Review Article

Strategies and influencing factors for the treatment of advanced non-small cell lung cancer based on epidermal growth factor receptor tyrosine kinase inhibitors: a narrative review

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Background and Objective: Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) are the primary treatment for advanced non-small cell lung cancer (NSCLC) patients with EGFR mutations, significantly enhancing patient prognosis. Despite the efficacy of EGFR-TKIs, monotherapy faces challenges such as variability among individuals and early drug resistance. This article aims to explore the treatment strategies and influencing factors for advanced NSCLC patients treated with EGFR-TKIs, optimize treatment plans, and improve the prognosis of patients with advanced NSCLC.

Methods: We undertook a comprehensive, narrative review of the latest literature to define the current application and progress of EGFR-TKIs in treating patients with advanced NSCLC.

Key Content and Findings: The efficacy and promise of EGFR-TKIs, both as monotherapy and combined with other agents, for treating patients with advanced NSCLC are outlined. The study delves into the mechanisms of resistance and the ongoing development of EGFR-TKIs. Various factors influencing the treatment of advanced NSCLC patients with EGFR-TKIs are also examined.

Conclusions: EGFR-TKIs alone improve survival in patients with advanced NSCLC. Combined with other agents, some regimens have shown improved benefits in overcoming drug resistance and prolonging patient survival. It is imperative to focus on developing novel EGFR-TKIs and investigate innovative combination therapies to maximize patient benefit.

Keywords: Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs); advanced non-small cell lung cancer (advanced NSCLC); EGFR mutations; prognostic analysis; combination therapy

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Introduction

Lung cancer, the most deadly malignant tumor globally, often goes undetected in its early stages, leading to diagnosis in advanced stages (1). Non-small cell lung cancer (NSCLC) is the most prevalent type, making up 85% of cases, with a grim prognosis (2). A significant portion of NSCLC patients (46.8–61.2%) receive a stage IV diagnosis initially (3). Advanced NSCLC is typically deemed incurable, palliative care is the primary approach. In the past, systemic chemotherapy was the primary treatment for advanced NSCLC patients. However, the advent of targeted therapy has significantly enhanced the survival rates of stage IV NSCLC patients, although the 5-year survival rate remains less than 10% (3,4).

Epidermal growth factor receptor (EGFR), a protein molecule found on cell surfaces, regulates cell growth and division. Altered EGFR function in EGFR-mutant NSCLC leads to accelerated growth (5). These mutations are the main driving force behind lung cancer, with approximately 50% of Asian NSCLC patients (6,7) and 10–20% of patients in other regions carrying EGFR mutations (5). The most common EGFR mutations are 19del (deletion of five amino acids in exon 19, in which delE746_A750 is the most common subtype) and L858R, each accounting for 45% of all EGFR mutations (5). High levels of EGFR expression are often linked to a poor prognosis in lung cancer (8). Targeted therapy with EGFR tyrosine kinase inhibitors (TKIs) is the standard first-line treatment for advanced NSCLC patients with EGFR mutations, improving survival in those with sensitive mutations (9). Researchers are now investigating treatment strategies combining EGFR-TKIs with anti-vascular endothelial growth factor (VEGF) therapies, Janus kinase (JAK) inhibitors, mesenchymal epithelial transition factor (MET) TKIs, immune checkpoint inhibitors (ICIs), chemotherapy, radiotherapy, and surgery to delay TKI resistance, extend progression-free survival (PFS), and enhance overall survival (OS) in patients (10-16). In this review, we aimed to explore treatment strategies and factors affecting outcomes in patients with advanced NSCLC treated with EGFR-TKIs, optimize treatment regimens, and improve the prognosis of patients with advanced NSCLC. We present this article in accordance with the Narrative Review reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-637/rc).

Methods

A comprehensive, narrative review of literature was conducted to determine the progress of EGFR-TKIs in treating patients with advanced NSCLC. Studies from 2017 to 2024 were reviewed from PubMed using the keywords "EGFR-TKIs", "epidermal growth factor receptor tyrosine kinase inhibitors", "advanced NSCLC", and "stage IV". Some important studies published before 2017 cited in the literature we searched were also added to our review.

Articles related to the topic of this study were thoroughly reviewed. *Table 1* summarizes the search strategy.

EGFR-TKIs monotherapy

First-generation EGFR-TKIs, such as gefitinib, erlotinib, and icotinib, are competitive inhibitors that bind reversibly to the adenosine triphosphate (ATP)-binding site of the EGFR (7,17-19). Studies have indicated that both first- and second-generation EGFR-TKIs are more effective

Table 1 The search strategy summary

Items	Specification
Date of search	November 3, 2023 to April 3, 2024; June 3, 2024 to June 6, 2024
Databases and other sources searched	PubMed
Search terms used	("EGFR-TKIs" OR "epidermal growth factor receptor tyrosine kinase inhibitors") and ("advanced NSCLC" OR "stage IV")
Timeframe	2017–2024
Inclusion and exclusion criteria	Inclusion criteria: clinical trial; meta-analysis; randomized controlled trial; review; systematic review; exclusion criteria: written in non-English language
Selection process	All authors selected studies together

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

Table 2 The efficacy of EGFR-TKIs alone in treating NSCLC is as follows

Representative drugs	Types of inhibitors	Targets of EGFR	PFS (months)	OS (months)	Ref
First-generation EGFR-TKIs					
Gefitinib	Reversible	19del, L858R	8.0	17.0	(11)
Erlotinib	Reversible	19del, L858R	13.1	22.8	(17,18)
Icotinib	Reversible	19del, L858R	11.2	30.5	(19)
Second-generation EGFR-TKIs					
Afatinib	Irreversible	19del, L858R	11.0	23.1	(22,24)
Dacomitinib	Irreversible	19del, L858R	14.7	34.1	(23,33)
Third-generation EGFR-TKIs					
Osimertinib	Irreversible	19del, L858R, T790M	18.9	38.6	(28,34)
Aumolertinib	Irreversible	19del, L858R, T790M	19.3	NR	(25)
Furmonertinib	Irreversible	19del, L858R, T790M	20.8	NR	(26)
Lazertinib	Irreversible	19del, L858R, T790M	11.1	NR	(29)

EGFR-TKI, epidermal growth factor receptor tyrosine kinase inhibitor; NSCLC, non-small cell lung cancer; PFS, progression-free survival; OS, overall survival; NR, not reached.

and tolerable than platinum-based chemotherapy (20-22), with the erlotinib group demonstrating a median PFS of 9.7 versus 5.2 months in the standard chemotherapy group. Furthermore, the incidence of treatment-related severe adverse events is lower in the erlotinib group compared to the chemotherapy group (20). Despite the initial efficacy, many EGFR-mutant NSCLC patients eventually develop resistance to first-generation EGFR-TKIs, with a significant proportion developing the EGFR T790M mutation (15).

