of acquired resistance, EGFR-TKIs can influence the expression of PD-L1 through mechanisms involving secondary gene mutations and the activation of bypass signaling pathways, exemplified by Mesenchymal-Epithelial Transition Factor (MET) amplification [42]. Moreover, the composition and metabolic state of TME directly modulate the expression of PD-L1. Notably, EGFR-TKI therapy may induce alterations in the TME, thereby driving fluctuations in PD-L1 levels [43]). A research team transplanted PC-9 cell line into severe immunodeficiency mice and applied gefitinib with a control group, and found that the PD-L1 expression in mice treated with gefitinib has been significantly lower than that

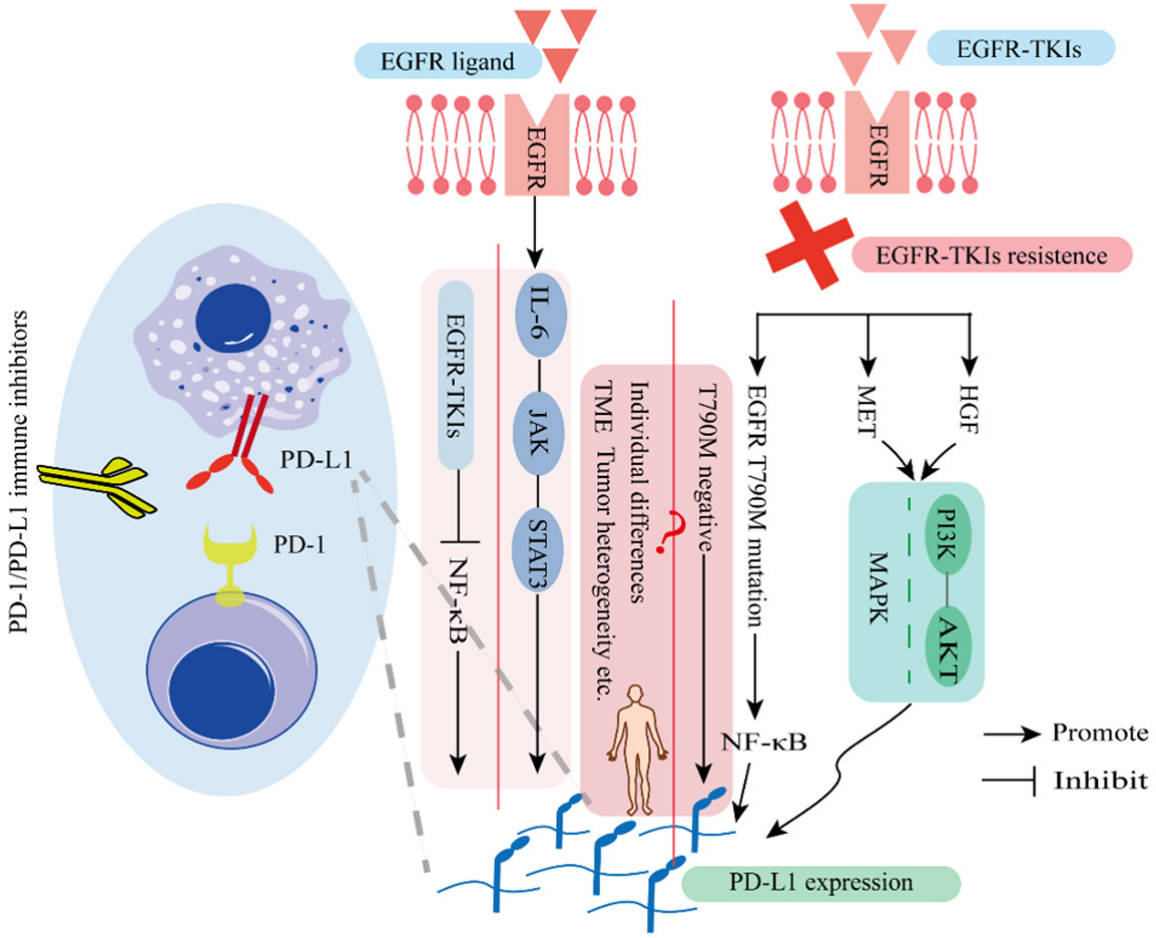

Figure 2. Different factors impact the efficacy of PD-1/PD-L1 immune inhibitors by regulating PD-L1 expression.

in the control group. Compared with previous studies, this study has further demonstrated that the application of EGFR-TKIs could reduce the PD-L1 expression of PC-9 cell line in mice by inhibiting NF-κB, thereby affecting the therapeutic effect of PD-L1 immune inhibitors (**Figure 2**) [44].

