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EGFR-TKIs for lung cancer treatment: development, application, and side effects

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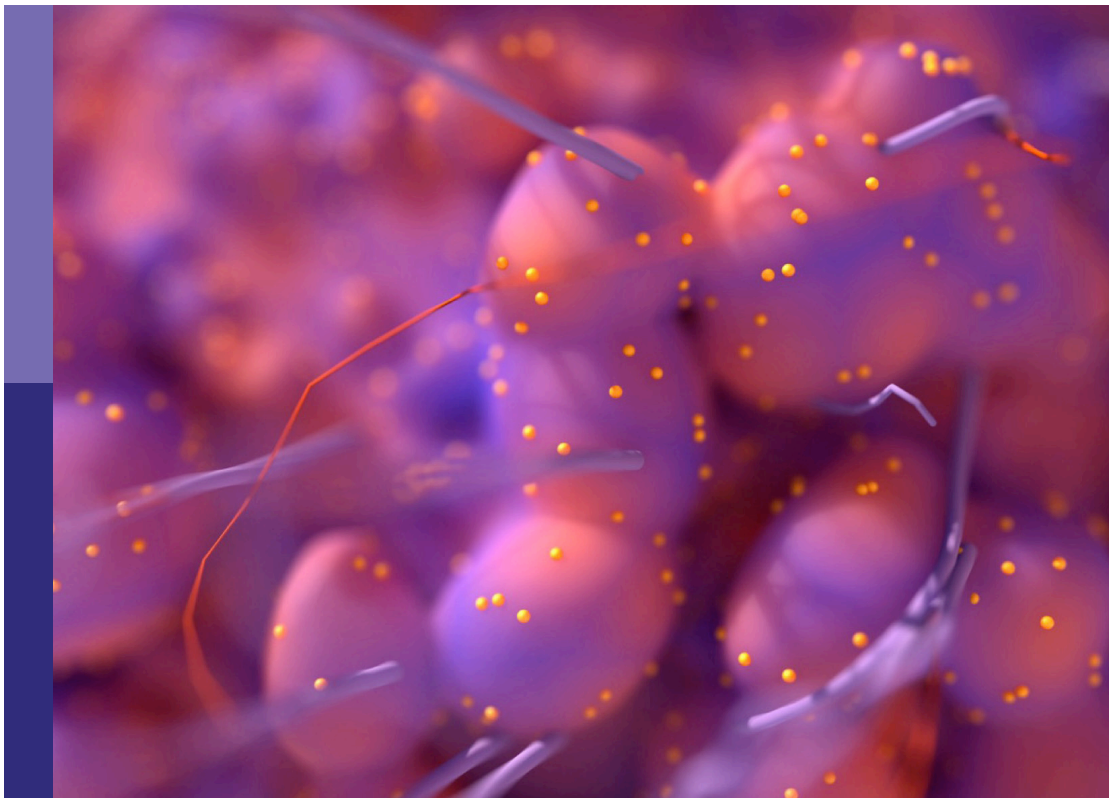

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EGFR-TKIs for lung cancer treatment: development, application, and side effects

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Editorial: EGFR-TKIs for lung cancer treatment: development, application, and side effects

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Editorial on the Research Topic
EGFR-TKIs for lung cancer treatment: development, application, and side effects

Introduction

Lung cancer remains one of the most challenging and lethal malignancies worldwide. Despite advances in early detection and prevention, non-small cell lung cancer (NSCLC), the most prevalent subtype, continues to be a clinical challenge. However, the field has been transformed by the advent of molecularly targeted therapies, particularly those aimed at the epidermal growth factor receptor (EGFR). These therapies have significantly prolonged survival and improved the quality of life for many patients. However, as this therapeutic era progresses, it brings increasing complexities, ranging from the emergence of drug resistance and treatment-related adverse effects to the shifting landscape of tumor biology.

This editorial explores the current landscape of EGFR-targeted therapy in NSCLC, highlighting clinical progress, emerging evidence, and the critical need for innovative approaches to overcome resistance and manage adverse events (Figure 1).

The advances in EGFR-TKI development

The discovery of EGFR mutations in 2004 and the subsequent development of small-molecule tyrosine kinase inhibitors (TKIs) marked a revolutionary step in lung cancer treatment (1). Osimertinib, afatinib, gefitinib, erlotinib, and newer agents such as aumolertinib and furmonertinib have redefined the standard of care for patients with EGFR-mutant NSCLC (2). These agents selectively target oncogenic drivers, disrupting cancer cell proliferation while sparing healthy tissue, thus offering a more tailored and less toxic alternative to chemotherapy.

Recent studies validate these advancements. For instance, a nationwide longitudinal study in Norway demonstrated a median overall survival (OS) of 23 months for EGFR+ patients diagnosed in recent years—a significant improvement compared to earlier cohorts (Nyen et al.). Meanwhile, aumolertinib, in addition to its efficacy, also showed remarkable

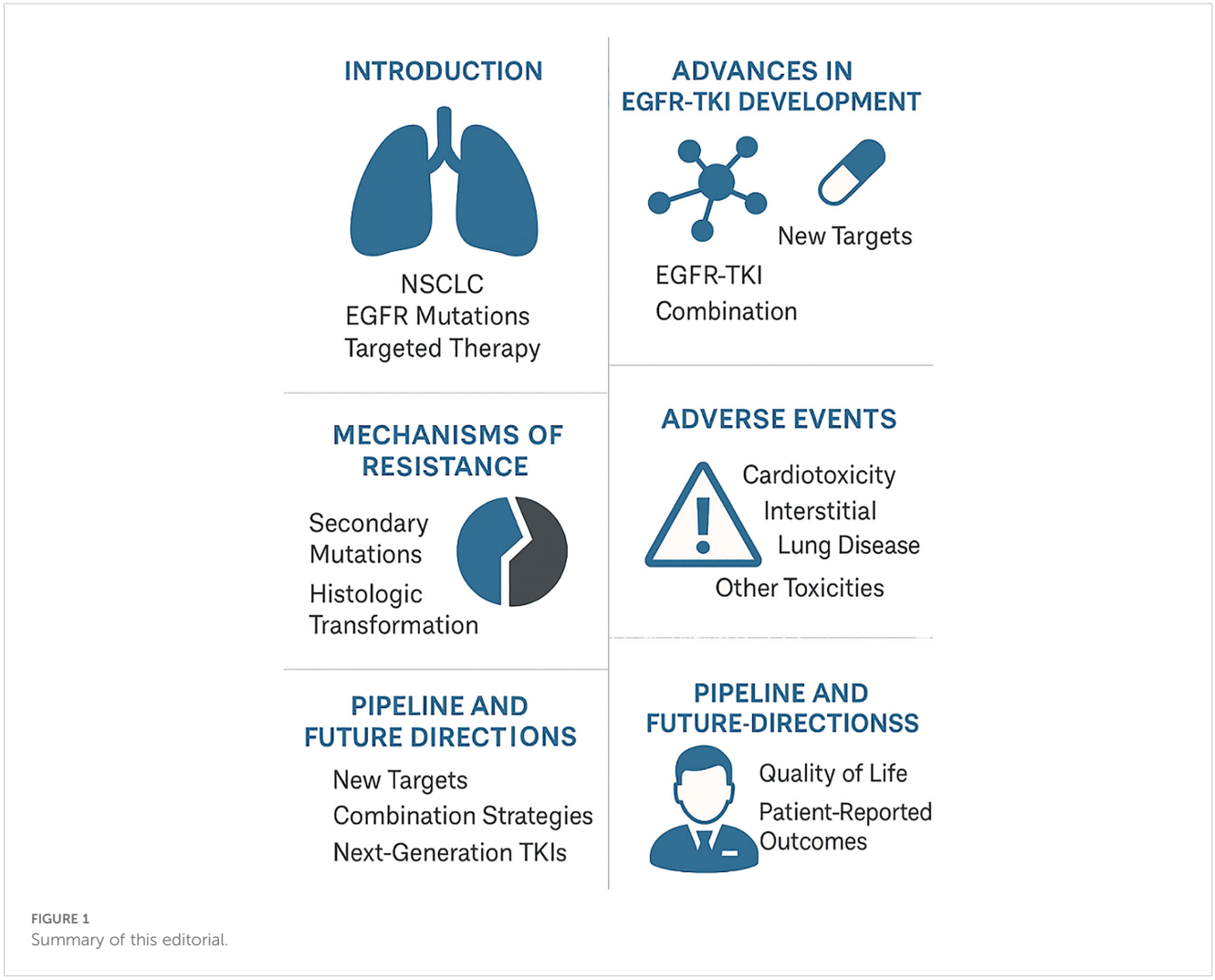

FIGURE 1
Summary of this editorial.

improvements in patient-reported outcomes (PROs), indicating not just prolonged life, but improved day-to-day well-being (Li et al.).

Resistance and transformation

Despite early successes, resistance to EGFR-TKIs remains almost inevitable. Tumor heterogeneity and adaptive signaling mechanisms, including secondary EGFR mutations (e.g., T790M), MET amplification, and transformation into other histologies like small cell lung cancer (SCLC), complicate the therapeutic landscape (3; 4).

Recent case reports underscore these transformations. One patient with an EGFR exon 19 deletion developed SCLC following osimertinib therapy and required a shift to etoposide and cisplatin combined with immunotherapy for disease control (Li et al.). Another case documented transformation to large cell neuroendocrine cancer (LCNEC) after almonertinib failure, emphasizing the importance of repeat biopsies to adapt treatment strategies (Cheng et al.).

Moreover, furmonertinib has shown promise in overcoming complex resistance. A single reported case yielded a progression-free survival (PFS) of 27 months in a heavily pre-treated patient with EGFR exon 20 insertion and PIK3CA mutations, supporting its potential in refractory settings (Sun and Wang).

Adverse events: an underestimated burden

While EGFR-TKIs are generally well tolerated compared to traditional chemotherapy, accumulating data reveal a non-trivial burden of adverse events (AEs), some of which can be severe or even fatal. Osimertinib, for instance, though highly effective, has been associated with increased cardiotoxicity—including heart failure, arrhythmias, and hypertension (Wang et al.). A recent observational study found a 21.6% incidence of cardiotoxicity among osimertinib-treated patients, with smoking history, hyperlipidemia, and concurrent chemo/radiotherapy identified as significant risk factors (Wang et al.).

Network meta-analyses and pharmacovigilance reports from the FDA Adverse Event Reporting System (FAERS) further highlight drug-specific AE profiles. Afatinib and osimertinib have higher toxicity rankings, while icotinib and erlotinib are comparatively safer in terms of overall AE incidence (Shi et al.).

Perhaps most concerning are the rare but serious complications. One patient developed interstitial lung disease from almonertinib (Yang et al.), and another developed type 1 diabetes following anlotinib treatment (Chen et al.), illustrating the importance of close monitoring and personalized risk-benefit assessment.

The pipeline and beyond: new targets and combination strategies

As resistance mechanisms continue to emerge, innovative therapeutic strategies must be developed in parallel. Whole exome sequencing (WES) has enabled the identification of rare and resistant EGFR mutations—such as G724E and K745L—that compromise drug efficacy (Nagarajan and Guda). Virtual screening against these mutations has yielded promising lead compounds, reigniting hopes for overcoming resistance at a molecular level.

Combination therapies are also gaining traction. Immune checkpoint inhibitors (ICIs), though traditionally less effective in EGFR-mutated NSCLC, have shown potential when combined with antiangiogenic agents and chemotherapy (Zhu et al.). A network meta-analysis suggests that this triplet regimen may offer the best survival outcomes, albeit with increased toxicity.

Co-targeting other HER receptors alongside EGFR represents a promising therapeutic avenue. Recently, a HER3-targeted antibody-drug conjugate, patritumab deruxtecan, received approval for the treatment of HER1-mutant non-small cell lung cancer (NSCLC) (5, 6) Moreover, targeting co-alterations such as HER2 overexpression with agents like disitamab vedotin (RC48) offers another frontier (Lan et al.). In a remarkable case, a patient with EGFR and HER2 co-alterations maintained stable disease through eight lines of therapy, culminating in disease control with RC48 and local interventions.

Clinical implications and future directions

The current studies reaffirm the transformative power of EGFR-TKIs in lung cancer treatment. However, it also reveals a landscape fraught with complexity. Resistance is complex and often unpredictable, while adverse effects can be severe and require proactive management (Tan et al.).

Future strategies should emphasize a comprehensive approach that includes personalized treatment planning through genomic profiling and assessment of comorbidities and adverse event risks to tailor both initial and follow-up therapies. Rigorous surveillance and early detection protocols should be implemented to monitor cardiotoxicity, interstitial lung disease, and metabolic disturbances. Mechanism-driven drug development is essential, focusing on next-generation TKIs that effectively target rare mutations while offering improved safety. Additionally, exploring innovative combination regimens that integrate TKIs with immune checkpoint inhibitors and antiangiogenic agents may help delay or overcome resistance. Finally, patient-centered care should remain a cornerstone, with patient-reported outcomes incorporated into clinical decision-making to enhance both survival and quality of life.