To address acquired resistance following treatment with first-generation EGFR-TKIs, researchers have developed second-generation EGFR-TKIs like afatinib and dacomitinib, which irreversibly inhibit the tyrosine kinase structural domain of EGFR (22,23). In a study by Wu *et al.*, 364 patients were randomized into targeted therapy and chemotherapy groups (242 received afatinib; 122 received gemcitabine and cisplatin), with the afatinib group showing significantly longer median PFS compared to the gemcitabine and cisplatin group (11.0 *vs.* 5.6 months, P<0.0001) (22). Data from phase III clinical trials (LUX-Lung 3 and LUX-Lung 6) demonstrate that afatinib significantly enhances OS in patients with 19del mutation compared to platinum-containing chemotherapy (24). However, second-generation EGFR-TKIs do not effectively address the T790M mutation nor improve survival in NSCLC patients who have progressed after initial treatment with first-generation EGFR-TKIs (15).

The third-generation EGFR-TKIs have been developed to target the T790M mutation, inhibiting EGFR activity from preventing, slowing, or halting the growth of NSCLC. These personalized treatment options include osimertinib, aumolertinib, furmonertinib, and lazertinib (5,25-29). Currently, osimertinib is the standard first-line treatment for metastatic EGFR-mutant NSCLC (5). For advanced EGFR-mutant NSCLC, receiving EGFR-TKIs is superior to chemotherapy, which is the consensus of many investigators (20). However, EGFR-TKIs are cytostatic rather than cytotoxic agents and cannot eradicate micrometastatic tumor cells, even with highly significant clinical efficacy (30). Despite durable remissions, the median PFS of first-generation EGFR-TKIs (gefitinib and erlotinib) is approximately 1 year due to acquired resistance (9). The FLAURA study shows a median PFS of 18.9 months in locally advanced or metastatic NSCLC patients treated with third-generation EGFR-TKI (osimertinib) (31). LUX-Lung 7 (afatinib *vs.* gefitinib, phase IIB) (32), ARCHER-1050 (dacomitinib *vs.* gefitinib, phase III) (33) and FLAURA trial (osimertinib *vs.* gefitinib or erlotinib, phase III) (34) demonstrate that second- and third-generation EGFR-TKIs have better outcome superior to first-generation EGFR-TKIs (*Table 2*).

Osimertinib, the most popular third-generation EGFR-TKI, demonstrates efficacy in EGFR T790M-positive NSCLC patients who experience disease progression

following treatment with first or second-generation EGFR-TKIs (7). The median PFS for patients with sensitive mutations treated with osimertinib is 19.17 months, while for EGFR T790M-positive patients, it is 10.58 months (35). Osimertinib's high selectivity in inhibiting EGFR-sensitive mutations and T790M mutations prevents the development of T790M mutations in patients when used as a first-line therapy (34,36). Some advanced EGFR T790M NSCLC patients may lose the mutation after initial treatment with osimertinib (37). However, not all EGFR-mutant NSCLC patients benefit from EGFR-TKIs and some still experience disease progression (2,38). Following resistance to third-generation EGFR-TKIs, patients have limited standard targeted agent options, with little benefit from cytotoxic chemotherapy or immunotherapy. Therefore, personalized treatment and combination therapy involving EGFR-TKIs are crucial to enhance patient survival outcomes (9).

Substituting the cysteine residue at position 797 in the ATP-binding pocket with a serine prevents the covalent binding of osimertinib to EGFR, resulting in acquired resistance to osimertinib in NSCLC patients. The incidence of the C797S mutation is 7% in first-line treatment with osimertinib and 26% in second-line treatment (36). Rare EGFR mutations that lead to osimertinib resistance include G796X, which disrupts osimertinib binding; L792X, affecting the kinase's 'hinge' region; L718X in the P-loop causing spatial blockage; and G724S inducing conformational changes incompatible with drug binding (39). Studies also suggest that the G796 R/S mutation, L792 residue mutation, transmutation of C797, and L718V mutation can interfere with osimertinib binding to EGFR (40). Understanding resistance mechanisms to EGFR-TKIs is crucial for progress in this field and the development of new therapies (39). Despite advancements, a large percentage of resistance mechanisms to EGFR-TKIs, particularly after first-line treatment with osimertinib, remain unknown. Resistance to EGFR-TKIs is complex, involving multiple mechanisms and potential tumor heterogeneity, posing a significant challenge to overcome (39).

ASP8273 has shown antitumor activity by inhibiting 19del, L858R, and T790M. In phase III clinical trials comparing ASP8273 with erlotinib or gefitinib, it effectively targeted inhibition of T790M but resulted in higher toxic effects like hyponatremia and peripheral sensory neuropathy. For stage IIIB/IV NSCLC patients, ASP8273 did not demonstrate improved PFS compared to erlotinib or gefitinib (9.3 *vs.* 9.6 months) (41). Ongoing development of new EGFR-TKIs includes third-generation EGFR-TKIs (rociletinib and PF 06747775) and fourth-generation EGFR-TKIs (EAI 045, CH 7233163, JBJ-04-125-02, BLU-945, and BLU-701). EAI 045 targets the C797S mutation found in third-generation drugs. *In vitro*, EAI 045 inhibits the L858R-T790M mutant form of EGFR alone but not *in vivo*; however, when combined with cetuximab, it successfully inhibits L858R-T790M and L858R-T790M-C797S-driven lung cancer in a mouse model. This combination significantly enhances efficacy, though the associated toxicity of cetuximab may restrict its clinical use (42,43). CH 7233163 has shown inhibition of NSCLC cells with the 19del-T790M-C797S triple EGFR mutation both *in vitro* and *in vivo* (44). JBJ-04-125-02 has demonstrated inhibition of the L858R-T790M-C797S form of EGFR in both *in vitro* and *in vivo* studies, potentially showing a more robust response when combined with osimertinib (45). BLU-945 and BLU-701 are new potent fourth-generation EGFR-TKIs that can cross the blood-brain barrier and retain wild-type EGFR. In preclinical studies, BLU-945 has demonstrated effectiveness against triple-mutant EGFR isoforms (L858R or 19del, T790M, and C797S), while BLU-701 has shown activity against double mutations (the sensitive mutation and C797S) (39,46). Given that T790M did not develop with first-line osimertinib treatment, BLU-701 could be a crucial treatment option. Both BLU-945 (NCT 04862780) and BLU-701 (NCT 05153408) are currently undergoing early clinical trials (39). Despite the recent success in EGFR-TKI research, there is still significant potential in exploring combination therapy regimens involving EGFR-TKIs (9).