Peng *et al.* focused their research on previously established EGFR-mutated NSCLC cell lines that exhibited both sensitivity and resistance to treatment. The result showed that three key EGFR-TKIs resistance mechanisms, including hepatocyte growth factor activation (HGF), MET amplification, and EGFR T790M mutation, can elevate PD-L1 expression in NSCLC cells, thereby enhancing the tumor's immune evasion capabilities (**Figure 2**). Notably, there may be differences in the relative regulatory mechanisms of PD-L1 expression among these three subtypes. Furthermore, it has suggested that signaling pathways such as PI3K-Akt, MAPK, NF-κB, and Activator Protein-1 (AP-1) (**Figure 2**) may serve as underlying mechanisms mediating the upregulation of PD-L1 induced by EGFR-TKIs resistance (**Table 1**) [45]. Additionally, other EGFR-TKI resistance mechanisms, including epithelial-mesenchymal transition (EMT), PTEN, and IGF-1 receptor activation, warrant further investigation to clarify their specific impacts on PD-L1 expression in EGFR-TKIs-resistant NSCLC.

In summary, their research findings potentially offer partial explanations for the varying states of PD-L1 in EGFR-TKIs-sensitive and drug-resistant tumors, providing novel insights into the expression of PD-L1 in different subgroups of EGFR-TKIs-resistant NSCLC. Furthermore, these discoveries deepen our understanding of the discrepancies in PD-L1 immune sensitivity observed across various studies. It

may have specific significance for immune checkpoint therapies of different subgroups of EGFR-TKI resistant NSCLC patients.

In addition to EGFR-TKIs, previous studies have suggested that traditional chemotherapy [46], radiotherapy [47], and anti-angiogenic therapy [48], can all influence the immune sensitivity of PD-L1. However, numerous clinical studies fail to comprehensively describe the previous treatment history before the study, leading us to speculate that prior administration of EGFR-TKIs or other medications may affect the immune sensitivity of PD-L1 in patients with EGFR-mutated NSCLC at later stages, thereby contributing to inconsistencies in research findings.

The impact of EGFR mutations on TME

Currently, multiple studies have indicated that EGFR mutations could impact the TME, further modulating the efficacy of PD-1/PD-L1 inhibitors. While the advent of immune checkpoint blockade has significantly controlled disease progression and improved survival in wild-type EGFR tumor patients, EGFR mutation-positive NSCLC exhibits low effect, including specific immunosuppressive TME characteristics and low levels of immune cell infiltration, resulting in limited response to immune checkpoint blockade. This may stem from EGFR mutations transforming the NSCLC's TME into an immune-excluded or immune-desert phenotype. Investigating the underlying mechanisms that convert the TME into an immune-inflammatory type is crucial [49], and useful for EGFR-mutated NSCLC patients to benefit from anti-PD-1/PD-L1 therapies.

Justin *et al.* have observed a reduced ORR to PD-1/PD-L1 inhibitors in EGFR-mutated patients compared with wild-type ones. They subsequently analyzed the immune microenvironment in a distinct EGFR-mutated cohort. Immunohistochemistry and image-based quantification revealed 65% of cases had $CD8^+$ TILs, but only 4.2% expressed high levels. Notably, just 2.1% of patients exhibited both PD-L1 expression (>5%) and abundant $CD8^+$ TILs in the same trial samples [31]. This finding underscores the absence of both high PD-L1 expression and high levels of $CD8^+$ TILs in the majority of EGFR-mutated NSCLC patients. Consequently, it is reasonable to postulate that the immune-excluded or immune-desert phenotype of the TME contributes to the lower ORR observed in EGFR-mutated patients treated with PD-1 pathway immune inhibitors. In addition, some other factors such as N^6-methyladenosine modification is also significantly correlated with the diversity and complexity of the TME, resulting varying responses to immunotherapy [50, 51].