Conclusion

The discovery of EGFR mutations and the advent of targeted therapies have revolutionized the treatment landscape for lung cancer patients. However, as we navigate the intersection of groundbreaking innovation and growing complexity, the oncology community must stay alert and adaptive. Resistance should not be seen as a barrier, but rather as a catalyst for deeper scientific exploration and therapeutic refinement. With the continued advancement of precision medicine, proactive monitoring, and robust translational research, there is a real opportunity to transform targeted therapy from a temporary solution into a pathway toward sustained remission.

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EGFR-TKIs - induced cardiotoxicity in NSCLC: incidence, evaluation, and monitoring

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The advent of targeted drug therapy has greatly changed the treatment landscape of advanced non-small cell lung cancer(NSCLC), but the cardioxic side effects of targeted drug anti-cancer therapy seriously affect the prognosis of NSCLC, and it has become the second leading cause of death in cancer patients. Therefore, early identification of the cardiotoxic side effects of targeted drugs is crucial for the prevention and treatment of cardiovascular diseases. The cardiotoxic side effects that may be caused by novel targeted drugs epidermal growth factor receptor inhibitors, including thromboembolic events, heart failure, cardiomyopathy, arrhythmia and hypertension, are discussed, and the mechanisms of their respective adverse cardiovascular reactions are summarized, to provide useful recommendations for cardiac management of patients with advanced lung cancer to maximize treatment outcomes for lung cancer survivors. Clinicians need to balance the risk-benefit ratio between targeted therapy for malignant tumors and drug-induced cardiotoxicity, and evaluate and monitor TKIs-induced cardiotoxicity through electrocardiogram, cardiac imaging, biomarkers, etc., so as to remove the susceptibility risk factors as soon as possible and provide a reference for the clinical use of such drugs in the treatment of malignant tumors.

KEYWORDS

non-small cell lung cancer, targeted drugs, cardiotoxicity, epidermal growth factor receptor inhibitors, evaluation and monitoring

1 Introduction

Whether in the world or in China, the incidence rate and mortality of primary bronchogenic lung cancer (hereinafter referred to as lung cancer) rank first among all malignant tumors (1). In 2022, it is estimated that there will be about 870,000 cases and 760,000 deaths of lung cancer in China (2), and non-small cell lung cancer (NSCLC) is the most common type of lung cancer, accounting for 80% of lung cancers (3). Most patients are at an advanced stage at the time of diagnosis, and miss the best time for surgical treatment, which significantly affects the prognosis of patients with advanced lung cancer, making

chemotherapy become the traditional standard of care for advanced NSCLC (4). However, the plateau phase of chemotherapy response and its adverse effects limit its clinical use. Molecularly targeted therapy has become the first-line treatment for advanced NSCLC due to its efficacy, specificity, and low adverse reactions (5). Clear-cut therapeutic targets for NSCLC include epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase, mesenchymal epidermal conversion factor, and human epidermal growth factor receptor (HER), as well as vascular endothelial growth factor, monoclonal antibodies, and multi-targeted small molecule inhibitors.

The aberrant expression of EGFR is closely related to the invasion and metastasis of tumor cells, tumor angiogenesis, chemotherapy resistance, and abnormal cell proliferation. Overexpression and mutations of EGFR have been found in patients with NSCLC (6), therefore, tumor cell proliferation can be effectively inhibited by counteracting EGFR expression. A large number of clinical trial studies (7) have shown that small molecule inhibitors targeting EGFR have a good effect on the treatment of NSCLC, so small molecule tyrosine kinase inhibitors (TKIs) are the first-line treatment for patients with locally advanced or metastatic NSCLC with EGFR gene mutations.

The discovery of genetic targets has brought infinite possibilities for the treatment of advanced lung cancer, but cardiovascular complications have forced anticancer therapy to be temporarily or prematurely terminated, reducing quality of life and even leading to premature death. This paper focuses on the cardiotoxic side effects and possible mechanisms associated with TKIs of several common targeted therapy drugs recommended by the Chinese Society of Clinical Oncology (CSCO) in 2020.

2 Epidermal growth factor receptor tyrosine kinase inhibitors

EGFR is a member of the ErbB family of intoxicine kinase receptors, which has four closely related members: EGFR/HER-1 (ErbB1), HER-2 (ErbB2), HER-3 (ErbB3), and HER-4 (ErbB4) (8). Since the discovery of anti-EGFR therapy for cancer, a variety of epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) have been synthesized and approved for clinical treatment. Resistance to first- and second-generation EGFR-TKIs inhibitors has enabled the discovery and development of third-generation TKIs inhibitors. Recently, fourth-generation EGFR-TKIs inhibitors have been clinically evaluated against the third-generation EGFR mutation (C797S) (9). Although the incidence of cardiotoxicity caused by TKIs is very low, there are increasing reports of cardiotoxicity caused by TKIs, which has gradually become the focus of cardiovascular and oncology scientists. The direct effects of TKIs on cardiomyocytes can lead to heart failure, cardiomyopathy, conduction alterations, and prolonged QT intervals, sometimes result in malignant arrhythmias and even cardiac arrest. In addition to cardiac effects, TKIs can also raise vascular effects, leading to arterial hypertension, arterial injury, and venous thromboembolism (10). Cardiotoxicity is one of the most challenging side effects of TKIs, and each TKIs may act on the cardiovascular system in a variety of ways through different targets (see Table 1).

2.1 First-generation EGFR-TKIs

2.1.1 Gefitinib

Gefitinib (GEF) acts reversibly on wild-type and certain mutant EGFRs and inhibits the autologous phosphorylation of EGFR tyrosine, thereby further inhibiting downstream signaling and promoting tumor metastasis. Unlike other tyrosine kinase inhibitors, GEF is not considered to be cardiotoxic and is not described in the label, but there has been an increase in reports of cardiotoxicity associated with GEF in recent years.

Lynch et al. (11) reported a case of GEF-related recurrent myocardial infarction. Other literature (12) has reported that the most likely cardiotoxicity in GEF therapy is acute coronary syndrome, and it is speculated that the risk is due to increased platelet reactivity. The first hypothesis is that GEF significantly increases the ability of platelets to produce thromboxane A2,

TABLE 1 Cardiotoxicity associated with EGFR-TKIs.

EGFR-TKIs		Related cardiotoxicity		Targets
		Instructions	Related literature	
1st Generation	Gefitinib	No relevant description	Acute coronary syndrome, cardiomyopathy, prolonged QT interval	Wild type and certain mutant EGFR
	Erlotinib	Myocardial infarction or ischemia, arrhythmia	Myocardial infarction, ischemia, prolonged QT interval, and cardiomyopathy	HER-1 /EGFR
	Icotinib	No relevant description	No relevant description	EGFR 19 deletion or L858R mutation
2nd Generation	Afatinib	Left ventricular dysfunction	Left ventricular dysfunction	The cysteine 797 site of EGFR and the corresponding cysteine 805 and 803 sites in HER-2 and HER-4
	Dacomtinib	No relevant description	No relevant description	EGFR/HER-1, HHER-2 and HER-4
3rd Generation	Osimertinib	Prolonged QT interval, asymptomatic decrease in left ventricular ejection fraction, symptomatic congestive heart failure	Heart failure, prolonged QT interval, pericardial effusion, myocarditis, and atrial fibrillation	EGFR and HER-2 with T790M mutation

thereby promoting thrombosis. Another hypothesis is that GEF directly damages the atherosclerotic plaque, causing it to rupture.

Notably, Shizuoka Cancer Center in Japan reported (13) a 56-year-old woman diagnosed with GEF-induced cardiomyopathy 7 months after GEF treatment for advanced NSCLC; Symptoms gradually improve after discontinuation of GEF and administration of angiotensin-converting enzyme inhibitors and B-blockers; After 3 months, there was a marked improvement in left ventricular ejection fraction (58% versus 28%), and chest x-ray showed improvement in cardiac enlargement. These results suggest that cardiomyopathy is reversible after discontinuation of the causative drug. This suggests that GEF may be at potential risk of cardiomyopathy. Therefore, when there are unexplained clinical symptoms of cardiomyopathy in patients, it is recommended to complete cardiac magnetic resonance imaging and myocardial biopsy to further determine whether it is caused by cardiac causes, but the specific mechanism of cardiomyopathy caused by GEF has not been clearly reported. It has also been reported in the literature (14, 15) that GEF may prolong the QT interval, but its reliability and mechanism are unknown due to the lack of clinical and experimental data.

In summary, the main cardiotoxic reactions that may be caused by GEF are acute coronary syndrome, cardiomyopathy, and QT interval prolongation. Alhoshani et al. (16) proposed that GEF induces cardiotoxicity by regulating the expression/function of the cardiac PTEN/Akt/Fox03a pathway and the formation of CYP1A1-induced reactive metabolites due to *in vivo* and *in vitro* rat studies, but due to the limited available information on the mechanism of cardiotoxicity caused by GEF, the exact mechanism needs to be further studied.

2.1.2 Erlotinib

Erlotinib is a potent and selective EGFR TKIs that blocks tumor cell division in EGFR-overexpressing human tumor cells, produces cell cycle arrest, and initiates programmed cell death which will inhibit the binding of ATP to the EGFR intracellular tyrosine kinase domain, thereby inhibiting receptor intracellular phosphorylation and blocking downstream signal transduction. Erlotinib drug inserts and the U.S. Food and Drug Administration (FDA) mention cardiovascular complications including myocardial ischemia or infarction and cardiac rhythm failure. In addition, it has been reported in the literature that patients taking erlotinib have a prolonged QT interval after treatment initiation (median QTc prolongation ranges from 7~24 ms) (17). Pinquie et al. (18) also reported a new case of dilated cardiomyopathy associated with erlotinib therapy, suggesting that long-term maintenance therapy with erlotinib may cause dilated cardiomyopathy. Kenji et al. (19) report a case of cardiomyopathy that developed during erlotinib treatment for NSCLC. Two months after erlotinib initiation, our 70-year-old female patient complained of progressive dyspnea, and a diagnostic endomyocardial biopsy confirmed non-specific cardiomyopathy, indicating erlotinib-induced cardiomyopathy.

How erlotinib causes cardiotoxic side effects has not yet been reliably documented, but it has been suggested in the literature (20) that erlotinib may be associated with a lower risk of cardiotoxicity, not necessarily because it inhibits EGFR alone, but because the signal sensor and activator of transcription 3 signaling are upregulated, allowing adaptive fatty acid metabolism to maintain cardiac function, so the specific mechanism of cardiovascular complications caused by targeted drugs may need to be comprehensively analyzed.

2.1.3 Icotinib

Icotinib is a first-generation EGFR-TKIs approved by the National Medical Products Administration of China (NMPA) and is currently only available in China for the treatment of EGFR 19-deletion or L858R-mutated NSCLC, with a similar molecular structure to two first-generation EGFR-TKIs (GEF and erlotinib) (21). Compared with GEF, icotinib has similar efficacy but a better safety profile (22). Although there are increasing literature reports of cardiotoxicity caused by GEF, icotinib, which is similar in molecular structure, has not been described in the drug label or in the literature.

It is worth noting that Peng et al. (23) reported that icotinib can significantly reduce the right ventricular systolic blood pressure and right ventricular hypertrophy index of cytroline-induced pulmonary hypertension in rats, and improve the pulmonary vascular remodeling induced by monocrotaline, and proposed that this effect may prevent the dysfunction of pulmonary artery smooth muscle cells by inhibiting the EGFR-Akt/ERK signaling pathway.

2.2 Second-generation EGFR-TKIS

2.2.1 Afatinib

Afatinib is a selective inhibitor of the ErbB family receptor slightly cohort kinase, irreversibly binding to cysteine 797 in EGFR and the corresponding cysteine 805 and 803 in HER-2 and HER4 (24).

Nuvola et al. (25) reported a 71-year-old female smoker with stage 4 EGFR-mutant lung cancer with a previous diagnosis of atrial fibrillation and hypertension, with a left ventricular ejection fraction of 60% on baseline echocardiography, 40% left ventricular ejection fraction, diastolic dysfunction, left ventricular dilation, and pericardial effusion on echocardiography 1 month after treatment with afratinib, and normal left ventricular ejection fraction (60%) 1 week after discontinuation of afatinib, thus presumed that cardiac dysfunction was related to HER-2 inhibition.

2.2.2 Dacomtinib

Dactinib irreversibly inhibits EGFR and is the first-line treatment for patients with EGFR mutation-positive advanced lung cancer, with activity against all 3 kinase-active ErbB family members (EGFR/HER-1, HER-2, and HER-4). Dactinib is superior to GEF in terms of progression-free survival and duration of response (26).