Analysis of the EGFR-TKIs' molecular structure allows us to gain a more comprehensive understanding. Like the first-generation TKIs, second-generation TKIs feature an anilinoquinazoline core, but they can form covalent bonds with the sulfur atoms of Cys797, enabled by the inclusion of an acrylamide slug moiety. However, second-generation TKIs exhibit reduced selectivity for mutant EGFR, potentially resulting in epithelial toxicity. Additionally, the quinazoline portion of second-generation TKIs interacts adversely with the side chain of Met790, necessitating the administration of relatively high doses. Third-generation TKIs offer irreversible, selective inhibition of the T790M mutation and use an anilinopyrimidine scaffold that maximizes and stabilizes their interactions within the ATP-binding pocket. To address the C797S mutation, researchers have developed fourth-generation TKIs that target triple mutants, including both variant and ATP-

competitive inhibitors. Variant inhibitors are derivatives of oxoisoindoline phenylacetamide. Currently, at least five fourth-generation ATP-competitive reversible EGFR-TKIs are undergoing clinical trials. These compounds share an anilinopyrimidine scaffold, highlighting the heterocyclic portion's critical role in interacting with the ATP-binding pocket (47).

Combination therapies based on EGFR-TKIs

Combining EGFR-TKIs with anti-VEGF therapy

VEGF is a group of genetically encoded polypeptide molecules, such as VEGF-A, -B, -C, and -D (48), that promote angiogenesis to support tumor growth (49). The VEGF and EGFR pathways share common downstream signaling pathways and interact to affect tumor growth (48). In EGFR-mutant NSCLC, overexpressed EGFR can upregulate hypoxia-inducible factors like HIF-1 through a mechanism independent of hypoxia, leading to increased VEGF expression (50). This elevated VEGF level contributes to the development of resistance to EGFR-TKIs (51). VEGF signaling also aids tumor growth by activating the pro-survival effects of the PI3K/AKT pathway and the MAPK pathway for proliferation (51). Anti-angiogenic monoclonal antibodies that block the VEGF pathway, bevacizumab, and ramucirumab, were approved by the United States Food and Drug Administration as first-line treatments for advanced or metastatic non-squamous NSCLC in 2006 and 2014, respectively (48,52). Bevacizumab inhibits tumor angiogenesis and improves EGFR-TKIs delivery, making it a promising antitumor agent (9). Ramucirumab selectively targets *VEGFR2* and blocks *VEGFA*, *VEGFC*, and *VEGFD*-mediated signaling in NSCLC. Thus, ramucirumab has the potential for broader antitumor activity than VEGF inhibitors (51). Vandetanib (53), nintedanib (54) and cediranib (55) are VEGFR-TKIs used for NSCLC. The mechanisms involved in combination therapy can be seen in *Figure 1*.

In clinical trials, the addition of anti-VEGF agents to EGFR-TKI therapy has significantly improved clinical outcomes (51). CTONG1706, the first phase III clinical trial conducted in China, evaluated gefitinib in combination with apatinib for first-line treatment of EGFR-mutant NSCLC. The study randomized 313 patients with primary advanced NSCLC harboring EGFR 19del or L858R mutations equally into the experimental group (gefitinib, 250 mg/d; apatinib, 500 mg/d) and the placebo group (gefitinib, 250 mg/d; placebo, 500 mg/d). The Independent Radiologic Review Board reported a median PFS of 13.7 months in the experimental group and 10.2 months in the placebo group. Although combination therapy led to more complications like hypertension (46.5%) and proteinuria (17.8%), it did not impact the quality of life (16). Stratified analysis based on mutation types showed that the combination therapy prolonged PFS in the 19del subgroup but not significantly in the L858R subgroup. Patients with TP53 exon 8 mutation tended to benefit from the experimental group, suggesting that TP53 mutation status could potentially serve as a biomarker to predict the efficacy of EGFR-TKIs combined with anti-angiogenic drugs (16).

Two-phase III clinical trials (CTONG1509, NEJ026) have shown that the median PFS with bevacizumab in combination with erlotinib was significantly longer than with erlotinib alone (9,56). Although Kawashima *et al.*'s study did not find a survival benefit with the combination, hypothesizing that the treatment regimen in advanced patients with disease progression may impact the efficacy of this combination (9). It is worth noting that the evidence category for erlotinib in combination with bevacizumab has been upgraded from 2B to 2A in the National Comprehensive Cancer Network guidelines (16).

Several studies have investigated the combination of EGFR-TKIs and anti-VEGF agents, including JO 25567 (bevacizumab + erlotinib *vs.* erlotinib; phase II), ACCRURC 1126 (bevacizumab + erlotinib *vs.* erlotinib; phase II), RELAY (ramucirumab + erlotinib *vs.* erlotinib; phase III), and BEVERLY (bevacizumab + erlotinib *vs.* erlotinib; phase III) (17). These studies demonstrated improved PFS with the combination therapy (57). The RELAY regimen has shown promise in treating advanced EGFR-mutated NSCLC patients (58). Clinical trials, such as the phase II trial NCT 02803203, have indicated that osimertinib, in combination with bevacizumab, can improve PFS (59). However, other trials have not shown the same benefit (60). Ongoing clinical trials also investigate the combination of osimertinib and ramucirumab, as seen in NCT 02789345 (58).

The selection of combination therapy regimens for patients with different EGFR-mutant NSCLCs is still controversial, particularly concerning the use of higher-generation EGFR-TKIs (16). Although this combination therapy may lead to more grade 3 or worse adverse events, it has not resulted in patient mortality (31). Further research is necessary to determine the optimal combination of EGFR TKIs and anti-VEGF therapies (9).

