Review Article

# Clinical advances in EGFR-TKI combination therapy for EGFR-mutated NSCLC: a narrative review

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**Background and Objective:** Mutations located in epidermal growth factor receptor (EGFR) tyrosine kinase domains have been described as the 'Achilles heel' of non-small cell lung cancer (NSCLC) and can be targeted by epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs). However, the clinical benefits of EGFR-TKIs are limited, and drug resistance inevitably occurs in NSCLC patients after long-term exposure to certain drugs. EGFR-TKI combination therapies, including combined targeted therapy, radiotherapy, chemotherapy, and immunotherapy, have shown promise in addressing this issue. This literature review analyzed the rationale and controversies of clinical research related to various EGFR-TKI combination therapies.

**Methods:** The PubMed database was searched to retrieve articles published from January 1, 2001 to April 15, 2023 using the following Medical Subject Headings (MeSH) terms: "EGFR-mutated non-small cell lung cancer" and "clinical trial". Google Scholar was also reviewed to retrieve additional articles. The search was limited to articles published in English.

**Key Content and Findings:** In this review, we summarized EGFR-TKI combination therapies, including combined targeted therapy, radiotherapy, chemotherapy, and immunotherapy, most of which have shown efficacy and safety in patients with EGFR-mutated NSCLC. A number of clinical studies with large sample sizes have analyzed the activity and toxicity of combined therapies and explored potential and well-tolerated treatment options.

**Conclusions:** EGFR mutations have been detected in many NSCLC patients and can be targeted by EGFR-TKIs. However, drug resistance after long-term exposure remains a significant challenge for this type of treatment. Most clinical trials have shown that the combination of EGFR-TKIs and targeted therapy, chemotherapy, radiotherapy or immunotherapy is efficacious and safe in the treatment of EGFR-mutated NSCLC. It should be noted that in some instances, serious adverse events have led to the termination of trials. However, EGFR-TKI combination therapy is indeed an effective approach for the treatment of patients with EGFR-mutated NSCLC and deserves further development.

**Keywords:** Combination therapy; epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs); non-small cell lung cancer (NSCLC)

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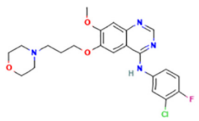
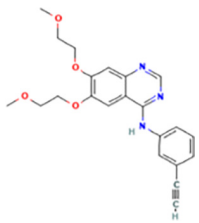
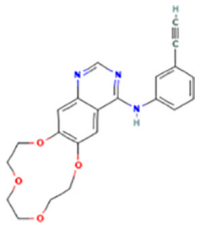
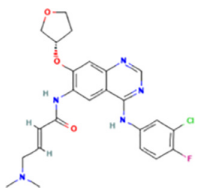
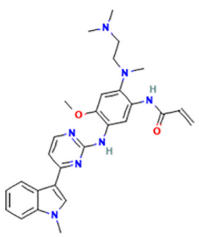
## Introduction

Lung cancer, which is one of the most common types of cancer, remains the leading cause of cancer-related deaths in both men and women (1). In 2022, there were approximately 2.21 million new diagnoses of lung cancer (accounting for 11.4% of all cancer cases) and 1.79 million deaths caused by lung cancer worldwide (2). Non-small cell lung cancer (NSCLC) is the most common form of lung cancer, accounting for about 80–85% of all lung cancers (3). Depending on the stage of the cancer, radical surgery, platinum-based chemotherapy, radiotherapy, and immunotherapy can be applied in the treatment of NSCLC (4).

In-depth research on the oncogenesis and progression of NSCLC has shown that most NSCLC patients have mutations of the epidermal growth factor receptor (EGFR) (5). EGFR is a kind of transmembrane tyrosine kinase protein and is becoming a landmark target in the treatment of NSCLC. EGFR is activated by receptor overexpression, a common phenomenon in various cancer tissues. EGFR overexpression, it has been reported to be associated with higher aggressiveness and poorer clinical outcomes in breast, lung, ovarian, cervical, bladder, esophageal, brain, head, and neck cancers (6-10). Additionally, EGFR activation and phosphorylation by the binding of the ligands, such as epidermal growth factor (EGF) (11), further activate several downstream signaling pathways, such as the rat sarcoma protein (Ras)/rapidly accelerated fibrosarcoma protein (Raf)/mitogen-activated protein kinases (MAPK), phosphatidylinositol-3 kinase (PI3K)/protein kinase B (AKT)/mammalian target of rapamycin (mTOR), Janus kinase (JAK)/signal transducer and activator of transcription (STAT) pathways (12), which play an important role in regulating multiple cellular processes, including proliferation, survival, and apoptosis.

Epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs), which target the EGFR kinase domain, have been proven to be clinically effective in addressing the above problems. The main EGFR-TKIs are summarized in *Table 1*. In recent decades, EGFR-TKIs have become the first-line standard treatment for patients with advanced NSCLC with EGFR mutations (13,14). The randomized, controlled, large-sample phase-III Iressa Pan-Asia Study (I-PASS) landmark clinical trial was the first to show that gefitinib significantly prolonged progression-free survival (PFS) in the first-line treatment of patients with advanced NSCLC with the EGFR mutation [median PFS: 9.5 *vs.* 6.3 months; hazard ratio (HR) =0.48, 95% confidence interval (CI): 0.36–0.64; P<0.001], improved the tumor response rate and quality of life (QoL), and had good safety (15). Subsequently, compared with standard chemotherapy, multiple prospective phase-III clinical trials with EGFR-positive patients, such as WJTOG3405 (16), NEJ002 (17), and EURTAC, have shown that the EGFR mutation is an important target and a key predictive marker for first-line EGFR-TKI therapy (18). In addition, the results of the CTONG0806 trial suggest that gefitinib does

**Table 1** Summary of the main EGFR-TKIs

| Classification | Drug | Approval | Structure |
|---|---|---|---|
| First-generation EGFR-TKI | Gefitinib (Iressa) | FDA, EMA, CFDA |  |
| | Erlotinib (Tarceva) | FDA, EMA |  |
| | Icotinib | CFDA |  |
| Second-generation EGFR-TKI | Afatinib (Gilotrif) | FDA, EMA |  |
| Third-generation EGFR-TKI | Osimertinib (Tagrisso) | FDA, EMA, CFDA |  |

EGFR, epidermal growth factor receptor; TKIs, tyrosine kinase inhibitors; FDA, Food and Drug Administration; EMA, European Medicines Agency; CFDA, China Food and Drug Administration.

**Table 2** The search strategy summary

| Items | Specification |
|---|---|
| Date of search | February 1 (first search), 2023 to July 15 (last search), 2023 |
| Databases and other sources searched | PubMed database, Google Scholar |
| Search terms used | "EGFR-TKIs", "combination therapy", "EGFR-mutated NSCLC", "acquired resistance", "clinical trial" |
| Timeframe | January 1, 2001 to April 15, 2023 |
| Inclusion and exclusion criteria | Inclusion: the search was limited to articles published in English. The research selection process was divided into the following three stages: title review, abstract review, and full-text review. Original articles and review articles appropriate to the topic of this review were included in the full-text review phase |
| | Exclusion: articles not published in English and not related to the research topic were excluded |
| Selection process | Q Zhang conducted the article selection independently. L Xu and R Wang supervised the article selection |

EGFR, epidermal growth factor receptor; TKIs, tyrosine kinase inhibitors; NSCLC, non-small cell lung cancer.

not significantly improve PFS, tumor response, and QoL in NSCLC patients without EGFR mutations. Thus, EGFR-targeted therapy should not be used in EGFR-negative patients, as it is not beneficial in reducing the risk of disease progression or death (19).

Unfortunately, after experiencing tumor regression, delayed progression and symptom improvement, research has shown that patients who are treated with EGFR-TKIs inevitably become drug resistant (most often within 9–12 months), which has been defined as "acquired resistance" (20-22). Possible mechanisms for acquired resistance have been extensively discussed; Threonine to Methionine substitution at position 790 (T790M), which is present in approximately 50% of EGFR-TKI resistant NSCLC patients, is the most common alteration (23). Other mechanisms leading to resistance include the human epithelial growth factor receptor 2 (HER2) mutation and amplification (24,25), mesenchymal-epithelial transition (MET) amplification (26), epithelial-mesenchymal transition (EMT) (27), and SCLC phenotypic transformation (28).

Due to the tumor heterogeneity and the possibility of simultaneous or sequential drug resistance mechanisms in patients, combination therapy has been put forward as a promising strategy for the treatment of EGFR-mutated NSCLC. Theoretically, in addition to overcoming or delaying the drug resistance, combination therapy could also enhance anti-cancer efficacy through its synergistic effects (29,30). Additionally, some combination therapy strategies may lower the dose of highly toxic drugs and minimize adverse reactions, and thus expand drug applications (31). In this review, we summarized EGFR-TKI combination strategies for treating EGFR-mutated NSCLC, including combined targeted therapy, radiotherapy, chemotherapy, and immunotherapy, which are of great significance in prolonging the survival of patients with NSCLC. This article is written in accordance with the Narrative Review reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-956/rc).

## Methods

The following Medical Subject Headings (MeSH) terms were used to search the PubMed database: "EGFR-mutated non-small cell lung cancer" and "clinical trial". Articles with those terms, published in English, from January 1, 2001 to April 15, 2023, were retrieved. Google Scholar was also reviewed to retrieve additional articles. The relevant literature was searched using the following keywords: "EGFR-TKIs", "combination therapy", "EGFR-mutated NSCLC", "acquired resistance", and "clinical trial". The research selection process was divided into the following three stages: title review, abstract review and full-text review. Original articles and review articles appropriate to the topic of this review were included in the full-text review phase. The search strategy is detailed in *Table 2*.