In a retrospective analysis of 138 Japanese EGFR-mutated patients treated with EGFR-TKIs, scientists have evaluated whether EGFR-TKI therapy could improve the TME of EGFR-positive NSCLC. The result has revealed that the density of $CD8^+$ TILs is significantly higher in PD-L1 strongly positive patients compared with PD-L1 negative or low-positive ones after EGFR-TKIs treatment. Mechanically, IFN-γ released by $CD8^+$ TILs induces PD-L1 expression in cancer cells [52]. In a heterotopic transplantation mouse model of EGFR-mutated NSCLC, Tu *et al.* have found that neither anti-PD-L1 nor anti-CD73 alone could effectively inhibit tumor growth. However, combination anti-PD-L1 and anti-CD73 significantly suppressed tumor growth, boosted the infiltration of $CD8^+$ T cells within tumor tissues, and augmented the release of TNF-α and IFN-γ by these immune cells, alongside altering expression of inflammation and T-cell functionality genes (**Figure 3**) [53]. This study have further validated that EGFR mutations can influence the TME, thereby modulating PD-1/PD-L1 inhibitors' efficiency in tumor eradication. Meanwhile, monitoring extracellular ATP may help us understand the energy status and immune response of TME, and further evaluate the potential effect of PD-L1 immunotherapy [54].

The impact of EGFR mutations on TMB

Increasing studies have delved into the significance of TMB in predicting outcomes for NSCLC immunotherapy, particularly its relationship with immune infiltration. Through analysis of the TCGA database, researchers found that patients with elevated TMB in lung adenocarcinoma (LUAD) exhibited better survival rates than those with low TMB, potentially linked to the immune infiltration of M1 macrophages, memory $CD4^+$ T cells, $CD8^+$ T cells, and high expression of CXCL17 (**Figure 3**) [55]. Moreover,

EGFR-mutated patients tend to have lower TMB, and elevated TMB has been associated with poor prognosis in EGFR-mutated NSCLC. Additionally, TMB has been proven to be an effective biomarker for predicting the efficacy and prognosis of EGFR-mutated advanced NSCLC. However, establishing a universally applicable cut-off value for TMB threshold remains challenging due to the variability in TMB distribution arising from the differing gene loci covered by different NGS panels. Furthermore, studies suggest that both EGFR-TKI usage and its resistance mechanisms can significantly increase TMB [56]. Moreover, the profound correlation between TMB and circulating tumor DNA (ctDNA) underscores the significance of ctDNA detection as a non-invasive means to quantify TMB. In a groundbreaking study, blood tumor mutational burden (bTMB) has been innovatively established as a predictive biomarker for the efficacy of Atezolizumab, enabling real-time monitoring and anticipation of immunotherapy outcomes. This advancement holds immense potential to offer more convenient and personalized treatment regimens for patients, thereby facilitating tailored and efficient care pathways [57]. In summary, prospective studies are necessary to further validate the application of TMB in EGFR-mutated and other sensitive driver gene-mutated NSCLC [58].

Therefore, we consider whether the different research contents and directions of previous studies have led to varying impacts on TME and TMB, resulting in the statistically insignificant findings regarding the influence of EGFR mutations on PD-L1 immune sensitivity, and the inconsistency observed in most research results.

Whether the integration of PD-1/PD-L1 immune inhibitors alongside diverse drugs has different effects on the treatment outcomes of EGFR-mutated NSCLC patients

Numerous clinical trials have conclusively demonstrated that, despite the burgeoning popularity of immunotherapy, monotherapy with immunotherapeutic agents alone has limited efficacy [59]. Several clinical trial outcomes suggest that only approximately 20% of patients with NSCLC derive benefit from such treatments [37], with the majority being unresponsive. A comprehensive literature search conducted across databases such as PubMed, Embase, and CNKI identified 13 studies involving a total of 7,281 patients. The meta-analysis indicated a notable enhancement in both OS and PFS when PD-1/PD-L1 immune checkpoint inhibitors were administered in conjunction with chemotherapy, surpassing the outcomes achieved with PD-1/PD-L1 inhibitor monotherapy [60]. To further enhance therapeutic outcomes, the field has rapidly progressed towards combination strategies based on PD-1/PD-L1 inhibitors, marking a transition from standalone anti-PD-1/PD-L1 therapy to an era of post-anti-PD-1/PD-L1 antibody therapy. In this new era, not only are combination therapies being explored, but also the development and integration of novel targets and antibodies [61]. This multifaceted approach holds promise for addressing the unmet needs of NSCLC patients and advancing the frontiers of immunotherapy.