Trials have shown that dacrotinib treatment lacks clinically relevant evidence on the effects of QT interval, heart rate, or PR interval (27), and no cardiotoxicity has been described in the drug label or other relevant literature reports.

2.3 Third-generation EGFR-TKIS

Osimertinib is a third-generation irreversible tyrosine kinase inhibitor approved by the European Medicines Agency for patients with EGFR mutations with the T790M mutation (28). Osimertinib was shown to have a favorable safety profile compared to first-generation EGFR-TKIs, with a lower incidence of adverse event grade = 3 (42% vs 47%), however, the incidence of cardiotoxicity was increased in the osimertinib-treated group, and an analysis of the FDA's adverse events database found that osimertinib raised the incidence of atrial fibrillation, ECG QT interval prolongation, and heart failure compared with first- or second-generation EGFR-TKIs (29). Kartik et al. reported that the reporting odds ratio (ROR) for cardiac failure, AF, and QT prolongation were higher due to the treatment of osimertinib compared with other TKIs. Electrocardiographic monitoring for QT prolongation and monitoring for signs and symptoms of heart failure should be considered in patients taking osimertinib (30). Karishma et al. presented a case of acute, severe biventricular cardio- myopathy due to osimeritinib in a patient with metastatic lung adenocarcinoma and malignant pericardial tamponade (31).

Osimertinib has been reported to cause reversible heart failure in cases (32–36), and 21 of the 558 patients treated with osimertinib in two trials conducted by Piper-Vallillo et al. (37) developed heart failure. It has been speculated that osimertinib-induced heart failure may be related to its inhibition of HER-2 (38). In the case shared by Schiefer et al. (39), a patient suddenly developed subgrade QT interval prolongation (560 ms) after 11 months of treatment with osimertinib, and the QT interval returned to normal within 5 days of drug withdrawal. Osimertinib has also been reported to cause severe cardiac dysfunction, such as myocarditis. Oyakawa et al. (40) reported a case of myocarditis caused by osimertinib, which showed no improvement in left ventricular ejection fraction 12 weeks after discontinuation of osimertinib. In summary, the cardiotoxicity that osimertinib may cause may not be limited to a few described conditions in the label, and the mechanism of cardiotoxicity imposed by osimertinib is not yet known, so caution is required during treatment. Osimertinib (41) may lead to Takotsubo (stress) cardiomyopathy (TC), which has the possibility of cause of heart failure, and osimertinib should not be resumed in patients diagnosed with symptomatic heart failure due to TC induced by osimertinib.

Numerous reports of cardiotoxicity after treatment with TKIs have exposed gaps in the prediction of cardiotoxic side effects from current preclinical drug trials. The diversity of cardiovascular complications caused by TKIs, the older age of most patients with NSCLC, and the fact that most patients have comorbid cardiovascular disease make cardiac management of patients with NSCLC more difficult. Unfortunately, there is currently limited understanding of the mechanisms underlying cardiotoxicity caused by TKIs, and there is no reliable way to predict cardiotoxicity during the treatment of TKIs. Therefore, cardiovascular surveillance for patients with advanced lung cancer receiving targeted drug therapy should not be underestimated. In order to strike for a balance between "life-saving" and "heart-to-heart", it is essential to implement preventive measures to identify patients at risk of cardiotoxicity throughout the course of targeted drug therapy.

Liraglutin, a glucagon-like brain 1 receptor agonist, has a strong cardioprotective effect, the mechanism of which is not well understood. There has been experimental evidence abroad showing that Liralu protects the heart from GEF-induced cardiac damage through its antioxidant properties and activation of survival kinase (42). The mechanism may provide protection for Liraluf by upregulating survival kinases (ERK1/2 and Akt) and downregulating stress-activated kinases (JNK and P38). There is no reliable clinical data on whether the use of lirarum can actually avoid the cardiac damage caused by GEF, and more animal experiments are needed to verify this idea.

HER-2 is a member of the transmembrane receptor family of tyrosine kinases, expressed in cardiomyocyte membranes, and plays a role in cardiomyocyte growth, survival, and protection against cardiotoxins. As a representative drug of HER-2 inhibitors, the mechanism of cardiotoxic side effects of trastuzumab is believed to be related to its inhibition of HER-2, and whether the mechanism of cardiovascular toxicity caused by TKIs such as afatinib, dactinib and osimertinib, which also inhibit HER-2, is similar to that of trastuzumab needs to be verified by more experimental data.

3 Evaluation and monitoring of EGFR-TKIs-induced cardiotoxicity

Although it is not possible to accurately predict the risk factors for the development of cardiotoxicity in patients treated with EGFR-TKIs, patient-specific complications should be considered in the drug selection process to understand the cardiotoxicity of each EGFR-TKIs. Clinical physicians need to balance the risk-benefit ratio between targeted therapy for malignant tumors and drug-induced cardiac toxicity. Therefore, EGFR-TKIs-induced cardiotoxicity safety profile, baseline risk assessment, active surveillance, and prophylactic treatment should be included as part of clinical work (43). The range of cardiotoxicity induced by EGFR-TKIs varies with the specific drug and is influenced by underlying cardiovascular disease or risk factors. Before initiating treatment with EGFR-TKIs, a rigorous baseline risk assessment must be performed on all patients, and baseline cardiovascular risk factors, including obesity, diabetes, hypertension, smoking, etc., must be carefully considered. Cardiac assessment at baseline level, regular dynamic monitoring in treatment with EGFR-TKIs, and post-treatment follow-up, including blood pressure measurement and electrocardiogram, cardiac imaging, and dynamic monitoring of biomarkers, should be routinely performed to determine whether patients would benefit from treatment with EGFR-TKIs and to adjust treatment prior to irreversible cardiac injury (44).

3.1 The role of ECG in the assessment and monitoring of EGFR-TKIs-induced cardiotoxicity

ECG can be used to detect some signs of cardiovascular toxicity, such as increased heart rate at rest, ST-T changes, conduction system abnormalities, QT interval prolongation, or arrhythmias.

However, ECG changes are often nonspecific and are often influenced by many factors. ECG changes are sometimes transient and unrelated to the progression of chronic heart disease.

3.2 The role of cardiac imaging in the assessment and monitoring of TKIs-induced cardiotoxicity

Cardiac imaging includes echocardiography, nuclear imaging, and magnetic resonance imaging (MRI), which can be used for early detection of cardiac toxicity. The purpose of cardiac imaging is to assess the structure and function of the heart and to identify early heart damage. Echocardiography is a non-invasive tool for measuring cardiac function without radiation exposure, and as a result, is still widely used. Compared to two-dimensional (2D) echocardiography, three-dimensional(3D) echocardiography and cardiac magnetic resonance imaging (CMR) provide quantitative volume analysis with greater accuracy and reproducibility (45). LVEF is the most commonly used indicator of mental dysfunction. Current definition of cancer therapeutics-related cardiac dysfunction (CTRCD) is a >10% decrease in LVEF from the previous level and below the lower limit of 50% of normal (46). In addition, compared with two-dimensional echocardiography, three-dimensional echocardiography has higher repeatability, and the measured LVEF has a good correlation with the LVEF measured by cardiac magnetic resonance, which is considered to be the preferred technique for monitoring cardiac insufficiency and cardiovascular toxicity in cancer patients. However, LVEF changes occur only after substantial myocardial injury and decompensation, and variability can be as high as 10% when measured, resulting in low LVEF sensitivity and difficulty in detecting subclinical myocardial injury (47, 48). The application of 2D spot tracking technology and ultrasound strain analysis can detect early myocardial injury. Strain echocardiography is a measure of morpho structural changes in the heart muscle that can provide a global and local assessment of cardiac function. Current studies in antineoplastic treatment of cardiac impairment have demonstrated that GLS assesses left ventricular systolic function more sensitively than LVEF, and a 15% decrease in GLS from baseline is suggestive of early subclinical left ventricular dysfunction. Left ventricular GLS has been recognized as the most sensitive indicator for early monitoring of cardiotoxicity by the American Society of Echocardiography (ASE), the European Society of Cardiovascular Imaging (EACVI), and the European Association of Heart Diseases (ESC) (49). Multi-layer radionuclide angiography was used to evaluate the cardiovascular toxicity and left ventricular function induced by targeted drug therapy with good accuracy and reproducibility, and there were few technical limitations. However, cardiac nuclear imaging is not commonly used to monitor cardiotoxicity because it provides only limited information about cardiac structure and hemodynamics and is limited by radiation exposure (50). When the time and possibility of reversibility of cardiac insufficiency caused by TKIs are not clear, CMR can be used as an important assessment tool to identify, and diagnose early cardiac damage that may be caused by such drugs by performing baseline and periodic cardiac vascular assessments in patients receiving targeted drug therapy (51). One study (52) showed that CMR assessed a decrease in LVEF and GLS in patients treated with low-dose anthracyclines from baseline to after 6 months. CMR can assess cardiac structure and function, measure left ventricular chamber size and systolic function, and provide quantification of chamber size and LVEF, independent of geometric assumptions and acoustic windows. In conclusion, CMR is preferred over echocardiography when more reliable LVEF measurements and assessment of early cardiac damage are required (53).

3.3 Role of biomarkers in the assessment and monitoring of TKIs-induced cardiotoxicity

As an important tool for the diagnosis of cardiovascular diseases, biomarkers have become increasingly valuable in the baseline risk assessment and diagnosis of myocardial injury in cancer patients in recent years. Studies (54) have shown that multi-targeted tyrosine kinase growth and angiogenesis inhibitors exert cardiotoxic effects by inhibiting vascular endothelial growth factor and vascular endothelial growth factor receptor tyrosine kinases from damaging vascular endothelial cells and disrupting cardiac contractility and vasodilation. Therefore, by identifying potential biomarkers that predict cardiotoxicity, it is expected that early detection of cardiotoxicity can guide treatment and improve the prognosis of patients on anticancer therapy.

3.3.1 The role of cardiac troponin in the assessment and monitoring of cardiotoxicity induced by EGFR-TKIs

In anticancer therapy, cancer itself and cardiotoxicity caused by anticancer therapy can also trigger abnormal expression of cTn through cell damage, oxidative stress, fibrosis and other pathways. A recent meta-analysis (55) showed that anticancer therapy can lead to an increase in serum cTn levels, and that increased cTn is associated with systolic dysfunction in patients receiving anticancer therapy, suggesting that it is of great value in predicting left ventricular dysfunction and warrants further investigation. Another study on the cardiotoxicity of anthracyclines in breast cancer patients (56) also showed that anthracyclines can increase hs-cTnT levels, and that an increase in hs-cTnT levels at the end of anthracycline therapy may indicate subsequent cardiotoxicity. In recent years, cTn has been widely used in clinical practice due to its advantages of simple detection, low cost, and high diagnostic value. Routine monitoring of cTn for early detection of cardiotoxicity in patients receiving anticancer therapy has become a trend. The latest European Society of Medical Oncology (ESMO) consensus also recommends that both baseline measurement and regular monitoring of hs-cTnTI/T be considered in high-risk patients (with prior cardiovascular disease) and those receiving high-dose cardiotoxic chemotherapy (e.g., anthracyclines) (57).

3.3.2 Brain natriuretic peptide and N-terminal prohormone of brain natriuretic peptide in the assessment and monitoring of TKIs-induced cardiotoxicity

BNP and NT-proBNP are hormones secreted under the stimulation of factors such as cardiomyocyte stretching, neurohormone activation and myocardial hypoxia, which can act on distant tissues and have the effects of diuresis, vasodilation and regulation of the body's water and sodium balance, both of which are widely used as clinical markers of heart failure and can also be applied in the monitoring of chemotherapy-induced left ventricular dysfunction. Studies [35] have shown that there is a consistent temporal correlation between NT-proBNP and cardiotoxicity during long-term follow-up, suggesting that NT-proBNP has some significance in predicting cardiotoxicity. BNP and NT-proBNP also have certain limitations as cardiotoxicity biomarkers, and their predictive and diagnostic value for cardiotoxicity caused by TKIs still needs to be further studied and verified. Due to its low cost and ease of use, BNP/NT-proBNP can be selected as a biomarker of cardiotoxicity in patients treated with cancer for cardiac function monitoring.

3.3.3 Soluble suppression of tumorigenecity-2, sST2

Role in the assessment and monitoring of EGFR-TKIs-induced cardiotoxicity sST2 as a biomarker of inflammation, fibrosis, and myocardial stress in the diagnosis and prognosis of heart failure and myocardial infarction has been increasingly studied. Studies (58) have shown that sST2 is less affected by age than NT-proBNP or hs-TnT, contributing to more accurate risk stratification and prognostic management of heart failure. A previous study (59) showed an increase in sST2 levels in breast cancer patients during and after anthracycline therapy, however, the study did not specify whether the elevated sST2 levels were caused by the breast cancer itself or by anthracyclines. Another study (60) followed breast cancer patients who received radiotherapy and found that sST2 levels were inversely correlated with cardiac systolic function. These studies suggest the potential value of sST2 in monitoring anticancer therapy-related dysfunction and its prognosis, and that larger clinical sample sizes, longer follow-up periods, and better clinical trial design are needed in the future to validate the effectiveness of sST2.