## EGFR-TKIs combined with targeted therapy

Targeted therapy has been defined as a method of treatment that blocks the growth of cancer cells by interfering with the specific cell molecules required for carcinogenesis and

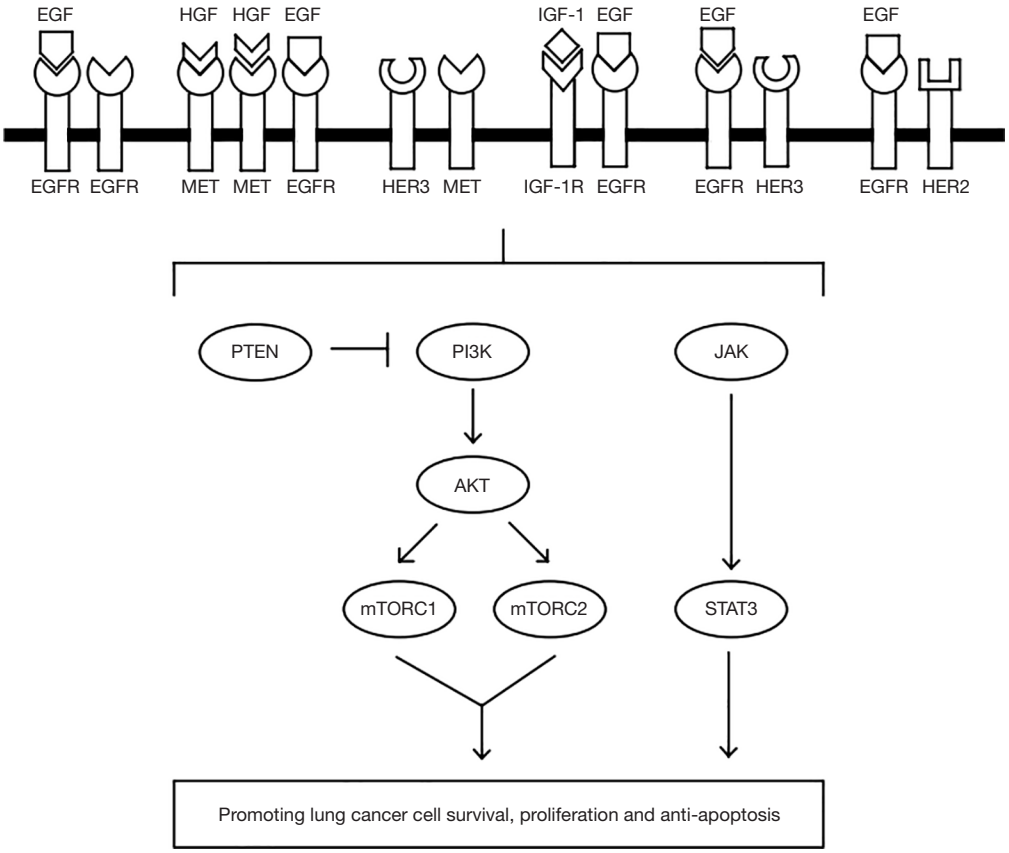



**Figure 1** Various mechanisms of EGFR-TKI resistance. EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; HGF, hepatocyte growth factor; MET, mesenchymal-epithelial transition; HER, human epidermal growth factor receptor; IGF-1, insulin-like growth factor-1; PTEN, phosphatase and tensin homolog deleted on chromosome 10; PI3K, phosphatidylinositol-3 kinase; AKT, protein kinase B; mTOR, mammalian target of rapamycin; JAK, Janus kinase; STAT3, signal transducer and activator of transcription 3; TKI, tyrosine kinase inhibitor.

tumor growth, and has fewer side effects than classical cytotoxic chemotherapy (32). In NSCLC patients with EGFR mutations, targeted drugs for different targets can be provided according to different drug resistance mechanisms (see *Figure 1*) to develop precise and individualized anti-tumor programs.

### *Targeting MET*

The MET receptor, a transmembrane tyrosine kinase receptor encoded by the proto-oncogene MET, is thought to be an important cause of acquired resistance to gefitinib or erlotinib in NSCLC (33). Hepatocyte growth factor (HGF) is a ligand of the MET receptor. It promotes the phosphorylation of MET tyrosine kinase by binding to the MET receptor and then activates the downstream PI3K/AKT/mTOR pathway, which is the key signaling pathway for cell proliferation, survival, and anti-apoptosis (33,34). Thus, targeting MET appears to be an effective approach for treating NSCLC.