The combination of Pembrolizumab with the Cytotoxic T-Lymphocyte-Associated Antigen 4 (CTLA-4) inhibitor Ipilimumab has been shown to potentially elicit clonal expansion of $CD8^+$ T lymphocytes, thereby inhibiting immune evasion and leading to tumor cell eradication. This therapeutic approach has emerged as a viable option after EGFR-TKIs resistance [62]. In the second-line treatment of EGFR-mutated patients with EGFR-TKI resistance, the KEYNOTE-021 study revealed antitumor activity of the Pembrolizumab-Ipilimumab combination in heavily pretreated patients, albeit with notable toxicity. Ongoing studies such as KEYNOTE-598 and phase 3 trials are further elucidating the efficacy and safety of anti-PD-1/PD-L1 combined with anti-CTLA-4 therapy in advanced NSCLC patients [63]. A separate study investigated 77 patients with advanced EGFR-mutated NSCLC who had progressed after EGFR-TKIs treatment. These patients were received combination therapy of Osimertinib with selumetinib, savolitinib, or durvalumab. The study confirmed the acceptable tolerability and preliminary anti-tumor activity of Osimertinib with Selumetinib or Savolitinib. However, the Durvalumab-Osimertinib combo was halted due to high interstitial lung disease (ILD) rates. Current PD-1/PD-L1 inhibitors +(-) EGFR-TKIs show limited clinical efficacy and increased

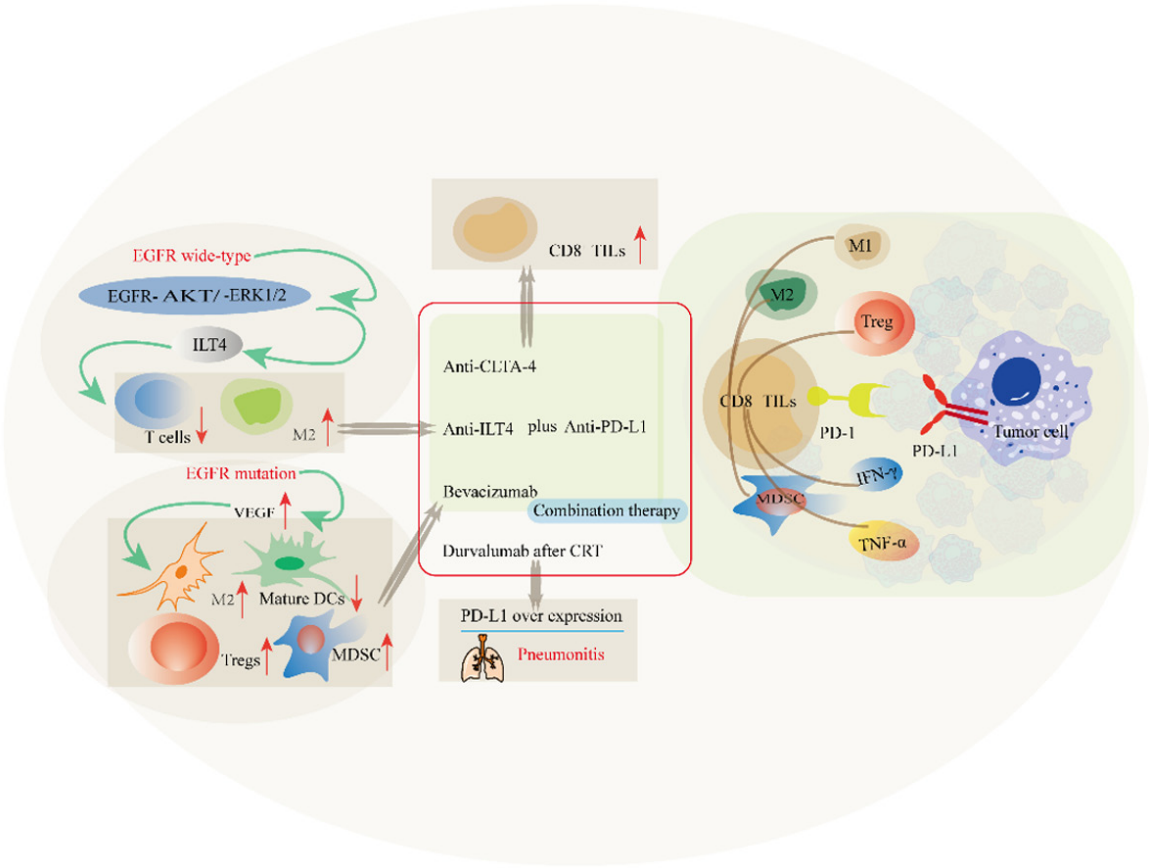

Figure 3. The effects of various drug combinations on the PD-L1 therapeutic outcomes of immunotherapy in patients with NSCLC. CRT: chemoradiotherapy.