4 Conclusion

In summary, the innovative development of new anti-tumor drugs has significantly improved the overall survival rate of patients with malignant tumors, but also produced more adverse reactions. In addition to secondary malignancies, the life-threatening complication of the treatment of malignant tumors is the induction of cardiotoxicity by targeted drugs. Therefore, a multidisciplinary approach is essential to find a balance between the need for targeted therapy of EGFR-TKIs and the potential induction of cardiotoxicity in the use of EGFR-TKIs. As with other diseases, prevention is better than cure, and in the course of targeted therapy for EGFR-TKIs, it is important to understand the cardiotoxicity induced by TKIs, according to our review of the literature. The cardiotoxic effects of EGFR-TKIs works diversely, and although there are commonalities, the main adverse effects are different among the drugs in question. This means that cardiotoxicity is not caused by a single mechanism of action of EGFR-TKIs, but varies from drug to drug. Secondly, each patient on EGFR-TKIs-targeted therapy should be carefully evaluated and monitored, including ECG, cardiac imaging, and biomarkers, to address susceptibility risk factors as early as possible and to appropriate treatment or drug modification for emerging cardiotoxicity. In conclusion, the clinically relevant results of EGFR-TKIs are combined with genetic, imaging features and biomarkers to evaluate EGFR-TKIs-targeted therapy at the baseline level and provide effective data support, so that more patients with malignancies can benefit from it.

Author contributions

YW: Conceptualization, Data curation, Investigation, Methodology, Writing – review & editing. QQ: Data curation, Methodology, Writing – review & editing, Resources. XD: Data curation, Methodology, Writing – review & editing, Investigation. MW: Conceptualization, Funding acquisition, Project administration, Writing – original draft.

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Conflict of interest

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Risk factors of osimertinib-related cardiotoxicity in non-small cell lung cancer

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Objective: To investigate the risk factors associated with cardiotoxicity in patients with non-small cell lung cancer (NSCLC) treated with osimertinib.

Methods: A total of 268 patients with NSCLC treated with osimertinib in our hospital from June 2019 to December 2023 were selected to observe the occurrence of cardiotoxicity and were divided into cardiotoxicity group and non-cardiotoxicity group. The differences in age, gender, body mass index (BMI), smoking, alcohol consumption, tumor stage, hypertension, diabetes, hyperlipidemia, chemotherapy, radiotherapy, antiangiogenic drugs, and osimertinib treatment time were recorded and analyzed. Logistic regression was used to analyze the risk factors for cardiotoxicity in patients with non-small cell lung cancer caused by osimertinib treatment.

Results: Among the 268 patients with NSCLC treated with osimertinib, 58 patients developed cardiotoxicity, and the incidence of cardiotoxicity was 21.64%. There were statistically significant differences between the cardiotoxicity group and the non-cardiotoxicity group in terms of smoking history, hyperlipidemia history, combined chemotherapy, and combined radiotherapy ($P < 0.05$). Further analysis showed that patients with a smoking history were at increased risk of cardiotoxicity compared with non-smoking patients (OR = 2.569, 95% CI = 1.398–6.523). Patients with hyperlipidemia were at increased risk of cardiotoxicity compared with those without hyperlipidemia (OR = 3.412, 95% CI = 2.539–7.628). Patients with chemotherapy were at increased risk of cardiotoxicity compared with those without combination chemotherapy (OR = 2.018, 95% CI = 1.426–4.517). Patients undergoing radiotherapy to the left chest were at increased risk of cardiotoxicity compared with those without combined radiotherapy (OR = 1.629, 95% CI = 1.273–4.206).

Conclusion: The incidence of cardiotoxicity in patients with NSCLC is high due to osimertinib treatment. A history of smoking, hyperlipidemia, combination chemotherapy, and radiotherapy to the left chest are independent risk factors for cardiotoxicity in patients with NSCLC treated with osimertinib.

KEYWORDS

osimertinib, non-small cell lung cancer, cardiotoxicity, risk factor, EGFR-TKIs

Introduction

Lung cancer is currently one of the most common malignant tumors in the world, with 2,206,771 and 1,796,144 new cases and deaths in 2020, accounting for 11.4% (second) and 18.0% (first) of the total number of new malignant tumor cases and deaths worldwide (1). Among them, non-small cell lung cancer (NSCLC) is the most common histological type of lung cancer, accounting for approximately 85% of all cases (2). Epidemiological data from the International League of Lung Cancer showed that EGFR mutations accounted for 35.0% of 4231 NSCLC patients who underwent epidermal growth factor receptor (EGFR) gene testing (3). Osimertinib is the world's first marketed third-generation tyrosine kinase inhibitor (TKI). The FLAURA study suggests that osimertinib can prolong the survival of NSCLC patients, and its common adverse effects include diarrhea, rash, paronychia, dry skin, and oral mucositis (4). Osimertinib-related cardiotoxicity is continuously rising cardiac abnormalities when patients are treated with osimertinib (5). The overall risk of osimertinib inducing serious (grade >3) adverse effects was lower than that of gefitinib or erlotinib (42% vs. 47%), but the incidence of cardiotoxicity was relatively higher (reduced left ventricular ejection fraction: 5% vs.2%; QT interval prolongation by 10% vs.4%) (6, 7).

Osimertinib has excellent antitumor performance, but its potential cardiotoxicity after treatment limits its wider clinical application (8). In addition, the toxic effects of osimertinib on the heart are diverse and the onset is hidden, difficult to detect, and irreversible, which seriously affects the quality of life of cancer patients and even endangers the lives of patients (9). Clinically, a significant proportion of cancer patients die not from tumors but from subsequent cardiac complications. Therefore, early diagnosis and early prevention are extremely important for the prevention and treatment of cardiotoxicity (10). Therefore, early detection of high-risk factors for osimertinib-related cardiotoxicity is a key link in the prevention and treatment of osimertinib-related cardiotoxicity. In this manuscript, we describe risk factors of osimertinib-related cardiotoxicity in NSCLC.

Materials and methods

Subject

This study is a single-center, retrospective, observational study conducted in Jiangxi Provincial People's Hospital. The records of NSCLC patients with EGFR mutations received osimertinib targeted anticancer therapy were retrieved through our medical record system. Eventually, a total of 268 patients with advanced NSCLC treated with osimertinib were enrolled in the study. All patients have signed the informed consent form, and this study has been reviewed by the medical ethics committee of our hospital.

Inclusion criteria

The inclusion criteria are as follows: (1) patients with histologically and cytologically confirmed advanced NSCLC; (2) be over 18 years old and under 90 years old; (3) the treatment regimen is osimertinib monotherapy or osimertinib in combination with other chemotherapy drugs (platinum-containing dual-drug regimen chemotherapy) (excluding anthracyclines); (4) electrocardiogram (ECG, including QT interval) was normal before targeted drug therapy; (5) BNP, myocardial injury markers, and left ventricular ejection fraction within normal limits before starting treatment.

Exclusion criteria

The exclusion criteria are as follows: (1) lack of ECG data at least once before and after medication; (2) duration of osimertinib for <2 weeks; (3) combined with coronary heart disease, including after cardiac vascular stent implantation and cardiac coronary artery bypass grafting; (4) patients whose ECG is not suitable for QT interval measurement, including atrial fibrillation, atrioventricular block of grade II and above, pacemaker or implantable cardioverter-defibrillator implantation, multiple premature ventricular contractions, multiple premature atrial contractions, preexcitation syndrome, and sick sinus syndrome; (5) are taking medications known to prolong the OT interval (e.g., anthracyclines); (6) patients with severe infection, renal failure on dialysis treatment, and immune diseases.

Methodology

Osimertinib was taken according to the instructions, the chemotherapy regimen was in line with the CSCO guidelines, and the specific dosage of each drug was calculated according to the body surface area. Radiotherapy depends on the condition, and the dose and fraction of radiotherapy are based on the actual situation.

Diagnostic criteria for cardiotoxicity: (1) cardiomyopathy with reduced left ventricular ejection fraction (LVEF), manifested by decreased overall function or significantly reduced ventricular septal motion; (2) symptoms associated with congestive heart failure (CHF); (3) CHF-related signs, such as gallop rhythm of the third heart sound, tachycardia, or both; (4) LVEF is reduced by at least 5% to <55% absolute from baseline, with symptoms of CHF, or LVEF is reduced by at least 10% to <55% absolute, with no symptoms or signs of CHF [8]. The enrolled patients were divided into groups according to the presence or absence of cardiotoxicity, which were cardiotoxicity group (n = 58) and no cardiotoxicity group (n = 210). The age, gender, body mass index (BMI), smoking, alcohol consumption, tumor stage, hypertension, diabetes, hyperlipidemia, chemotherapy, radiotherapy, antiangiogenic drugs, osimertinib treatment time, and other clinical data were recorded.

Statistical methods

With SPSS 20. 0. Software statistical analysis data. Count data are expressed in cases or percent. Univariate analysis was used to perform chi-square test or Fisher test, and then according to the results, the statistically significant indicators were used as the independent variable, the occurrence of cardiotoxicity was used as the dependent variable, and the logistic regression analysis was performed. $P < 0.05$ statistically significant for the difference.

Results

Incidence of cardiotoxicity

A total of 268 patients with non-small cell lung cancer were treated with osimertinib, of which 58 developed cardiotoxicities, with a cardiotoxicity rate of 21.64%. The incidence of QT interval prolongation, LVEF decrease, heart failure, cardiac tamponade, myocardiopathy, supraventricular tachycardia, myocardial infarction, and cardiac arrest is 39 (10.6%), 20 (5.4%), 4 (1.1%), 6 (1.6%), 7 (1.9%), 6 (1.6%), 5 (1.4%), and 4 (1.1%), respectively.

Analysis of influencing factors of cardiotoxicity

There were significant differences between the cardiotoxic group and the non-cardiotoxic group in terms of smoking history, hyperlipidemia history, combined chemotherapy, and left thoracic radiotherapy history ($P < 0.05$). There were no significant differences in age, gender, body mass index (BMI), alcohol consumption, tumor stage, history of hypertension, history of diabetes mellitus, combination of anti-angiogenic drugs, and duration of osimertinib treatment between the two groups ($P > 0.05$), as shown in Table 1.

Multivariate logistic regression analysis

The factors of $P < 0.05$ screened in the univariate analysis were used as independent variables, including smoking history (no smoking = 0, quit smoking = 1, smoking = 2; the dumb variable was set, taking no smoking as the reference), history of lipidemia (no history of hyperlipidemia = 0, history of hyperlipidemia = 1), combination chemotherapy (no chemotherapy = 0, chemotherapy = 1, dumb variables, with no chemotherapy as a reference), and combination with radiotherapy (no radiotherapy = 0, right chest radiotherapy = 1, left thoracic radiotherapy = 2; set the dummy variable, with no radiotherapy as the reference); dichotomous logistic regression analysis was performed with the occurrence of cardiotoxicity as the dependent variable (no cardiotoxicity = 0, occurrence of cardiotoxicity = 1). The results showed an increased risk of cardiotoxicity in patients with a history of smoking (OR = 2.569, 95% CI = 1.398–6.523). Patients with hyperlipidemia were at increased risk of cardiotoxicity compared with those without hyperlipidemia (OR = 3.412, 95% CI = 2.539–7.628). Patients with chemotherapy were at increased risk of cardiotoxicity compared with those without combination chemotherapy (OR = 2.018, 95% CI = 1.426–4.517). Patients with radiotherapy to the left chest were at increased risk of cardiotoxicity compared with patients without combined radiotherapy (OR = 1.629, 95% CI = 1.273–4.206), as shown in Table 2.

Discussion

As far as we know, our study is the first to investigate the risk factors of osimertinib-induced cardiotoxicity in patients with NSCLC. Our study shows that the osimertinib-related cardiotoxicity rate is 21.64%. Moreover, the smoking history, hyperlipidemia history, combination chemotherapy, and combination radiotherapy to the left chest are independent risk factors for osimertinib-related cardiotoxicity. Osimertinib-related cardiotoxicity is a type II cancer treatment-related cardiac dysfunction (CTRCD), which may have serious consequences, but myocardial damage is generally reversible, so early diagnosis and timely intervention are particularly important (11, 12). It is recommended that clinicians should conduct a baseline risk assessment of patients before starting osimertinib, including previous history (e.g., hypothyroidism, interstitial lung disease, or heart disease), past history (e.g., history of chest radiation therapy), and family history (e.g., long QT syndrome).