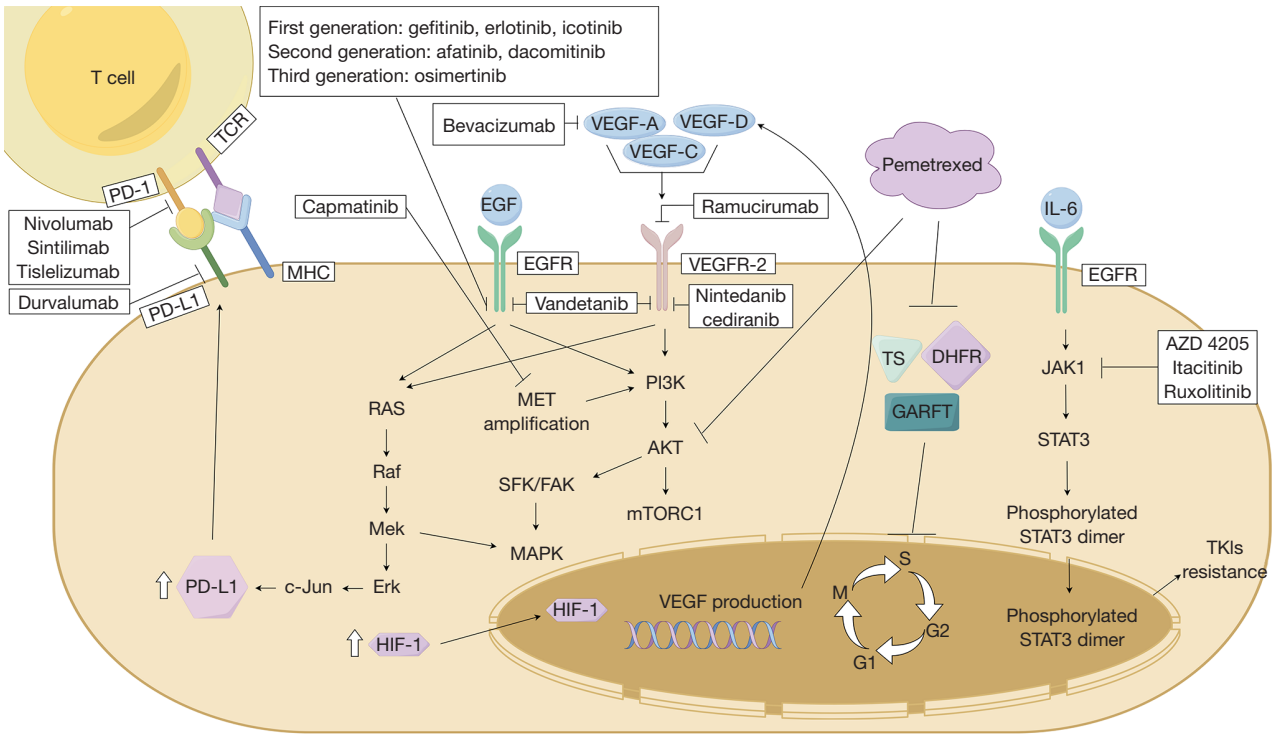

Figure 1 Molecular mechanisms of drug combination therapy for advanced NSCLC. Both EGFR and VEGFR-2 signaling activate the PI3K/AKT and Ras/Raf/Mek pathways. EGFR activation induces HIF-1 upregulation, leading to *VEGF* gene expression and a subsequent positive feedback loop. Small molecule inhibitors of the EGFR (erlotinib, gefitinib, icotinib, afatinib, dacomitinib, osimertinib, and vandetanib), small molecule inhibitors of VEGFR-2 (vandetanib, nintedanib and cediranib), as well as monoclonal antibodies targeting the extracellular structural domain of VEGFR-2 (ramucirumab) or inhibiting the VEGF-A protein (bevacizumab) have demonstrated efficacy. Pemetrexed inhibits thymidylate synthase, dihydrofolate reductase, and glycinamide ribonucleotide formyltransferase activities to impede DNA synthesis and cell division. Pemetrexed also suppresses the Akt pathway. MET amplification activates the PI3K/Akt pathway; capmatinib is an inhibitor of MET. Activation of the EGFR pathway up-regulates PD-L1 expression; durvalumab inhibits PD-L1 while nivolumab, sintilimab, and tislelizumab inhibit PD-1. IL-6 triggers JAK1/STAT3 signaling pathway activation leading to TKI resistance; AZD 4205, itacitinib and ruxolitinib are inhibitors of JAK1. This picture was drawn using Figdraw (www.figdraw.com). AKT, protein kinase B; c-Jun, jun proto-oncogene; DHFR, dihydrofolate reductase; EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; Erk, extracellular signal-regulated kinases; FAK, focal adhesion kinase; GARFT, glycinamide ribonucleotide formyltransferase; HIF-1, hypoxia-inducible factor 1; IL-6, interleukin-6; JAK1, Janus kinase 1; MAPK, mitogen-activated protein kinase; Mek, mitogen-activated extracellular signal-regulated kinase; MET, mesenchymal epithelial transition factor; MHC, major histocompatibility complex; MTORC1, mechanistic target of rapamycin complex 1; PD-1, programed death receptor-1; PD-L1, programed death ligand-1; PI3K, phosphatidylinositol 3-kinase; Raf, rapidly accelerated fibrosarcoma; Ras, rat sarcoma; SFK, Src family kinase; STAT3, signal transducer and activator of transcription 3; TCR, T-cell receptor; TKIs, tyrosine kinase inhibitors; TS, thymidylate synthase; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor; NSCLC, non-small cell lung cancer.

Combining EGFR-TKIs with JAK inhibitors

The signal transducer and activator of transcription (STAT) is phosphorylated by JAK, dimerizes, and then translocates through the nuclear membrane into the nucleus to regulate the expression of relevant genes. This pathway is known as the JAK/STAT signaling pathway (61). In the presence of EGFR-TKIs, NSCLC cells with the EGFR T790M mutation develop drug resistance by producing interleukin-6 and activating the JAK1/STAT3 signaling pathway (15).