Clinical trials have shown exciting results. For example, the INSIGHT study suggests that MET inhibitor tepotinib plus gefitinib results in increased anti-activity compared with standard chemotherapy in patients with EGFR-mutant NSCLC and MET amplification. Unfortunately, the study was prematurely terminated due to insufficient enrollment (35). However, the interim results of this multicenter, open-label, phase-Ib study and the TATTON study suggest that the combination of osimertinib and the MET inhibitor volitinib has an acceptable risk-benefit profile and encouraging anti-tumor activity (36,37). In phase-I studies examining the MET antibody

emibetuzumab as a monotherapy or in combination with erlotinib, emibetuzumab showed good tolerance, and no dose-limiting toxicities were observed (38). Based on this study, Camidge *et al.* conducted a multicenter, randomized, non-controlled, open-label phase-II study, and found that the median PFS and median overall survival (OS) were similar in both the treatment groups, and neither emibetuzumab plus erlotinib nor emibetuzumab monotherapy reversed the acquired resistance to erlotinib in MET positive patients. The study did not meet its primary endpoint; however, a subset of patients obtained meaningful clinical benefits in both treatment groups, including a partial response (PR) lasting up to 11 months (39). It should also be noted that the association of meaningful clinical benefits with the combination treatment strategy has yet to be investigated (39). In addition, exploratory biomarker analyses of other MET-targeted drugs, such as onartuzumab or tivantinib, in combination with erlotinib have shown that favorable trends in PFS were associated with increased MET expression by immunohistochemistry (40,41). Thus, MET remains a valid target in the treatment of EGFR-mutated NSCLC.

### *Targeting HER2/human epidermal growth factor receptor 3 (HER3)*

Other than EGFR, HER2 is one of the most popular targets of NSCLC targeted therapy. HER2 is a transmembrane glycoprotein receptor with intracellular tyrosine kinase activity. Alterations in HER2, including mutation, amplification, and overexpression, have the potential to induce oncogenic effects, and have been detected in many cancers, such as NSCLC (42). Notably, the other target, HER3, cannot be autophosphorylated due to impaired kinase activity but can be tyrosine phosphorylated if it is coupled with other receptor tyrosine kinases (RTKs), such as EGFR and HER2. EGFR and HER2 must recruit and transphosphorylate PI3K through HER3 (43,44). Activated HER3 provides multiple docking sites for PI3K, and amplifies signaling in the PI3K/AKT/mTOR pathway, ultimately promoting cellular survival (45). Thus, HER3 is also considered one of the targets for anti-cancer treatment, especially in EGFR-mutated NSCLC (44).

The results of monotherapies with anti-HER drugs are not optimistic. In a multicenter international trial, trastuzumab (an anti-HER2 drug) was found to lead to a high proportion of remission and provide lasting clinical benefits in patients with advanced HER2-mutated NSCLC; however, the safety of the drug has yet to be studied, and issues such as drug-related interstitial lung disease (ILD) are important risks of the treatment that require careful monitoring and management (46). Additionally, positive results from clinical studies of combination therapies with anti-HER drugs and EGFR-TKIs have rarely been reported. Hughes *et al.* published the results of a phase-II study exploring the combination of pertuzumab (an anti-HER2/HER3 drug) and erlotinib in 41 patients with relapsed NSCLC. Contrary to the original intention to produce greater activity by targeting the HER family, the combination therapy showed only moderate anti-tumor efficacy and was generally poorly tolerated, which limits its clinical applicability (47). Thus, further research needs to be conducted to discover combinations of drugs that can effectively interfere with HER receptor signaling while demonstrating enhanced tolerability profiles. Further, until powerful, safe and effective drugs targeting HER are developed, treatments in combination with EGFR-TKIs and other target inhibitors, such as mTOR in the downstream pathway, should be preferred.

### *Targeting PI3K/AKT/mTOR*

PI3K-AKT-mTOR is a signaling pathway controlled by the EGFR. PI3K is triggered when extracellular ligands bind to receptors (e.g., when EGF binds to EGFR resulting in the phosphorylation and activation of receptor tyrosine kinase (RTK) to catalyze the phosphorylation of phosphatidylinositol diphosphate into phosphatidylinositol 3-phosphate (PIP3). The accumulation of PIP3 localizes AKT to the plasma membrane, where AKT is phosphorylated by 3-phosphoinositol-dependent kinase 1 indirectly or directly. The activated AKT regulates the phosphorylation of the downstream effectors, instigating alterations in gene expression and cell behavior. The major downstream effectors are mammalian target of rapamycin 1 (mTORC1) and mammalian target of rapamycin complex 2 (mTORC2) (48). Hyperactivation of PI3K/AKT/mTOR signaling not only explains the formation and growth of many tumors, but also illustrates the resistance to targeted inhibitors, such as EGFR-TKIs (49,50). Phosphatase and tensin homolog (PTEN) is a known tumor suppressor gene that can counteract the activation of AKT driven by PI3K. PTEN inactivation is associated with resistance to EGFR-TKI treatment and lower survival in NSCLC patients (50).