Smoking increases the hazard of the cardiovascular system, even sudden death (13, 14). Smoking also effects the nitric oxide (NO) reduction and leads to vasomotor dysfunction, pro-thrombogenic effects, and alteration of lipid metabolism (increase in oxidative LDL) and induces inflammation and oxidative stress (14). Smoking significantly increases the risk of hypertension and insulin resistance, which gradually facilitate the development of cardiovascular diseases (15). Smoking mainly damages endothelial cells and leads to side effects (16). Therefore, smoking may act as a synergy and as a risk factor osimertinib-related cardiotoxicity.

During osimertinib therapy, attention should be paid to the patient's combination of medications (e.g., moxifloxacin, bevacizumab, or granisetron) and to the possible harm caused by drug interactions. Healthcare providers should focus on patients with these risk factors and promptly monitor biochemical markers (e.g., B-type brain natriuretic peptide, troponin, myoglobin, and electrolytes) and imaging markers [e.g., ECG, echocardiography, or magnetic resonance imaging (MRI)] that suggest cardiac dysfunction (17, 18). Similarly, radiotherapy, as an effective antitumor treatment for lung cancer patients, may have a synergistic effect with the combination of osimertinib, leading to an increased cardiotoxicity. The results of our study suggest that radiotherapy may increase the risk of cardiotoxicity by 1.629 times. Risk of developing cardiovascular toxicity after RT is closely linked

TABLE 1 Characteristics of the patients with and without cardiotoxicity (n = 268).

Variable		Cardiotoxicity group (N=58) n (%)	Non-Cardiotoxicity group (N=210) n (%)	x^2	*p*
Age				0.095	0.446
	< 60 years	17 (20.5)	66 (79.5)		
	≥ 60 years	41 (22.2)	144 (77.8)		
Gender				0.324	0.337
	Male	26 (20.2)	103 (79.8)		
	Female	32 (23.0)	107 (77.0)		
BMI (kg/m2)				0.102	0.992
	< 18.5	2 (18.2)	9 (81.8)		
	18.5~24	23 (21.5)	84 (78.5)		
	24~28	29 (22.1)	102 (77.9)		
	≥28	4 (21.1)	15 (78.9)		
Smoking				14.226	**0.000***
	current	41 (30.8)	92 (69.2)		
	former	13 (15.5)	71 (84.5)		
	No	4 (7.8)	47 (92.2)		
Excessive alcohol consumers				1.510	0.140
	Yes	37 (24.3)	115 (75.7)		
	No	21 (18.1)	95 (81.9)		
Clinical stage				3.373	0.338
	I	2 (16.7)	10 (83.3)		
	II	15 (21.1)	56 (78.9)		
	III	26 (19.0)	111 (81.0)		
	IV	15 (31.3)	33 (68.7)		
Hypertension				0.804	0.227
	Yes	31 (19.7)	126 (80.3)		
	No	27 (24.3)	84 (75.7)		
Diabetes				1.256	0.166
	Yes	36 (24.2)	113 (75.8)		
	No	22 (18.5)	97 (81.5)		
Hyperlipidemia				5.231	**0.016***
	Yes	38 (27.1)	102 (72.9)		
	No	20 (15.6)	108 (84.4)		
Chemotherapy				3.680	**0.037***
	Yes	42 (25.5)	123 (74.5)		
	No	16 (15.5)	87 (84.5)		

(Continued)

TABLE 1 Continued

Variable		Cardiotoxicity group (N=58) n (%)	Non-Cardiotoxicity group (N=210) n (%)	x^2	*p*
Thoracic radiotherapy				6.247	**0.045***
	Left	32 (29.1)	78 (70.9)		
	right	21 (15.9)	111 (84.1)		
	No	5 (19.2)	21 (80.8)		
Antiangiogenic drugs				0.111	0.427
	Yes	39 (21.1)	146 (78.9)		
	No	19 (22.9)	64 (77.1)		
Treatment time of Osimertinib				0.161	0.984
	< 1 year	4 (19.0)	17 (81.0)		
	2~3 years	13 (21.0)	49 (79.0)		
	3~4 years	21 (21.6)	76 (78.4)		
	≥4 years	20 (22.7)	68 (77.3)		

BMI, body mass index, *p<0.05. The bold values means the P value is less than 0.05.

to the mean heart dose (MHD), a reflection of cardiac radiation exposure, and also depends on dose distribution and exposure of specific cardiac substructures. Generally, >15 Gy to 25 Gy MHD is considered high risk, and >25 Gy MHD confers very high risk (19).

In our study, we found that hyperlipidemia is one of the risk factors of osimertinib-induced cardiotoxicity in patients with NSCLC. Previous studies have shown that hyperlipidemia was one of the highly prevalent cardiovascular risk factors among lung cancer patients (20). Furthermore, statin initiation is currently recommended in primary prevention for patients with atherosclerotic cardiovascular disease (21). Therefore, hyperlipidemia is one of the main factors to avoid osimertinib-induced cardiotoxicity in lung cancer patients.

TABLE 2 Multiple logistic regression analysis of influencing factors of osimertinib - related cardiotoxicity.

Factors	*β*	S.E.	Wald	df	Exp(B)	95% C.I.for Exp(B)	Sig.
Univariate							
Age	0.339	0.867	1.794	1	0.823	0.257–7.673	0.696
Gender	1.243	1.642	3.458	1	0.914	0.926–6.513	0.457
BMI	0.466	1.863	1.492	1	0.627	0.348–4.271	0.589
Hypertension	1.323	1.029	1.537	1	0.725	0.623–3.819	0.268
Diabetes	1.465	1.712	2.537	1	0.993	0.517–5.432	0.721
Smoking	3.526	0.852	4.618	1	1.457	1.347–2.963	0.029*
Hyperlipidemia	2.242	0.768	3.397	1	2.713	2.198–4.629	0.001*
Chemotherapy	1.516	0.628	2.849	1	2.365	1.426–5.193	0.003*
Thoracic radiotherapy	1.626	0.724	2.658	1	1.813	1.037–3.263	0.048*
Multivariate							
Smoking	1.152	0.437	6.729	1	2.569	1.398–6.523	0.008
Hyperlipidemia	1.580	0.693	3.527	1	3.412	2.539–7.628	0.000*
Chemotherapy	0.723	0.268	5.146	1	2.018	1.426–4.517	0.016*
Thoracic radiotherapy	0.916	0.417	2.238	1	1.629	1.273–4.206	0.036*

*p<0.05.

Our study is a monocentric study, so there are many limitations. The small number of patients, nationality, and diagnostic criteria of cardiotoxicity may affect the incidence of osimertinib-induced cardiotoxicity in NSCLC.

Osimertinib plays an important role in the treatment of NSCLC as a representative drug of the third-generation EGFR-TKIs (22). Due to the large population base of lung cancer and the wide clinical application of osimertinib, the reports of cardiotoxicity have been increasing in recent years and may have serious consequences, and medical personnel should pay full attention to it, especially when patients have risk factors such as heart disease, electrolyte imbalance, hypothyroidism, or inappropriate drugs. In addition, as a targeted preparation for oral administration, osimertinib is self-administered outside the hospital to increase the risk of medication for patients, and clinicians and pharmacists should inform patients of the possibility of osimertinib inducing cardiac injury, strengthen drug education, and advise them to undergo regular cardiac function tests to ensure drug safety.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by the medical ethics committee of Jiangxi Provincial People's Hospital. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

YW: Conceptualization, Investigation, Methodology, Project administration, Writing – review & editing. XD: Data curation, Formal analysis, Software, Writing – review & editing. QQ: Data curation, Formal analysis, Investigation, Writing – review & editing. MW: Conceptualization, Funding acquisition, Methodology, Project administration, Resources, Supervision, Writing – original draft, Writing – review & editing.

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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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Identification of potential inhibitors for drug-resistant EGFR mutations in non-small cell lung cancer using whole exome sequencing data

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Epidermal growth factor receptor (EGFR) gene mutations are prevalent in about 50% of lung adenocarcinoma patients. Highly effective tyrosine kinase inhibitors (TKIs) targeting the EGFR protein have revolutionized treatment for the prevalent and aggressive lung malignancy. However, the emergence of new EGFR mutations and the rapid development of additional drug resistance mechanisms pose substantial challenge to the effective treatment of NSCLC. To investigate the underlying causes of drug resistance, we utilized next-generation sequencing data to analyse the genetic alterations in different tumor genomic states under the pressure of drug selection. This study involved a comprehensive analysis of whole exome sequencing data (WES) from NSCLC patients before and after treatment with afatinib and osimertinib with a goal to identify drug resistance mutations from the post-treatment WES data. We identified five EGFR single-point mutations (L718A, G724E, G724K, K745L, V851D) and one double mutation (T790M/L858R) associated with drug resistance. Through molecular docking, we observed that mutations, G724E, K745L, V851D, and T790M/L858R, have negatively affected the binding affinity with the FDA-approved drugs. Further, molecular dynamic simulations revealed the detrimental impact of these mutations on the binding efficacy. Finally, we conducted virtual screening against structurally similar compounds to afatinib and osimertinib and identified three compounds (CID 71496460, 73292362, and 73292545) that showed the potential to selectively inhibit EGFR despite the drug-resistance mutations. The WES-based study provides additional insight to understand the drug resistance mechanisms driven by tumor mutations and helps develop potential lead compounds to inhibit EGFR in the presence of drug resistance mutations.

KEYWORDS

NSCLC, EGFR, cancer drug resistance, afatinib, osimertinib, precision drug discovery

1 Introduction

Lung cancer, ranking amongst the most prevalent and deadliest malignancies worldwide, poses a significant threat to human health and quality of life. In 2020 alone, over 2.2 million new cases were identified and about 1.80 million people succumbed to this disease (Sung et al., 2021). The 5-year survival rates for lung cancer are

notably low, with 17% for men and 24% for women (Bray et al., 2018). The increased expression of epidermal growth factor receptor (EGFR) has been associated with the development of various human cancers, including non-small cell lung cancer (NSCLC) (Ohsaki et al., 2000; Inamura et al., 2010). EGFR is a transmembrane receptor kinase that is expressed in epithelial, mesenchymal, and neurogenic tissues. Several studies have shown that higher EGFR expression in NSCLC is correlated with poorer survival rates (Scagliotti et al., 2004), increased incidence of lymph node metastasis (Fang et al., 2014), and diminished response to chemotherapy (Ogawa et al., 1993; Swinson et al., 2004). First-generation EGFR tyrosine kinase inhibitors (TKIs) such as erlotinib, gefitinib, icotinib, and lapatinib have been widely used to inhibit EGFR activity, reversibly and ATP-competitively. These EGFR TKIs have demonstrated enhanced cytotoxic effects on mutated forms of EGFR (Guardiola et al., 2019).

However, despite the initial efficacy of first-generation EGFR TKIs, nearly all NSCLC patients eventually develop resistance to these drugs within 10–14 months, primarily due to the emergence of the EGFR mutation, T790M (Wu and Shih, 2018). Second-generation EGFR TKIs have been developed to overcome this resistance with a more potent inhibitory effect on EGFR (Guardiola et al., 2019). Second generation agents such as afatinib, neratinib, and dacomitinib have demonstrated superior anticancer activity compared to their first-generation counterparts (Guardiola et al., 2019). In response to the growing resistance challenge, FDA has also approved osimertinib, a third-generation irreversible EGFR TKI, for treating patients who have developed resistance to both first- and second-generation drugs. In addition, Osimertinib was also approved as a first-line therapy for patients with EGFR mutation-positive tumors. Despite the substantial progress made with third-generation TKIs, patients continue to acquire resistance and fail to respond to these inhibitors. Over time, all patients eventually develop resistance, indicating that acquired resistance mechanisms diminish the efficacy of these medications. Despite the significant therapeutic advancements and improved understanding of the genetic foundations, developing resistance to EGFR TKIs remains inevitable, leading to disease progression (Westover et al., 2018; Del Re et al., 2019). This is partly due to the genetic heterogeneity among the NSCLC patients. Therefore, gaining insights into the unique genetic makeup of individuals can pave the way for precision treatment approaches tailored to a patient's mutational profile.

Genomic sequencing has revolutionized precision drug discovery by offering valuable insights into the mutational profiles of the genetically heterogeneous diseases (Strianese et al., 2020). Recent advancements in sequencing technology have made it feasible to sequence the entire tumor genome or specific regions of interest, quickly and affordably, to enable the monitoring of acquired mutations linked to drug resistance throughout the cancer life cycle. This paradigm shift in genome sequencing technologies has fuelled the development of personalized medicine approaches by empowering researchers to pinpoint genetic and drug-resistant mutations linked to a particular disease such as cancer.