Knockdown of STAT3 through siRNA or JAK inhibitors enhances the antitumor effects of afatinib in

the EGFR T790M NSCLC xenograft model. In a study by Park *et al.*, 30 advanced NSCLC patients who had progressed after EGFR-TKI treatment were treated with afatinib monotherapy for 8 days, followed by concurrent administration of ruxolitinib and afatinib until disease progression. The median PFS was 4.9 months [95% confidence interval (CI): 2.5–7.3] in T790M+ patients and 3.1 months (95% CI: 0–8.8) in T790M– patients (P=0.21). While this was lower than results from other studies like the AURA study, the AURA study phase II extension, and the AURA phase III study with osimertinib, the combination of afatinib and ruxolitinib showed promising clinical efficacy in T790M+ patients. Targeting the JAK1/STAT3 pathway could be a potential therapeutic strategy for EGFR-mutant NSCLC patients, although it may not be sufficient to overcome drug resistance in T790M NSCLC (15). A novel JAK1 inhibitor, AZD 4205, has shown enhanced antitumor activity when combined with osimertinib in mouse transplantation models of NSCLC (62). Clinical trials also investigate the combination of osimertinib with itacitinib (JAK1 inhibitor) for NSCLC (NCT 02917993) (7).

Combining EGFR-TKIs with MET-TKIs

MET plays a crucial role in promoting tumor cell migration, invasion, and proliferation through various transduction pathways, including PI3K-AKT-mTOR, RAS-MAPK, RASCDC42-PAK-Rho kinase, and β-collagen signaling pathways. Driver mutations in MET, such as exon 14 jump alterations and MET amplification, have been linked to cancer progression and a poorer prognosis for patients (63). Specifically, patients with MET amplification have shown limited response to EGFR-TKIs in targeted therapy for NSCLC (64). Approximately 3–4% of stage IV non-squamous NSCLC patients exhibit tumor progression due to MET pathway activation through MET mutations or amplification. MET amplification is a known mechanism of acquired resistance to EGFR-TKIs, particularly after treatment with third-generation EGFR-TKIs like osimertinib, with around 15% of resistant patients showing MET amplification. However, the actual prevalence may be higher, as this data was derived from liquid biopsy analysis, which is less sensitive than tissue testing (14).

In EGFR-mutant NSCLC patients, combining EGFR-TKIs with MET-TKIs like capmatinib shows promise in improving outcomes for patients resistant to various generations of EGFR-TKIs. Capmatinib, a potent MET pathway inhibitor, demonstrates antitumor activity in NSCLC both *in vitro* and *in vivo*. The combination therapy may help overcome resistance to EGFR-TKIs through the MET pathway (14). Studies indicate that capmatinib treatment leads to tumor regression in MET-dependent models (65,66) and reverses the effects of MET activation on EGFR and HER-3 pathways (65), potentially restoring sensitivity to EGFR-TKIs in resistant NSCLC cell lines (67). These findings highlight the potential of capmatinib in inhibiting the MET pathway and enhancing the effectiveness of EGFR-TKIs in treating resistant tumors (14).

A study evaluating the use of third-generation EGFR-TKI (nazartinib) in combination with capmatinib for NSCLC treatment reported an overall response rate (ORR) of 42% across all dose levels, increasing to 50% at the 400 mg capmatinib/100 mg nazartinib dose level. Initial antitumor activity was observed at various dose levels (14). Another phase Ib/II study combining capmatinib with gefitinib in NSCLC patients with acquired resistance to EGFR-mutated disease (without T790M mutation but altered MET) showed an ORR of 23% and disease control rate (DCR) of 57% across all dosage groups, irrespective of MET status. In a subgroup analysis by *MET* gene copy number category, the best ORR observed was 47% in patients with *MET* gene copy number ≥6 (n=36), compared with 32% in patients with *MET* immunohistochemistry 3+ (n=78) (68). In EGFR-mutant NSCLC patients with acquired resistance due to high MET amplification, the combination of EGFR-TKIs and MET-TKIs demonstrated promising outcomes in advanced cases (14).

Combining EGFR-TKIs with ICIs

Cell adhesion molecules play a crucial role in tumor progression and immune evasion. ICIs combat tumor development by targeting irregularly expressed cell adhesion molecules. Among these molecules, programmed cell death-1 protein/ligand (PD-1/L1) and cytotoxic T-lymphocyte associated protein 4 (CTLA-4) have been extensively studied for their role in inducing tumor immunosuppression (69). Anti-PD-1/L1 and anti-CTLA-4 therapies have been utilized as primary or secondary treatments for advanced NSCLC, often in combination with radiotherapy, chemotherapy, yielding positive outcomes (69). ICIs have been advocated as standard treatment for advanced NSCLC without EGFR or ALK mutations. This is because few previous studies have used ICIs for advanced EGFR-mutant NSCLC, and ICIs

should not be used in EGFR-mutant NSCLC based on several retrospective single-agent studies of ICIs (70). The preclinical study indicates that activation of the EGFR pathway may upregulate PD-L1 expression on tumor cells, supporting the potential benefit of combining EGFR-TKIs with ICIs to enhance antitumor effects (71).

Yang *et al.* compared the efficacy and safety of osimertinib in combination with durvalumab (n=12) with osimertinib monotherapy (n=17) in 29 advanced EGFR-mutant patients who had acquired the T790M mutation after treatment with an EGFR-TKI in the phase III clinical trial (CAURAL). CAURAL enrollment was terminated early due to the high incidence (38%, 13/34) of interstitial lung disease in a phase Ib clinical trial of osimertinib combined with durvalumab for EGFR-mutant NSCLC (NCT 02143466). Unfortunately, the small sample size of the CAURAL trial did not allow for formal safety and efficacy comparisons (12). However, trials in which erlotinib and nivolumab were treated proved that the combination was tolerable (72). There is no clear evidence that PD-1/L1 inhibitors combined with EGFR-TKIs can enhance anti-NSCLC efficacy and benefit advanced EGFR-mutant NSCLC patients (12,73). The other study showed that the use of osimertinib after treatment with ICIs was associated with a high incidence of severe immune-related adverse reactions (irAEs) (14.6%, 6/41), which did not occur in patients receiving osimertinib or other EGFR-TKIs followed by ICIs. These cases guide the clinical use of ICIs in advanced NSCLC patients resistant to EGFR-TKIs (70). In advanced NSCLC patients with the T790M mutation, the sequential administration of nivolumab followed by osimertinib can lead to grade 3 or higher hepatotoxicity (69). While ICIs have shown significant advancements in NSCLC treatment, drug resistance, and irAEs have hindered their full potential (69). Interestingly, one study found that responders had a higher incidence of irAEs compared to non-responders (65.2% *vs.* 19.3%, P<0.01), suggesting a potential link between irAEs and treatment efficacy (74). Common irAEs include pruritus, colitis, cardiovascular toxicity, peritonitis, and interstitial lung disease (69). Sintilimab and tislelizumab are two cost-effective domestic anti-PD-1 monoclonal antibodies. The future of NSCLC treatment may involve dual ICI therapy (combination of anti-PD-1 and anti-CTLA-4), as well as exploration of tumor vaccines and CAR-T cell therapies (69). Further research on the combination of EGFR-TKIs with ICIs holds promise for achieving more excellent treatment outcomes.