Buparlisib (BKM120) is an oral pan-class I, reversible

inhibitor of PI3K. Tan *et al.* observed mild anti-tumor activity with gefitinib and buparlisib in patients resistant to EGFR-TKIs. However, given the late toxicity and long half-life period of buparlisib, other alternatives need to be explored, such as copanlisib (BAY80-6946), duvelisib (IPI-145), and pictilisib (GDC-0941) (51). In addition, there are dual PI3K/mTOR inhibitors, such as dactolisib (NVP-BEZ235), and apitolisib (GDC-0980). Despite a reasonable theoretical basis and demonstrable pharmacodynamic tumor activity in the relevant tumor population, it is not possible to determine a dose and schedule for this class of drugs that is both tolerated and provides clear efficacy in the population evaluated. Thus, their combination with EGFR-TKIs is still in the early clinical development stage (52).

Molife *et al.* and Lin *et al.* each conducted a phase-I trial evaluating the oral AKT inhibitor MK-2206 plus erlotinib or gefitinib, and both reported that they were well tolerated and found early evidence of anti-tumor activity (53,54). Based on these promising results, Lara *et al.* conducted a phase-II study and found that the combination of MK-2206 plus erlotinib was more effective in patients with EGFR wild-type NSCLC than in patients with EGFR-mutant NSCLC. Some efficacy was observed in the EGFR-mutated NSCLC; however, this did not exceed the previous estimates. Thus, AKT pathway inhibition merits additional clinical assessment in EGFR wild-type NSCLC (55). In general, there is limited literature on the combination of AKT inhibitors and EGFR-TKIs in the treatment of NSCLC in recent years, and relevant clinical studies are not yet mature.

Rapamycin and its analogues are currently the inhibitors most commonly used to target the PI3K/AKT/mTOR pathway. Among them, everolimus (RAD001), an orally bioavailable derivative of rapamycin, is a potent mTOR inhibitor. It has been shown to be highly effective in restoring the sensitivity of gefitinib-resistant NSCLC cell lines with the PIK3CA mutation or PTEN deletion (56,57). Many clinical trials have been conducted to assess the efficacy of combining everolimus with EGFR-TKIs. Compared with promising pre-clinical trial results, the efficacy of this combination in patients with EGFR-mutated NSCLC appears to be unsatisfactory (58). In a multicenter, open-label, phase-II study, 133 patients received everolimus-erlotinib (n=66) or erlotinib alone (n=67), and at 3 months, had disease control rate (DCR) of 39.4% and 28.4%, respectively. It was estimated that the probability that the difference in the DCR at 3 months would be ≥15% was 29.8%, which was below the prespecified probability threshold of ≥40%. The median PFS for the patients who received everolimus-erlotinib (n=66) and those who received erlotinib alone was 2.9 and 2.0 months, respectively. Grade 3/4 adverse events occurred in 72.7% and 32.3% of these patients, respectively. Thus, everolimus plus erlotinib was not considered effective enough, and the combination does not warrant further investigation due to the increased toxicity and the lack of substantial improvement in disease stabilization (59). Similarly, a phase-II study by Price *et al.*, which achieved a partial response (PR) in eight of 62 patients and a response rate of only 13%, did not meet the prespecified response threshold to warrant further investigations of everolimus in combination with gefitinib (60). In addition, Fang *et al.* also found that everolimus, whether combined with gefitinib, afatinib, or osimertinib, showed very limited anti-tumor activity in EGFR-TKI-resistant NSCLC patients (61).

### *Targeting JAK2/signal transducer and activator of transcription 3 (STAT3)*

Ligand-binding receptors recruit and phosphorylate JAK2 (a member of the JAK family that also includes JAK1, JAK3, and Tyk2, among which, JAK2 plays a prominent role in tumorigenesis), which ultimately leads to STAT3 protein phosphorylation, dimerization, and activation (62). It should be noted that in addition to JAK, STAT3 activation can also be mediated by the Src family, Abl family, EGFR, and insulin-like growth factor-1 receptor (IGF-1R) (63). After STAT3 is activated by JAK2, it is transported into the nucleus through the nuclear membrane, regulates the expression of related genes, and participates in important biological processes, such as cell proliferation, differentiation, apoptosis, and angiogenesis (62,64). Similar to PI3K/AKT/mTOR, JAK2/STAT3 also has a significant role in tumorigenesis, and its abnormal activation is also involved in the decreased sensitivity of NSCLC to EGFR-TKIs (65).

The phase-Ib study by Park *et al.* demonstrated that the combination of afatinib and the JAK1/2 inhibitor ruxolitinib was tolerated by patients, with moderate clinical activity observed in NSCLC patients with acquired resistance to EGFR-TKIs. The 30 patients had an objective response rate (ORR) of 23.3%, a DCR of 93.3% (no patients achieved a complete response, seven achieved a PR, and 21 achieved stable diseases), and a median PFS of 4.9 (95% CI: 2.4–7.5) months (66). However, another phase-Ib study concluded that JAK1/2 inhibitor momelotinib in combination with erlotinib did not appear to produce any

improved benefits compared to findings based on historical data of erlotinib monotherapy in patients diagnosed with EGFR-mutated NSCLC (67). Thus, the efficacy of different combinations of JAK inhibitors and EGFR-TKIs needs to be further explored in clinical studies.