In this study, we examined two genomic cohorts of NSCLC patients (SRA IDs PRJEB21459 and PRJNA616048/dbGaP: phs002001) who exhibited resistance to the second and third-generation drugs, afatinib and osimertinib, respectively. By analyzing the whole exome sequences (WES) of NSCLC patients before and after the development of drug resistance, we identified EGFR mutations associated with this resistance for each drug. Subsequently, we conducted molecular modeling and docking studies to assess the binding affinity between the mutant EGFR and the FDA-approved drugs (afatinib and osimertinib) used for the treatment. Following that, we performed virtual screening to identify promising structurally-similar lead compounds capable of inhibiting EGFR despite the presence of drug-resistance mutations. To gain further insights, molecular dynamic simulations were carried out to evaluate the binding efficacy of the screened compounds with the drug-resistant mutant structures of EGFR. The overall workflow of our approach is depicted in Figure 1.

2 Methodology

2.1 Data collection

In this study, we utilized WES data obtained from the tumor samples of two NSCLC patient cohorts. These data were collected from the SRA (Sayers et al., 2022) and dbGAP (Wong et al., 2017) databases. The first cohort contains 38 patients who received the initial treatment with Erlotinib/Gefitinib (SRA ID PRJEB21459) (van der Wekken et al., 2017) and subsequently were treated with the second-generation drug, Afatinib. The second cohort of 34 patients were treated with the same first and second-generation drugs as the first cohort but also received an additional treatment with a third-generation drug, osimertinib (PRJNA616048/dbGaP: phs002001). The crystal structure of the EGFR protein (PDB ID: 3VJO) was obtained from the RCSB-PDB database, and using PyMOL software (PyMoL, 2010), water molecules and other bound molecules were removed. Mutant models were constructed using SPDBV 4.10 software (Guex et al., 1997).

2.2 Whole exome sequencing data analysis

We employed *Nextflow-Sarek 3.1.2* to analyse whole exome sequencing (WES) data, which is a comprehensive workflow designed for quality control, germline and somatic variant detection, and annotation using the recommended best practices in the field (Garcia et al., 2020). During the pre-processing step, sequencing reads were aligned to the human reference genome (GRCh38/hg38) using *BWA-MEM* (Li et al., 2013) and deduplication and recalibration were carried out using *GATK* (McKenna et al., 2010). Since our objective was to identify somatic variants in patients with drug resistance, we utilized *GATK4 Mutect2* (Cibulskis et al., 2013) and *Strelka2* (Kim et al., 2018) to detect somatic single-base mutations (SSM) and small somatic insertion/deletion mutations (SIM). We employed

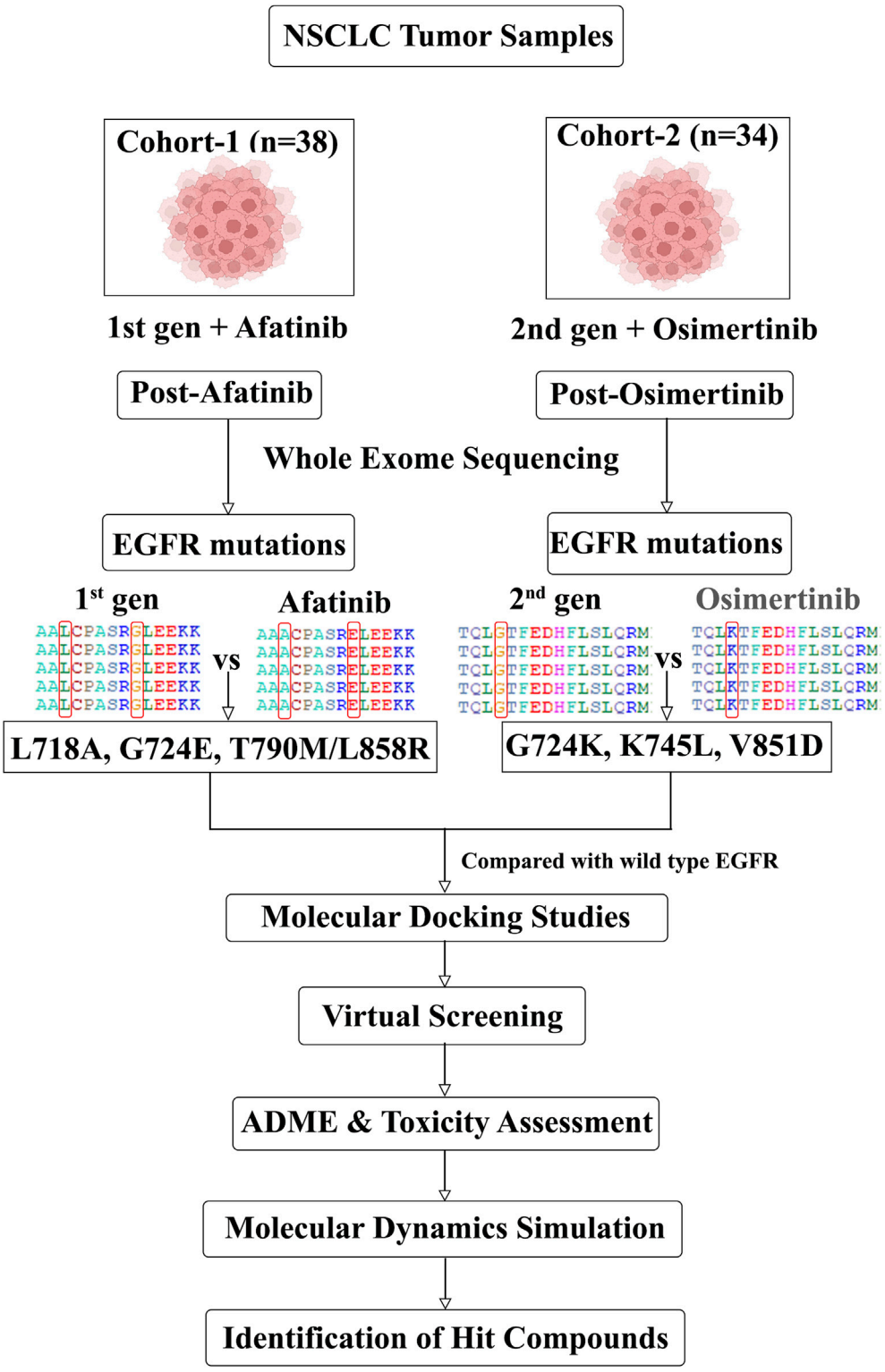

FIGURE 1
Schematic showing the *in silico* workflow from mutation detection to drug discovery.

Manta to detect somatic structural variants, including copy-number variation, ploidy, and sample purity (Chen et al., 2016). In order to evaluate the potential functional impacts of the identified variants, we annotated them using *snpEff* (Cingolani et al., 2012) and *VEP* (McLaren et al., 2016) The *nf-Sarek* workflow generates comprehensive quality control metrics, including *FastQC* (Li et al., 2009; Li, 2011; Okonechnikov et al., 2016) and *VCFtools* (Danecek et al., 2011), which are aggregated and visualized across samples using *MultiQC* (Ewels et al., 2016).

2.3 Preparation of EGFR wild-type (WT) and mutant-type structures

We employed the *Schrodinger suite's* prime module and protein preparation wizard to ensure the integrity of the EGFR wild-type (WT) and mutant structures. This step involved the removal of artifacts such as incorrect bond orders, missing hydrogen atoms, misaligned groups, erroneous charge states, and the missing side chains (Schrodinger Release 2020-1. Protein Preparation Wizard; Schrodinger Release 2020-1. Prime). Additionally, restrained energy minimization was performed to alleviate strained bonds, angles, and steric hindrance, allowing heavy atoms to move within a range of 0.3 Å.

2.4 Preparation of compounds for molecular docking and virtual screening

The three-dimensional structures of FDA-approved EGFR inhibitors, namely, afatinib (CID:10184653) and osimertinib (CID:71496458), were obtained from the PubChem database (Kim et al., 2023). Using their structure information, 3505 and 3880 compounds that are structurally similar to afatinib and osimertinib, respectively, were retrieved from the PubChem and DrugBank (Wishart et al., 2018) databases. The *Maestro* tool was employed to prepare all the compounds for further analysis. *Ligprep*, a software tool, was used to generate 2D or 3D structures and corresponding low-energy 3D structures of both the approved EGFR inhibitors as well as the retrieved structurally similar compounds to make them ready for docking using the *Glide* program. Default parameters were used, except for the chirality feature, for which all combinations of chirality were considered. Subsequently, tautomer generation, desalting, and adjustment of probable ionization states at pH 7 ± 2 were performed (Zagaliotis et al., 2022). The *S. suite's* Epik module, an integrated tool, was utilized to predict the ionization states of the molecules (Rajamanickam et al., 2022).

2.5 Molecular docking

The Schrodinger suite's *Glide* module was employed to conduct site-specific molecular docking of FDA-approved EGFR inhibitors and virtually screened compounds against both EGFR WT and mutant targets. Receptor grid preparation was performed using the *Glide* tool with default parameters, including a partial charge cutoff of 0.25 and van der Waals radius scaling factor of 1.0 (Schrodinger Release 2020-1, Glide). For the screening process, *Glide* was utilized at extra precision (XP), which signifies a clear correlation between high-quality poses and favorable scores, ensuring an accurate evaluation of the libraries.

2.6 ADME and toxicity analysis

QikProp is a specialized tool designed to rapidly predict the ADME (absorption, distribution, metabolism, and excretion) properties of compounds with high accuracy (Schrodinger Release 2020-1. QikProp). It provides predictions for key physicochemical descriptors and pharmaceutical properties of organic molecules, either for individual compounds or in a batch mode. The predicted ADME properties encompass various parameters such as molecular weight, number of H-bond acceptors and donors, indicated octanol/water partition coefficient (MLogP), total polar surface area (TPSA), Lipinski's rule of five (drug-likeness), Rat LD50, and hepatotoxicity. These predictions are crucial for assessing the pharmacokinetic and toxicological profiles of the compounds in the early drug discovery and development stages.

2.7 Molecular dynamics simulation

To assess the structural stability of the docked complexes involving WT and mutant EGFR targets with FDA-approved EGFR inhibitors (Afatinib and Osimertinib) as well as the virtually screened compounds, a 50 ns(nano seconds) molecular dynamics (MD) simulation was performed using *GROMACS gromacs/2021.1* software (Abraham et al., 2015). The topological parameters of the WT and mutant EGFR inhibitors were generated using the *PRODRG* web server (Schuttelkopf and van Aalten, 2004). The WT and mutant structures were solvated in cubic boxes using the SPC (single point charge) water model, ensuring a minimum distance of 1 nm from the box edges. For the structures complexed with ligand molecules, a similar solvation procedure was followed, with water molecules positioned at a 1 nm distance from the box borders, and counter ions (sodium and chloride) were added to neutralize the system. The structures underwent two rounds of energy minimization using the steepest descent technique followed by the conjugate gradient algorithm for 5000 steps to relax the system. Subsequently, the minimized systems were equilibrated under position-restrained ensemble conditions (NVT and NPT) at 300 K for 50,000 picoseconds (ps). Berendsen's weak coupling was employed to maintain a constant pressure of 1 bar, and the Parrinello-Rahman approach (Martonak et al., 2003) was used to control the temperature at 300 K. The calculation of electrostatic interactions utilized the Fast Particle-Mesh Ewald electrostatics (PME) method (Hess et al., 1997) and a 50 ns long-range production MD run was conducted for both WT and mutant systems for each complex. To analyze the MD trajectories, *GROMACS* utility tools such as *g_rmsd, g_hbond, g_mindist, and g_sasa* were employed to examine the RMSD (Root Mean Square Deviation), number of hydrogen bonds, minimum distance between the protein and ligand, and solvent-accessible surface area of the protein, respectively. These analyses provided insights into the stability and dynamic behavior of the studied complexes during the MD simulation.

3 Results

3.1 Whole exome sequencing analysis identifies single- and double-point mutations

WES data analysis was conducted to identify EGFR drug resistance mutations in NSCLC patient samples. A total of

TABLE 1 Detected EGFR mutations in the samples collected after afatinib and osimertinib treatments.

EGFR mutations present in the post-afatinib treatment samples (n = 38)		EGFR mutations present in the post-osimertinib treatment samples (n = 34)	
Identified EGFR mutations	Number of samples with mutation(s)	Identified EGFR mutations	Number of samples with mutation(s)
L718A	2	G724K	1
G724E	1	K745L	1
T790M/L858R	16	V851D	13

TABLE 2 Molecular docking analysis between WT and Mutant EGFR with FDA-approved drugs: Afatinib and osimertinib. Table showing the respective targets, binding energy, hydrogen bonds formed between target and ligand, and the amino acids involved in the hydrogen bond formations.