Combining EGFR-TKIs with chemotherapy

Chemotherapy and EGFR-TKIs synergistically induce apoptosis and inhibit Akt and extracellular signal-regulated kinase phosphorylation, potentially delaying the development of resistance (75). Pemetrexed reduces thymidine synthase expression and inhibits T790M production, exerting its anti-NSCLC effect (76,77). Gefitinib selectively inhibits EGFR into the nucleus, reduces DNA-dependent protein kinase activity, and enhances the cytotoxicity of cisplatin in NSCLC. This is how targeted agents are combined with chemotherapy to enhance efficacy (78).

Multiple studies have shown that combining EGFR-TKIs and chemotherapy is more effective in advanced EGFR-mutant NSCLC patients (11,79-81). Combination chemotherapy with gefitinib plus pemetrexed and platinum significantly improved PFS and OS, with more significant benefit achieved in the combination therapy group (estimated median PFS 16 months; OS not reached) compared with the gefitinib group (estimated median PFS =8 months; OS =17 months). However, this benefit came at the cost of a higher incidence of grade 3 or higher toxicity in the combination therapy group (75%) compared to the gefitinib group (49.4%) (11). Previous studies on gefitinib combined with chemotherapy for the initial treatment of advanced EGFR-mutant NSCLC have reported improvements in PFS and OS in the combination therapy group (11,82-84). A meta-analysis involving 1,349 individuals concluded that first-generation TKIs combined with platinum-based two-agent chemotherapy provided significant benefits in terms of ORR, PFS, and OS (85). Patients with low-abundance EGFR-mutated NSCLC had inferior outcomes compared to those with high-abundance EGFR-mutated phenotypes when treated with EGFR-TKIs (86). However, combining EGFR-TKIs with chemotherapy improved both PFS and OS in patients with low-abundance EGFR-mutated phenotypes (87). A study demonstrated that concurrent treatment with gefitinib in combination with pemetrexed and carboplatin leads to longer OS compared to sequential therapy (88). Therefore, concurrent administration of TKI and chemotherapy is recommended for patients with T790M-negative advanced lung cancer who have experienced progression after initial EGFR-TKI therapy (89). In a study comparing gefitinib or icotinib combined with pemetrexed for EGFR-mutant advanced NSCLC, stratified analysis revealed that patients

with concurrent mutations in TP53, KRAS, PIK3CA, and MLH1 had a poorer PFS with EGFR-TKIs monotherapy (P=0.002) (79). In a retrospective study, patients with advanced NSCLC who progressed during treatment with osimertinib had a higher survival rate when receiving chemotherapy regimens compared to non-chemotherapy regimens. The median OS was 25.0 months for those receiving chemotherapy regimens, compared to 11.8 months for those receiving non-chemotherapy regimens (90). Shang *et al.* evaluated the safety and efficacy of EGFR-TKIs monotherapy (Group T) or combined with pemetrexed-based chemotherapy (Group TC) in 95 advanced NSCLC patients with EGFR/TP53 co-mutations and compared with Group T, Group TC showed significantly improved ORR (55.9% *vs.* 34.4%, P=0.042), median time to progression (16.1 *vs.* 11.1 months, P=0.002) were improved, but OS was not significantly prolonged. The median OS of patients without brain metastases in Group TC was longer than in Group T (48.4 *vs.* 28.8 months, P=0.003) (91). Although grade 3 treatment-related AEs occurred higher in Group TC than in Group T (32.4% *vs.* 13.1%), combination therapy remains a promising treatment approach for advanced NSCLC patients harboring EGFR/TP 53 co-mutations without brain metastases, especially considering that there are no drugs on the market that specifically target TP53 for the treatment of advanced NSCLC (91).

Brain metastases are a significant challenge in EGFR-mutant NSCLC patients undergoing first-generation EGFR-TKI treatment (92). The combination of gefitinib, carboplatin, and pemetrexed can delay drug resistance but does not prevent brain metastases (84). Approximately 30% of NSCLC patients develop brain metastases, with around half presenting with brain metastases at the time of diagnosis and the remainder developing them during treatment (93). Systemic therapy and whole-brain radiotherapy show promise in treating intracranial progression of baseline brain tumors (40). Osimertinib, particularly when combined with platinum-based chemotherapy, demonstrates superior efficacy in patients with brain metastases, leading to fewer central nervous system progressions, improved remission rates, and enhanced quality of life (80). Despite limited central nervous system penetration by certain drugs, such as cisplatin, carboplatin, and pemetrexed (80), there is speculation that their efficacy in treating brain metastases may be linked to blood-brain barrier disruption (94).

Combining EGFR-TKIs with radiotherapy

Previous randomized trials have demonstrated the efficacy of radiation therapy in treating oligometastatic NSCLC. However, the effectiveness of this treatment in advanced EGFR-mutant NSCLC patients remains uncertain (95,96).

The SINDAS phase III clinical trial revealed that local radiotherapy is safe and improves PFS and OS in patients with oligometastatic disease and EGFR mutations. Median PFS was 12.5 months in the EGFR-TKI-treated group and 20.2 months in the group that received TKI + radiotherapy. Median survival was 17.4 and 25.5 months, respectively, indicating a statistically significant difference (97). A prospective study involving advanced NSCLC patients with EGFR-sensitive mutations compared EGFR-TKI treatment alone and stereotactic body radiation therapy (SBRT) + EGFR-TKI treatment. After 3 months of EGFR-TKI treatment, patients in the combination group received SBRT. As of February 14, 2022, the SBRT + EGFR-TKI group had a median PFS of 17.6 months and a median OS of 33.6 months, while the EGFR-TKI group had a median PFS of 9 months and a median OS of 23.2 months. The addition of SBRT delayed the onset of acquired resistance to EGFR-TKIs, leading to prolonged PFS and OS. This study highlights the potential of SBRT in improving outcomes for patients with oligometastatic EGFR-mutant advanced NSCLC receiving first-generation EGFR-TKIs. Notably, patients who received primary site radiotherapy alone had the most favorable prognosis, with PFS and OS of 27.3 and 49.1 months, respectively (10).