Research is still being conducted on the safety and anti-tumor efficacy of STAT3 inhibitors as monotherapies. For example, the STAT3 inhibitor OPB-51602 has been shown to display significant anti-tumor activity, especially in NSCLC; however, its long half-life period and the poorer tolerability of continuous dosing, compared with intermittent dosing, suggests that less frequent dosing should be explored (68). Zheng *et al.* also found that the STAT3 inhibitor W2014-S showed significant anti-tumor activity in NSCLC (69). This suggests that combinations of STAT3 inhibitors and EGFR-TKIs may be a potential strategy for overcoming EGFR-TKI-acquired resistance in NSCLC patients.

### *Targeting IGF-1R*

IGF-1R is a transmembrane heterotetramer comprising two extracellular α and β subunits (70). Upon the binding of IGF-1 and IGF-2 to the extracellular subunit domain of IGF-1R, the tyrosine kinase activity of IGF-1R is activated, and the activation of IGF-1R initiates cascades involving signal transduction pathways, such as Ras, Raf, and MAPK (71). The overexpression of IGF-1R has been reported to promote tumor growth, progression, invasion, and metastasis (72). IGF-1R also plays an important role in promoting the progression of NSCLC (73).

Many pre-clinical studies have shown that the joint administration of IGF-1R inhibitors, such as α-IR3, AG1024, and R1507, with EGFR-TKIs amplifies the suppressive effects on growth and apoptosis initiated by EGFR-TKIs, which could provide a potential way of treating EGFR-TKI-resistant NSCLC (74,75). However, very few relevant clinical studies have been conducted in this area.

### *Targeting rearranged during transfection (RET)*

The RET proto-oncogene encodes a transmembrane RTK involved in normal embryonic development (76). Due to an aberrant DNA repair process, RET fuses with another irrelevant gene (77), activating various downstream signaling cascades that play essential roles in cell proliferation and survival; that is, the PI3K/AKT, JAK2/STAT3 pathways (78). It has emerged as a rare but targetable acquired resistance mechanism in EGFR-mutated NSCLC patients undergoing treatment with EGFR-TKI (79,80).

Thus, a combination therapy of anti-EGFR and anti-RET therapy will likely be required to overcome this resistance. Notably, two highly potent RET inhibitors, selpercatinib and pralsetinib, have been proven to be effective in treating advanced or metastatic RET-altered NSCLC (80). Additionally, RET fusions are more likely to be associated with EGFR-mutant NSCLC patients who received therapeutic interventions targeting EGFR through third-generation EGFR-TKIs (80). In a multicenter, prospectively treated cohort, Rotow *et al.* found that the addition of selpercatinib to osimertinib was feasible and safe and provided clinical benefits to patients with EGFR-mutant NSCLC with an acquired RET fusion (81). Additionally, Piotrowska *et al.* reported that RET fusions mediate resistance to EGFR inhibitors and demonstrated that combined EGFR and RET inhibition with osimertinib/pralsetinib (BLU-667) may be a well-tolerated and effective treatment strategy for EGFR-mutant NSCLC (82). Urbanska *et al.* also found that EGFR-mutated patients displayed sustained ongoing objective response (OR) to an osimertinib-pralsetinib combination for more than 12 months, which provides clinical evidence of the effectively targetable mechanism of osimertinib resistance (83).

## EGFR-TKIs combined with chemotherapy

As the first-line treatment for NSCLC patients without clear therapeutic targets, chemotherapy has always played an important role in tumor treatments (84). Platinum-based therapy is the mainstay of chemotherapy for NSCLC patients and is usually administered in combination with a tubulin binding agent [such as taxanes (paclitaxel or docetaxel) and vinca alkaloids (vinorelbine or vincristine)], a camptothecin analogue (irinotecan or opotecan), gemcitabine, and pemetrexed (85). It should be noted that pemetrexed has significant activity, favorable tolerance, and low toxicity compared to other cytotoxic agents. Extensive research has been conducted to explore its administration either alone or in combination with other regimes (86). To ameliorate the inevitable drug-resistant outcome of EGFR-TKI therapy, combining it with chemotherapy could provide an effective treatment option for EGFR-mutated NSCLC patients.