FDA-approved drugs	Drug targets	XP gscore (Kcal/mol)	Number of hydrogen bonds between target and ligand	Amino acids in hydrogen bonding
Afatinib	WT EGFR	−8.378	2	LEU718, MET793
	L718A	−8.643	2	MET793
	G724E	−7.876	1	ASP855
	T790M/L858R	−7.857	1	MET793
Osimertinib	WT EGFR	−8.376	3	LEU718, MET793, CYS797
	G724K	−8.314	3	LEU718, MET793, CYS797
	K745L	−7.887	2	LEU718, MET793
	V851D	−7.378	1	CYS797

72 patients containing pre- and post-treatment WES data with osimertinib and afatinib were analyzed using *Nextflow Sarek 3.1.2*. In the post-treatment samples, five single-point mutations and one double mutation were identified, as shown in Table 1. Mutations L718A, G724E, T790M/L858R were found in post-afatinib treatment samples, while mutations G724K, K745L, and V851D were identified in post-osimertinib treated samples. All of these mutations except V851D have been previously reported as drug resistant on EGFR in various studies (Lu et al., 2018; Lu et al., 2020; Du et al., 2021; He et al., 2021). Further analysis of the binding modes of mutant EGFR variants with drug compounds will provide insights into the mechanism of drug resistance.

3.2 Ligand binding affinity and hydrogen bonding pattern differ between WT and mutant EGFR variants

Comparative docking of EGFR WT and mutant structures with the FDA-approved drugs, osimertinib and afatinib, was performed using the *Glide* module of the *Schrodinger suite* (Schrodinger Release, Glide; Schrodinger, 2020; Halgren et al., 2004). The binding affinity of the ligands was evaluated based on the *Glide XP* Gscore, which was used to rank the poses of the ligands (Table 2). Previous studies have identified the drug-binding residues of EGFR at VAL726, ALA743, ILE744, LYS745, MET766, LUE789, THR790, GLN791, LEU792, MET793, GLY796, CYS797, ASP800, LEU844, and THR854 (Kashima et al., 2020). We observed that both afatinib and osimertinib bind to the EGFR mutant structures in a slightly different orientation than to the WT EGFR. For afatinib docking with the WT and mutant L718A, G724E, and T790M/L858R structures, the binding energies were −8.378, −8.6434, −7.8765, and −7.857 kcal/mol, respectively. Similarly, the binding energies for osimertinib docking with the WT, G724K, K745L, and V851D structures were −8.376, −8.314, −7.887, and −7.378 kcal/mol, respectively. The lower the binding energy, the higher the binding affinity, and *vice versa*. The binding energy between the mutant structure L718A and afatinib is almost similar to the binding energy of WT with afatinib, but the other mutant structures (G724E and T790M/L858R) obtained higher binding energy compared to the WT-Afatinib complex. Similarly, the binding energy between the mutant structure G724K and osimertinib is almost similar to that of the WT with osimertinib, but the other mutant structures (K745L and V851D) obtained higher binding energies compared to the WT-osimertinib complex. Because G724E, T790M/L858R, K745L, and V851D mutant structures obtained higher binding energies, that negatively affects their binding affinity with the corresponding drugs. Hence, these mutant structures were considered for further virtual screening studies taking into account their drug interaction patterns and dynamics.

The interaction patterns based on hydrogen bonding between WT EGFR and its mutant's post-treatment with afatinib and osimertinib were examined (Supplementary Figures S1, S2). Osimertinib formed three hydrogen bonds with both WT and G724K mutant EGFR structures, involving the same amino acid residues: LEU718, MET793, and CYS797 (Supplementary Figures S1A, S1B). On the other hand, this drug established two hydrogen bonds involving residues LEU718 and MET793 (Supplementary Figure S1C) with

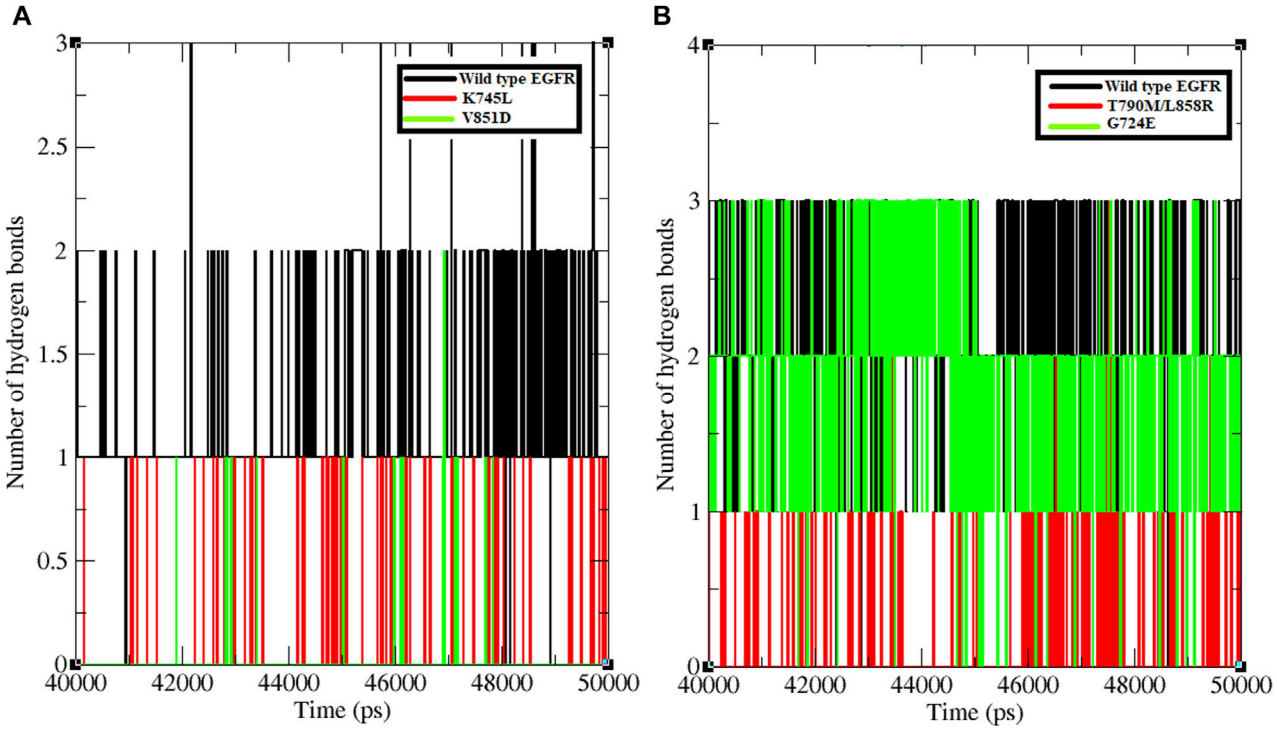

FIGURE 2
Number of hydrogen bonds formed between protein and ligand. **(A)** Number of hydrogen bonds formed between WT and mutant EGFR with drug osimertinib. **(B)** Number of hydrogen bonds formed between WT and mutant EGFR with drug afatinib.

K745L mutant structure and only one hydrogen bond with ASP855 in the V851D mutant structure (Supplementary Figure S1D). With afatinib, two hydrogen bonds were established each in WT and L718A mutant both involving MET793 (Supplementary Figures S2A, S2B). However, afatinib formed only one hydrogen bond each in G724E mutant (with MET793) and T790M/L858R double mutant (with MET793) structures (Supplementary Figures S2C, S2D). The mutant structures K745L, V851D, G724E, and T790M/L858R exhibited high binding energies and fewer hydrogen bonds with their corresponding drugs compared to the wild type (WT). Consequently, these four mutant structures G724E, T790M/L858R, K745L, and V851D with corresponding docked drugs were selected for further molecular dynamics simulations.

3.3 Comparison of binding efficacy, stability, and conformational dynamics between WT and mutant complexes with drugs using MD simulations

The primary objective of the extended molecular dynamics (MD) simulations was to investigate the comparative binding efficacy between the docked mutant complexes and WT complexes. A 50 ns MD simulation was performed for the following six protein-ligand complexes that include three for each drug: WT EGFR-Osimertinib, K745L-Osimertinib, V851D-Osimertinib, WT EGFR-Afatinib, T790M/L858R-Afatinib, and G724E-Afatinib. The GROMOS 53a6 force field in GROMACS was employed for energy minimization. Our analysis was focused on the backbone root-mean-square deviation (RMSD), hydrogen bonds, minimum distance, and the solvent-accessible surface area. For the complexes of WT EGFR, K745L, and V851D with osimertinib, the backbone RMSD analysis (Supplementary Figure S3A) revealed that WT EGFR exhibited a lower deviation pattern (~0.25 nm) compared to the mutant structures, K745L (~0.3 nm), and V851D (~0.35 nm). Similarly, for the complexes of afatinib (Supplementary Figure S3B), WT EGFR displayed a lower deviation pattern (~0.25 nm) compared to the mutant structure, G724E (~0.35 nm), and double mutant, T790M/L858R (~0.35 nm). Higher deviations in RMSD may impact the structural stability of the protein and subsequently lower the binding efficacy of the drugs.

Hydrogen bond formation between EGFR WT and mutant structures with osimertinib and afatinib was also analysed. The number of hydrogen bonds formed between osimertinib and WT EGFR, K745L, and V851D structures during the last 10 ns of the simulation was examined (Figure 2). WT EGFR in complex with osimertinib formed 1–3 hydrogen bonds, whereas the mutant complexes, K745L-osimertinib and V851D-osimertinib, formed fewer hydrogen bonds ranging from 0–1 and 0–2, respectively. Likewise, the number of hydrogen bonds between afatinib and WT EGFR or G724E complexes ranged from 1–3, while those between afatinib and T790M/L858R complex were fewer (0–2), as shown in Figure 2B. A lower number of hydrogen bonds may impact the stability of the protein-drug complex.

The minimum distance between WT EGFR, K745L, and V851D with osimertinib was analysed during the last 10 ns of the simulation period (Figure 3A). In the WT EGFR-Osimertinib complex, this distance was maintained at approximately 0.15–0.20 nm. However, the mutant complexes, K745L-Osimertinib and V851D-

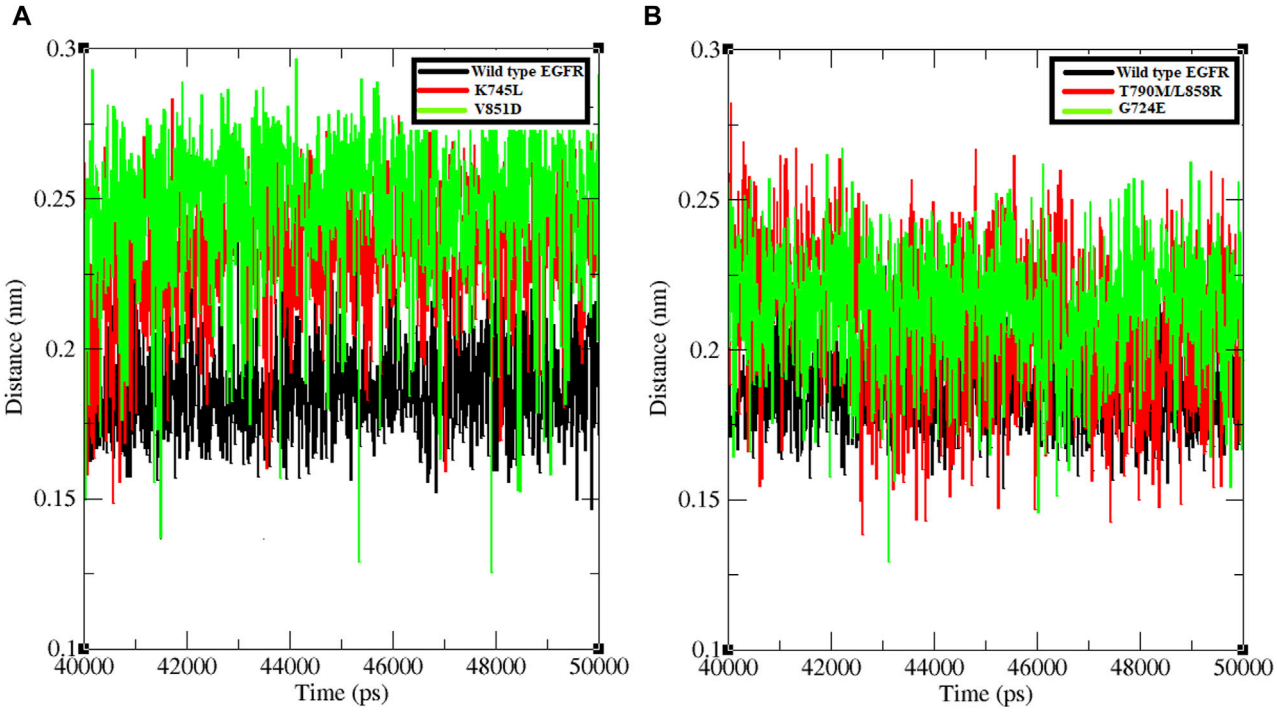

FIGURE 3
Minimum distance formed between protein and ligand. **(A)** Minimum distance formed between WT and mutant EGFR with drug osimertinib. **(B)** Minimum distance formed between WT and mutant EGFR with drug afatinib.