The SINDAS trial illustrated the potential survival benefits of radiotherapy in patients with oligometastatic EGFR-mutant NSCLC. However, this study had limitations, such as excluding patients with brain metastases at enrollment and focusing on first-generation EGFR-TKIs (gefitinib, erlotinib, and icotinib) without considering other TKIs (97). The NORTHSTAR trial, utilizing osimertinib and allowing for some brain metastases, will address the gaps identified in the SINDAS trial (98). Combining EGFR-TKIs with local radiotherapy may still provide additional benefits to patients. Therefore, radiation therapy should be considered even when targeted therapy is being administered (97).

Combining EGFR-TKIs with surgery

Resistance to targeted therapies leads to tumor recurrence

in a majority of patients with oncogene-driven advanced NSCLC. Around 60% of NSCLC patients experience their initial disease progression at the primary site (99,100). Following a positive response to EGFR-TKIs, local consolidation therapy directed at residual cancer cells may help overcome resistance and enhance survival (30). Traditionally, treating advanced NSCLC has focused on disease control, symptom management, and enhancing quality of life rather than curative surgery (101). Nevertheless, several studies have highlighted the survival advantages of surgical resection in carefully selected advanced patients, some of whom have extended their survival through surgery (102,103). Surgery can play a critical role in a comprehensive treatment strategy (13).

Kuo *et al.* conducted a retrospective analysis comparing stage IV patients who underwent primary tumor resection and targeted therapy (n=56) to those who only received targeted therapy (n=224). The long-term follow-up revealed a median PFS of 29.6 months (95% CI: 18.9–40.3) for the surgical group and 13.0 months (95% CI: 11.8–14.2) for the control group (P<0.001). Progression rates were 51.8% and 92.4% for the surgical and control groups, respectively, indicating the potential benefits of primary tumor resection alongside EGFR-TKIs for EGFR-mutant NSCLC patients (13). Park *et al.* retrospectively analyzed 44 patients who underwent lung surgery post-targeted therapy, reporting 2-year PFS and OS rates of 70.8% and 95.0%, respectively, with minimal complications. However, the long-term impact of pneumonectomy on survival post-targeted therapy requires further investigation, particularly considering the inclusion of patients with non-EGFR mutations in the study (30). The survival benefits observed after resection of primary lung tumors may be attributed to reduced tumor load and increased heterogeneity at the primary site (13).

Lung surgery is a viable option for advanced NSCLC patients who have previously undergone targeted therapies. It can provide adequate specimens for detailed genetic analysis, aiding in developing newer treatment plans. Moreover, surgery can uncover pleural metastases that may be missed by imaging and assess the thoracic cavity for metastases (30). As targeted therapies continue to advance, surgery may have a role in local consolidation therapy for these patients (101). The combination of EGFR-TKIs with surgery shows promise as a therapeutic approach. Several important aspects need to be carefully considered and further investigated in this study. These include the optimal timing of surgery, the duration of preoperative targeted therapy, specific patient selection criteria for surgery, and the extent of surgical resection (30). Some cited articles did not provide trial numbers. *Table 3* only summarizes a part of clinical trials.

Factors affecting EGFR-TKIs in treating patients with advanced NSCLC

Various factors influence the clinical prognosis and effectiveness of EGFR-TKIs in treating advanced NSCLC patients, with genetic mutations playing a significant role. These include EGFR mutations (19del, L858R, T790M, exon20ins), and other conditions (20,104-106). Research indicates that patients with 19del mutations may have a more favorable prognosis than those with L858R mutations (20,104,107). Moreover, a retrospective study has shown that osimertinib demonstrates superior efficacy in patients who develop T790M mutations following first-line EGFR-TKI treatment (104). Additionally, analysis by Bazhenova *et al.* involving 2,825 patients treated with EGFR-TKIs revealed that patients with exon20ins mutations had a poor prognosis and minimal benefit, with a median real-world OS of 2.9 months compared to 10.5 months in patients with common EGFR mutations (107). Genetic factors such as BIM deletion polymorphisms, MET amplification, HER2 amplification, and AXL activation and amplification have been observed to impact the clinical outcomes and effectiveness of EGFR-TKIs in treating advanced NSCLC patients (7). A study examined the impact of PD-L1 expression on the prognosis of advanced NSCLC patients treated with first/second-generation EGFR-TKIs. Patients with high PD-L1 expression had a PFS of 6.6 months and an OS of 11.5 months, significantly lower than those with low PD-L1 expression (PFS: 13.0 months, OS: 32.9 months). This suggests that high PD-L1 expression is linked to early EGFR-TKIs resistance and lower survival rates, making it a more effective predictive biomarker than physical status, mutation type, and disease site (105). Additionally, the presence of seven driver genes (*ALK*, *KRAS*, *BIM*, *PIK3CA*, *MET*, *IGF1R*, and *PTEN*) as resistance genes was identified through multigene coanalysis of EGFR-sensitive mutations in advanced patients. It was observed that carriers of resistance genes with aberrant alterations in the EGFR signaling pathway had significantly lower PFS compared to those with normal EGFR signaling. Furthermore, phosphatase and tensin homolog (PTEN) deletion, low expression, and MET fluorescence in situ hybridization (FISH)+ were identified