Studies of the combination of EGFR-TKIs and chemotherapy in patients with EGFR mutations have shown

promising results. The NEJ009 study showed that patients with advanced NSCLC with EGFR mutations treated with gefitinib combined with carboplatin plus pemetrexed had better PFS (20.9 *vs.* 11.2 months, respectively, HR =0.493, P<0.001) with an acceptable toxicity profile than those treated with gefitinib alone. The benefits of this combined treatment in terms of OS require further validation (but the results of the study showed that the patients had an OS of 52.2 *vs.* 38.8 months, respectively, HR =0.695, P=0.0013) (87). Additionally, Planchard *et al.* and Watanabe *et al.* found that at the recommended doses, osimertinib or afatinib in combination with carboplatin and pemetrexed also had manageable safety and tolerability, and good clinical efficacy in patients with EGFR-mutated NSCLC (88,89). A meta-analysis of 18 eligible trials involving 4,628 patients and 12 treatments indicated that osimertinib and gefitinib plus pemetrexed-based chemotherapy were associated with the best PFS and OS benefits for patients with advanced EGFR-mutated NSCLC compared with other first-line treatments (90). Another meta-analysis of eight randomized controlled trials involving 1,349 advanced NSCLC patients with the sensitive EGFR mutation had similar findings, which suggests that compared with EGFR-TKI monotherapy, the combination of first-generation EGFR-TKI and chemotherapy, especially when applying the concurrent delivery of platinum-based doublet chemotherapeutic drugs, significantly improves the ORR, PFS, and OS in the first-line treatment of advanced EGFR-mutated NSCLC. Despite the increased incidence of chemotherapy-induced toxicities in the combination group, it is well tolerated and can be effectively managed from a clinical perspective (91). However, Gijtenbeek *et al.* demonstrated that the effects of erlotinib with cisplatin-pemetrexed were not favorable, as the toxicity rate was high and not negligible (92). Moreover, another systematic analysis reported that the combination of chemotherapy and EGFR-TKIs did not achieve satisfactory results, and that while there was no notable difference in OS and the ORR, there was an increased incidence of grade 3/4 anemia, rash, and other adverse events in the patients (93). As the role of EGFR-TKIs combined with chemotherapy remains controversial, it has not yet been widely used in clinical practice, and further clinical trials need to be conducted to explore and verify its use (31).

## EGFR-TKIs combined with radiotherapy

Radiotherapy is an important way of treating NSCLC, and its role in locally advanced and early-stage disease, recurrence, postoperative, central early stage NSCLC, and multiple primary lung cancer has been fully demonstrated (94). Several studies have been carried out to test the hypothesis that the combination of EGFR-TKIs and radiotherapy may confer better survival benefits than monotherapy.

A retrospective study of 380 patients reported that the EGFR-TKI + thoracic stereotactic body radiation therapy (SBRT) group had a median PFS of 19.4 months and the EGFR-TKI group had a median PFS of 13.7 months (P=0.034) with tolerable toxicity and no significant effect in relation to OS (P=0.557) (95). The clinical trials by Zheng *et al.* and Akamatsu *et al.* also validated the efficacy and tolerability of erlotinib or gefitinib plus thoracic radiotherapy in a subset of NSCLC patients harboring EGFR mutations (96,97). Notably, an especially high incidence of grade two or worse radiation pneumonia was observed in patients receiving osimertinib combined with thoracic radiotherapy (63.6%) compared with those receiving erlotinib or gefitinib combined with thoracic radiotherapy, which should serve as a warning to physicians to exercise caution when using this combination regimen (98).

In addition to thorax, between 25% and 40% of NSCLC patients reportedly develop brain metastases during the course of the disease, usually within 2 years of diagnosis of the primary tumor and have poor prospects (99). Current treatments for patients with brain metastases include whole-brain radiation therapy (WBRT) with or without stereotactic radiosurgery (100). The blood-brain barrier renders most chemotherapeutic agents ineffective, but it has been established that EGFR-TKIs can permeate the blood-brain barrier (101) with limited penetration into cerebrospinal fluid (102,103), and thus could be administered with WBRT.

Many studies have reported on the feasibility of WBRT combined with EFGR-TKIs in the treatment of NSCLC patients with the EGFR mutation and brain metastases. Fan *et al.* reported a median survival time of 22.0 months for patients with EGFR mutations and 7.5 months for those with wild-type EGFR (P=0.0001), which suggests that patients with EGFR mutations benefit more from icotinib combined with WBRT (104). Additionally, a meta-analysis of 18 prospective clinical studies reported that the ORR of WBRT combined with erlotinib/gefitinib was also superior to that of WBRT alone (odds ratio =2.67; 95% CI: 2.10–3.38; P<0.05) (105). Moreover, He *et al.* found that in first-line therapy for NSCLC patients with EGFR mutations,

the combination therapy of EGFR-TKIs and WBRT significantly improved OS and intracranial PFS (iPFS), and patients with symptomatic brain metastasis, an older age, and exon 19 deletion may benefit more from combination therapy (106). However, He *et al.* also suggested that EGFR-TKI alone may be an option as a first-line therapy for patients with three or less brain metastases, which may defer or avoid the neurocognitive sequelae caused by WBRT (106). In addition, one case report demonstrated that the combination of WBRT and afatinib might cause serious dermatological toxicity (107). Thus, more multi-institutional, prospective randomized clinical trials need to be conducted to further explore the combination of EGFR-TKIs and radiotherapy to better guide clinical treatment.