risks of interstitial pneumonia and liver issues, warranting deeper investigation into its practicality [64]. A study has shown that patients with EGFR-mutated NSCLC who have previously undergone radiotherapy and chemotherapy exhibit significant benefit from Durvalumab treatment, comparable to those with EGFR wild-type. However, a higher incidence of pneumonia was observed following Durvalumab treatment in these patients [25] (**Figure 3**). Chen *et al.* found that in NSCLC cells, ILT4 is induced through the activation of the EGFR-AKT and ERK1/2 signaling pathways. Overexpression of ILT4 inhibits the immune response against tumor cells by recruiting M2-like Tumor-Associated Macro-phages and impairing T-cell function. Inhibiting ILT4 can block these immunosuppressive effects, thereby benefiting the clinical treatment of NSCLC patients (**Figure 3**) [34]. Additional research indicates that in patients with EGFR-mutated NSCLC, high expression of Vascular Endothelial Growth Factor interacting with Vascular Endothelial Growth Factor Receptor can impair immunotherapy efficacy by inhibiting dendritic cells (DCs) maturation, promoting the expansion of Tregs and Myeloid-Derived Suppressor Cells, and reducing T-cell immune infiltration. Combination therapy with Bevacizumab and immunosuppressants can improve the outcomes of immunotherapy [65, 66] (**Figure 3**).

Discussion

In summary, immunotherapy represented by PD-1/PD-L1 immune inhibitors is in the ascendancy. With the finding of new mechanisms, as well as the optimization of combination therapies, immunotherapy has shown tremendous potential and development prospects. However, it is undeniable that most current clinical studies are retrospective, with confounding factors and biases in the data, and varying numbers of patients included. Some studies have enrolled relatively few patients, making it diffi-

cult to ensure the accuracy and completeness of the research results.

We believe that most studies fail to comprehensively consider the impact of pre-immunotherapy treatment regimens for NSCLC patients on subsequent research. Additionally, it is undeniable that there are differences in the immunotherapy protocols adopted by researchers in various studies. Factors such as prior EGFR-TKIs, chemotherapy, radiotherapy, drug resistance, and even monotherapy or combination therapy can all lead to changes in important elements regulating immunotherapy such as varying levels of PD-1/PD-L1 expression, complexity and non-standardization of the TME, and TMB, resulting in heterogeneity in research results and significant differences in treatment outcomes among different patients. Furthermore, while PD-1/PD-L1 immune inhibitors provide survival benefits to patients, immune-related adverse reactions and infusion reactions often occur with ICIs [67], as well as severe hyper-progressive disease (HPD) [68], leading to the premature termination of studies and affecting the feasibility of the research results. Additionally, patients' heterogeneity in terms of gender, age, lifestyle habits, geographical distribution, pathological classification, and staging can all influence study outcomes [69]. Relevant studies have shown that in the clinical treatment of LUAD, women, smokers, patients with spiculated signs, air bronchograms, and papillary adenocarcinoma have a higher risk of EGFR gene mutations [70]. Moreover, the mutation rate of EGFR in Asians is higher than that in non-Asians, accounting for 39.6% of NSCLC and up to 50% in patients with LUAD in Asian [69].

In conclusion, the inability to standardize and integrate experimental samples and their collection processes leads to a lack of uniformity in research standards, thereby affecting the accuracy of research results. However, it is worth acknowledging that PD-1/PD-L1 immune checkpoint inhibitors have provided NSCLC patients with new treatment options, revolutionizing traditional treatment approaches. Accurately applying PD-1/PD-L1 inhibitors to bring maximize clinical benefits to NSCLC patients while reducing related adverse reactions remains a critical challenge and collective scientific obligation. As traditional Chinese medicine and modern medicine continue to intertwine, natural compounds are rising in prominence. Merging the personalized approach of Traditional Chinese Medicine's syndrome differentiation with the application of PD-1/PD-L1 immune checkpoint inhibitors could potentially pave the way for tailored treatments for cancer patients [71].

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Disclosure of conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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