Table 3 Some clinical trials of the combination therapy are as follows

Experiment registration number	Phase	Pts	Stage	Treatment arm(s)	Primary endpoint(s)	Ref
JPRN-UMIN 000017069	3	226	IIIB, IV	Erlotinib + bevacizumab; erlotinib	PFS	(9)
NCT02824458	3	313	IIIB, IV	Gefitinib + apatinib; gefitinib	PFS	(16)
NCT02759614	3	311	IIIB, IV	Bevacizumab + erlotinib; erlotinib	PFS	(56)
NCT02633189	3	160	IIIB, IV	Erlotinib + bevacizumab; erlotinib	PFS	(17)
NCT02411448	3	211	IV	Ramucirumab + erlotinib; erlotinib	PFS	(57)
NCT02803203	1/2	49	IV	Osimertinib + bevacizumab	Number of patients who were progression-free at 12 months	(59)
JPRN-UMIN 000023761	1/2	80	IV	Osimertinib + bevacizumab; osimertinib	PFS	(60)
NCT02145637	1	30	IV	Afatinib + ruxolitinib	RP2D, DLT, MTD	(15)
NCT02454933	3	29	IIIA, IIIB, IV	Osimertinib + durvalumab; osimertinib	AEs	(12)
NCT01454102	1	21	IIIB, IV	Nivolumab + erlotinib;	AEs	(72)
CTRI/2016/08/007149	3	350	IIIB, IV	Gefitinib + pemetrexed + carboplatin; gefitinib	PFS	(11)
NCT02148380.	3	81	IIIB, IV	Pemetrexed + carboplatin + gefitinib; gefitinib	PFS	(82)
JPRN-UMIN 000006340	3	345	IIIA, IIIB, IV	Pemetrexed + carboplatin + gefitinib; gefitinib	PFS, PFS2, OS	(83)
NCT02886195	2	21	IV	Gefitinib + carboplatin + pemetrexed	PFS	(84)
JPRN-UMIN 000002789	2	80	IIIB, IV	Concurrent gefitinib + carboplatin + pemetrexed; sequential alternating gefitinib + carboplatin + pemetrexed	PFS	(88)
NCT03544814	2	99	IIIB, IV	First icotinib and then pemetrexed + cisplatin; icotinib combined with pemetrexed + cisplatin	PFS	(89)
NCT02893332	3	133	IV	First-generation TKI (gefitinib/erlotinib/icotinib); first-generation TKI (gefitinib/erlotinib/icotinib) + RT	PFS	(97)
NCT03595644	2	62	IV	First-generation TKI (gefitinib/erlotinib/icotinib); first-generation TKI (gefitinib/erlotinib/icotinib) + SBRT	PFS	(10)
NCT03410043	2	143	IIIB, IV	Osimertinib + surgery or RT; osimertinib	PFS	(98)

Pts, patients; PFS, progression-free survival; RP2D, recommended phase 2 dose; DLT, dose-limiting toxicities; MTD, maximum tolerated dose; AEs, adverse events; PFS2, progression-free survival 2; OS, overall survival; TKI, tyrosine kinase inhibitor; RT, radiotherapy; SBRT, stereotactic body radiation therapy.

as independent predictors of PFS in patients with EGFR-TKI prolongation after adjusting for multiple factors (108).

In addition to genetic background, clinical factors can impact the effectiveness of EGFR-TKIs in treating advanced EGFR-mutant NSCLC patients. Lin *et al.* conducted a study on 94 patients and found that various factors such as gender, smoking history, pathology type, EGFR mutation type, brain metastasis, and duration of targeted therapy did not significantly affect patient outcomes. The Eastern Cooperative Oncology Group score was identified as an independent prognostic factor for PFS in advanced NSCLC patients, while both the Eastern Cooperative Oncology Group score and brain metastasis were identified as independent prognostic factors for OS (109). Interstitial lung disease grade was also found to influence the efficacy and prognosis of EGFR-TKIs, with higher grades correlating with a higher risk of early progression (110). Studies on serum tumor markers have shown that negative pro-gastrin-releasing peptide (ProGRP) and neuron-specific enolase (NSE) levels, as well

as a history of never smoking, may indicate longer PFS in patients treated with EGFR-TKIs. However, the predictive value of ProGRP and NSE is limited (111). However, additional studies of advanced patients have identified several factors that may affect the benefit of EGFR-TKIs, including EGFR mutation type, gender, performance status and smoking status (112-114).

Discussion

Primary tumor cells are anticipated to be conditionally reprogrammed, and single-cell level drug sensitivity assays can help determine the most effective medication for lung cancer patients (115,116). The selection of optimal medication is based on the overall response of the patient population to the drug, as in the current practice. The urgent need to identify drug resistance mechanisms and develop new targeted drugs is highlighted to overcome the challenge of long-term effective treatment for NSCLC patients with EGFR-TKIs. A comprehensive understanding of drug resistance mechanisms will assist physicians in exploring personalized treatment options, achieving precision therapy, and improving lung cancer patients' quality of life and survival rates. The type of EGFR mutation can vary during drug therapy, necessitating dynamic long-term patient management. Non-invasive liquid biopsy technology should be employed to monitor patients' EGFR mutation status continuously, and drug selection should be guided by the mutation status determined through histological biopsy (7). Several drugs currently in development, such as EAI 045, CH 7233163, JBJ-04-125-02, BLU-945, and BLU-701, hold promise for benefiting NSCLC patients in the future. Various therapeutic approaches for advanced EGFR-mutant NSCLC, including combinations of EGFR-TKIs with VEGF inhibitors, MET-TKIs, surgery, chemotherapy, and radiotherapy, have shown varying degrees of efficacy. However, no significant survival advantage has been observed when combined with JAK inhibitors and ICIs.

Conducting research and analysis on EGFR-TKIs to treat advanced EGFR-sensitive mutant NSCLC patients will enhance our understanding of the current landscape in this field and shed light on this specific patient population. This article offers a comprehensive overview of the current status of both monotherapy and combination therapy involving EGFR-TKIs, drawing insights from real-world data obtained from multiple clinical trials. It delves into treatment trends and influential factors and provides recommendations for clinicians on the selective use of medications and novel approaches for assessing the efficacy and prognosis of EGFR-TKIs in advanced NSCLC treatment. The limitations of this paper are objective, and since it is a summary of the current study, some of the findings need to be validated and explored in further large clinical trials.

Conclusions

Although EGFR-TKIs have largely improved the survival and prognosis of patients with EGFR mutations, more efforts are needed to benefit patients in the long term. Developing new EGFR-TKIs and combining other drugs based on EGFR-TKIs for lung cancer treatment will become a hotspot for future research. Overcoming drug resistance mechanisms, finding new targets, and improving efficacy through combination therapy will become the hope for patients with advanced lung cancer.

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Footnote

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