## EGFR-TKIs combined with immunotherapy

Immunotherapy has become popular as the preferred option for cancer treatment in recent years (108). It aims to improve the anti-tumor immune response. Related drugs stimulate or promote the activation of the immune system to kill tumor cells that have escaped previous immunological surveillance. Compared to chemotherapy and other drugs that kill cancer cells directly, immunotherapy has fewer off-target effects (108). Thus, immunotherapy exerts a powerful anti-cancer effect by improving the immune microenvironment and has been approved for the treatment of NSCLC (109). The combination of immunotherapy with EGFR-TKIs is also under evaluation.

The programmed cell death protein-1 (PD-1) and its key ligand, the programmed cell death ligand-1 (PD-L1), are key therapeutic targets for NSCLC therapy. PD-L1 induces T cell apoptosis by binding to its receptor PD-1, which is mainly expressed in activated T cells (110,111). The overexpression of PD-L1 is associated with a poor prognosis in many cancers, such as NSCLC and breast cancer (112). A phase-I open-label multicenter study (NCT02088112) observed encouraging activity in durvalumab (an anti-PD-L1 antibody) and gefitinib in NSCLC patients with sensitizing EGFR mutations (113). The TATTON study is a multi-arm, open-label, phase-Ib study designed to evaluate the safety and tolerability of osimertinib based combinations (osimertinib + MEK1-2 inhibitor selumetinib, osimertinib + MET-TKI savolitinib, and osimertinib + anti-PD-L1 monoclonal antibody durvalumab) in patients with EGFR-mutated NSCLC. As part of the TATTON study, Oxnard *et al.* found that while osimertinib (80 mg orally once a day) combined with durvalumab (3–10 mg/kg intravenously every 2 weeks) was tolerable, there was a higher than expected frequency of ILD (22%). However, the mechanism underlying the high incidence of ILD remains unclear, which led to the discontinuation of this combination (114).

Cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) is another immune checkpoint receptor that induces T cell non-reactivity by binding to the B7 molecule and participates in the negative regulation of the immune response (115). It has also been developed as a prospective target for therapy in cases of NSCLC (115). In a small phase-I trial, Chalmers *et al.* evaluated a combination of ipilimumab (anti-CTLA-4 antibody) plus erlotinib in 11 NSCLC patients with EGFR mutations. This combination was associated with excessive short-term gastrointestinal toxicity (36%), which exceeded the pre-planned conventional definition of an unacceptable toxicity frequency of 33%, leading to the early termination of the study. However, the long-term follow-up revealed an unexpected prolongation of patient survival, with a median PFS of 27.8 months and a median OS of 42.3 months (116). Based on the study by Chalmers *et al.*, Puri *et al.* replaced erlotinib with osimertinib to decrease the toxicity of the combination therapy to assess the efficacy of the combination of ipilimumab and osimertinib in patients with EGFR-mutated NSCLC. The study is ongoing and the results are expected to be published in the near future (117).

In addition, high levels of circulating vascular endothelial growth factor (VEGF) stimulate tumor angiogenesis, which plays an important role in the growth, proliferation, and metastasis of tumor cells in NSCLC patients (118). ARTEMIS-CTONG1509, a multicenter phase-III study, found that bevacizumab (an anti-VEGF antibody) plus erlotinib significantly improved PFS in patients with EGFR-mutated NSCLC, including those with brain metastases at the baseline (119). Kuo *et al.* found that a bevacizumab combination treatment showed moderate efficacy in afatinib-treated NSCLC patients with the EGFR-sensitizing mutation (120). However, a treatment of osimertinib plus bevacizumab failed to show any efficacy in improving the PFS of EGFR-mutated NSCLC patients, with similar findings reported in the studies of Soo *et al.* and Kenmotsu *et al.* (121,122).

As mentioned above, most studies have shown that a combination of immunotherapy drugs and EGFR-TKIs could be comparatively clinically effective. However, EGFR-TKIs can cause several serious adverse events, notably including interstitial pneumonia. Given the

potential toxicity challenges associated with combination therapies, some studies have had to be terminated prematurely. Widespread safety concerns indicate a lack of understanding of antibody-based immunotherapy and should be addressed before the extensive clinical use of immunotherapy drugs.

## Conclusions

In summary, the use of EGFR-TKI combination therapy is case-dependent. Most clinical trials have shown the efficacy and safety of EGFR-TKI combination therapy in patients with EGFR-mutated NSCLC; however, in some instances, several serious adverse events have led to the early termination of trials. Thus, more clinical studies with large sample sizes need to be conducted to analyze the activity and toxicity of combination therapies to explore potential and well-tolerated options. In addition, retrospective studies should be carried out from which the classification of patient subgroups should be analyzed to select patients who might benefit from combination therapy in terms of cost-effectiveness, increased longevity, and improved QoL. In conclusion, EGFR-TKI combination therapy is an effective approach for the treatment of patients with EGFR-mutated NSCLC and deserves further development.

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