Osimertinib, exhibited higher distances of around 0.15–0.27 and 0.15–0.30 nm, respectively. Similar measurements in the afatinib associated complexes with WT EGFR, G724E, and T790M/L858R structures recorded these distances around 0.15–0.22, 0.15–0.25, and 0.15–0.27 nm, respectively. A higher distance between the components may impact the formation of non-bonded interactions within the complexes.

Further, SASA analysis was performed to compare the solvent accessible surface area in response to the overall protein conformational changes in the complex structures of EGFR WT and mutants with the two drugs. In the osimertinib-associated complexes, WT EGFR had a higher accessible area of approximately 170 nm^2 than the mutants, K745L (~155 nm^2) and V851D (~150 nm^2) (Supplementary Figure S4A). Similarly, with afatinib complexes, the WT EGFR had a higher accessible area of approximately 160 nm^2 than the mutants, G724E (~152 nm^2) and T790M/L858R (~155 nm^2) (Supplementary Figure S4B). A lower accessible surface area suggests fewer possibilities for interactions with other molecules.

3.4 Virtual screening identifies potential inhibitors of mutant EGFR structures

Virtual screening plays a pivotal role in identifying potential small molecules by systematically screening chemical libraries for compounds that can bind to a target protein (Cuccioloni et al., 2020). In this study, we screened a total of 7385 chemical compounds obtained from the PubChem and DrugBank databases against the mutant EGFR structures (G724E, K745L, V851D, and T790M/L858R) using the *Schrodinger Glide* virtual screening workflow. The top ten compounds were selected for each mutant structure based on their binding energies and the number of hydrogen bond interactions with the mutant EGFR structures. Subsequently, independent docking analyses were performed for each compound against each mutant structure to identify three compounds (CID 71496460, 73292362, and 73292545) that show the potential to selectively inhibit EGFR despite drug-resistance mutations (Supplementary Figure S5). These compounds were selected based on their favorable binding energies and ability to form higher number of hydrogen bonds with the mutant proteins as shown in Table 3. For instance, compound CID 71496460 exhibited a favorable binding energy of −8.376 kcal/mol and formed three hydrogen bonds with the mutant G724E structure at residues PHE795, MET793, and ASP855 (Figure 4A). This compound also demonstrated a promising binding energy of −8.002 kcal/mol and formed four hydrogen bonds with the EGFR mutant, K745L, at residues MET793, GLU804, and ASP855 (Figure 4B). Similarly, CID 73292362 displayed an intense binding energy of −9.110 kcal/mol with the double mutant, T790M/L858R (Figure 4C) and CID 73292545 exhibited a considerable binding energy (−7.649 kcal/mol) with V851D (Figure 4D).

3.5 ADME assessment highlights the promise of the screened drug candidates

QikProp, a computational tool, provides valuable predictions on important molecular descriptors and pharmaceutical properties of

TABLE 3 Molecular docking between virtually screened best compounds with their respective mutant structures shows binding energy, hydrogen bond number, and the amino acids involved in hydrogen bond formation.

Mutant EGFR's	PubChem ID	XP gscore (Kcal/mol)	Number of hydrogen bonds between the target & compound	Amino acids involved in hydrogen bond formations
G724E	71496460	−8.376	3	PHE795, MET793, ASP855
K745L	71496460	−8.002	4	MET793, GLU804, ASP855
T790M/L858R	73292362	−9.110	3	LEU718, MET793, ASP804
V851D	73292545	−7.649	3	MET793, ASP800, ASP855

organic compounds. The ADME (Absorption, Distribution, Metabolism, and Excretion) profile, which assesses the drug-like behavior of a chemical agent, was evaluated for the three compounds and the results were presented in Table 4. Notably, none of the screened compounds violated the Lipinski rule criteria, as indicated by a star value of zero. The star rating system, ranging from 0 to 5, suggests that compounds with fewer stars possess more extraordinary drug-like characteristics. Additionally, the molecular weight, number of H-bond donors and acceptors, and logP values of the screened compounds fall within the acceptable ranges defined by the Lipinski rule. Based on these favorable properties, these three compounds merit consideration for further investigation.

3.6 MD simulation reveals higher binding efficacies between the screened compounds and mutant EGFR structures

Binding efficacies were evaluated based on both the distance between the compound and protein structure and the number hydrogen bonds between them using a 50 ns MD simulation (Figure 5). In the last 10 ns of the simulation, G724E-71496460, K745L-71496460, T790M/L858R-732992362, and V851D-73292545 have maintained approximately 0–4, 0–6, 0–4, and 0–4 hydrogen bonds, respectively. Notably, compared to the FDA-approved drugs, osimertinib and afatinib, all the screened compounds exhibited higher number of hydrogen bonds during the MD simulation period. Similarly, in the last 10 ns of the simulation period, G724E-71496460, K745L-71496460, T790M/L858R-732992362, and V851D-73292545 maintained minimum distance ranges of approximately 0–0.25 nm, 0.15–0.27 nm, 0.15–0.22 nm, and 0.15–0.25 nm, respectively (Figure 6). Again, compared to the FDA-approved drugs, all the screened compounds exhibited shorter distances with corresponding mutant structures, indicating their potential to inhibit the EGFR mutant proteins more effectively.

4 Discussion

EGFR plays a critical role in the development and progression of various cancers (Inamura et al., 2010). It is a cell surface receptor belonging to the receptor tyrosine kinase (RTK) family, involved in regulating cell growth, proliferation, and survival (Ohsaki et al., 2000). Dysregulation of EGFR signaling has been implicated in multiple cancer types, making it an attractive target for cancer therapy (Guardiola et al., 2019). EGFR overexpression is observed in a significant subset of colorectal cancers and elevated EGFR signaling is associated with enhanced tumor growth and metastasis (Oh et al., 2011). Anti-EGFR monoclonal antibodies like cetuximab and panitumumab have been developed to target EGFR in colorectal cancer, particularly in patients with wild-type RAS status (Karapetis et al., 2008). These therapies have shown clinical benefit in patients with EGFR overexpressing tumors. EGFR amplification and mutations are frequent events in Glioblastoma Multiforme (GBM) (Marvalim et al., 2023). EGFRvIII, a constitutively active EGFR variant, is commonly observed in GBM and associated with a more aggressive phenotype. Targeting EGFR signaling in GBM has been challenging, but various approaches, including EGFR-specific TKIs and monoclonal antibodies, are being investigated in clinical trials (Marvalim et al., 2023). EGFR is frequently overexpressed and activated in Head and Neck Squamous Cell Carcinoma (HNSCC) (Vermorken et al., 2008). This overexpression is associated with poor prognosis and resistance to conventional therapies. EGFR-targeted therapies, such as cetuximab, have been approved for the treatment of recurrent or metastatic HNSCC, improving patient outcomes (Bonner et al., 2006). EGFR mutations are prevalent in NSCLC, particularly in adenocarcinoma. These mutations lead to constitutive activation of the EGFR pathway, promoting uncontrolled cell growth and cancer development. EGFR TKIs like gefitinib, erlotinib, and osimertinib have been developed to target these mutations in NSCLC (Paez et al., 2004). Osimertinib, a third-line drug, is specifically designed to overcome EGFR resistance that arises after treatment with second-like TKIs like afatinib. Nevertheless, despite the remarkable clinical efficacy of osimertinib, patients inevitably develop acquired resistance, posing a significant challenge due to the limited availability of post-osimertinib pharmacological options.

This study utilizes a combination of sequence data analysis, molecular docking, virtual screening, and molecular dynamics simulation to detect drug resistance mutations in NSCLC patients and identify three compounds that show promise to inhibit EGFR mutant proteins. We identified five EGFR-specific somatic mutations within the WES dataset that include five single-point (L718A, G724E, G724K, K745L, V851D) and one double (T790M/L858R) mutations associated with drug resistance. All these mutations are activating, causing the EGFR protein to become hyperactive, leading to uncontrolled cell growth and division in NSCLC patients (Lv et al., 2020). L718A, the most common EGFR mutation found in approximately 40% of NSCLC patients,

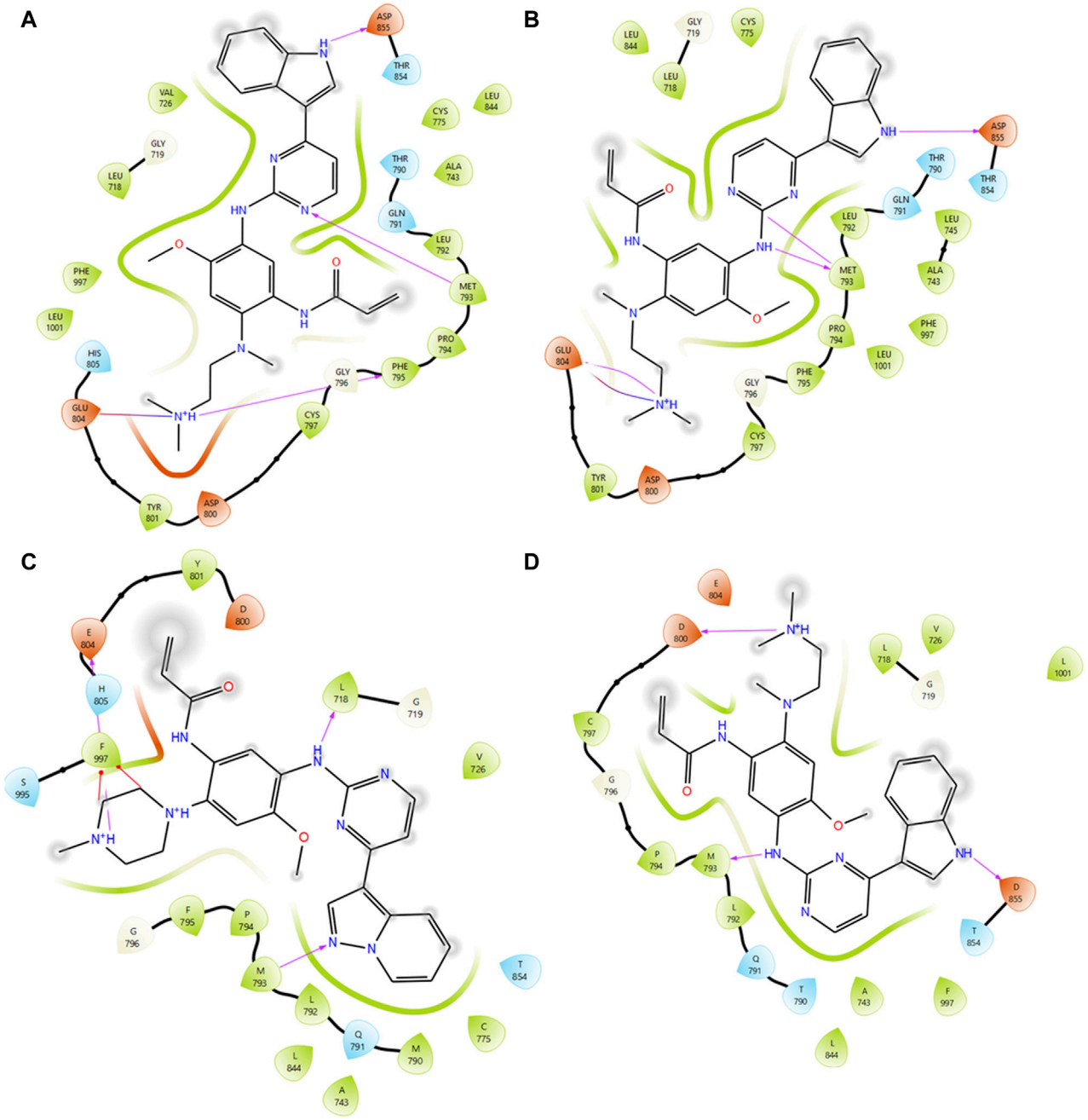

FIGURE 4
Interaction analysis between mutant type EGFRs with virtually screened compounds. **(A)** Interaction analysis between G724E with CID:71496460. **(B)** Interaction analysis between K745L with CID:71496460. **(C)** Interaction analysis between mutant T790M/L858R with CID 73292362. **(D)** Interaction analysis between mutant V851D with CID 73292545.

TABLE 4 ADME analysis for the screened lead compounds displayed along with the screened compound molecular properties.

Screened lead molecules	Stars	Molecular weight (Dalton)	Hydrogen bond donor	Hydrogen bond acceptor	Log-*p*-value
71496460	0	485.588	3	8	4
73292362	0	484.56	2	9	3
73292545	0	483.572	3	8	4

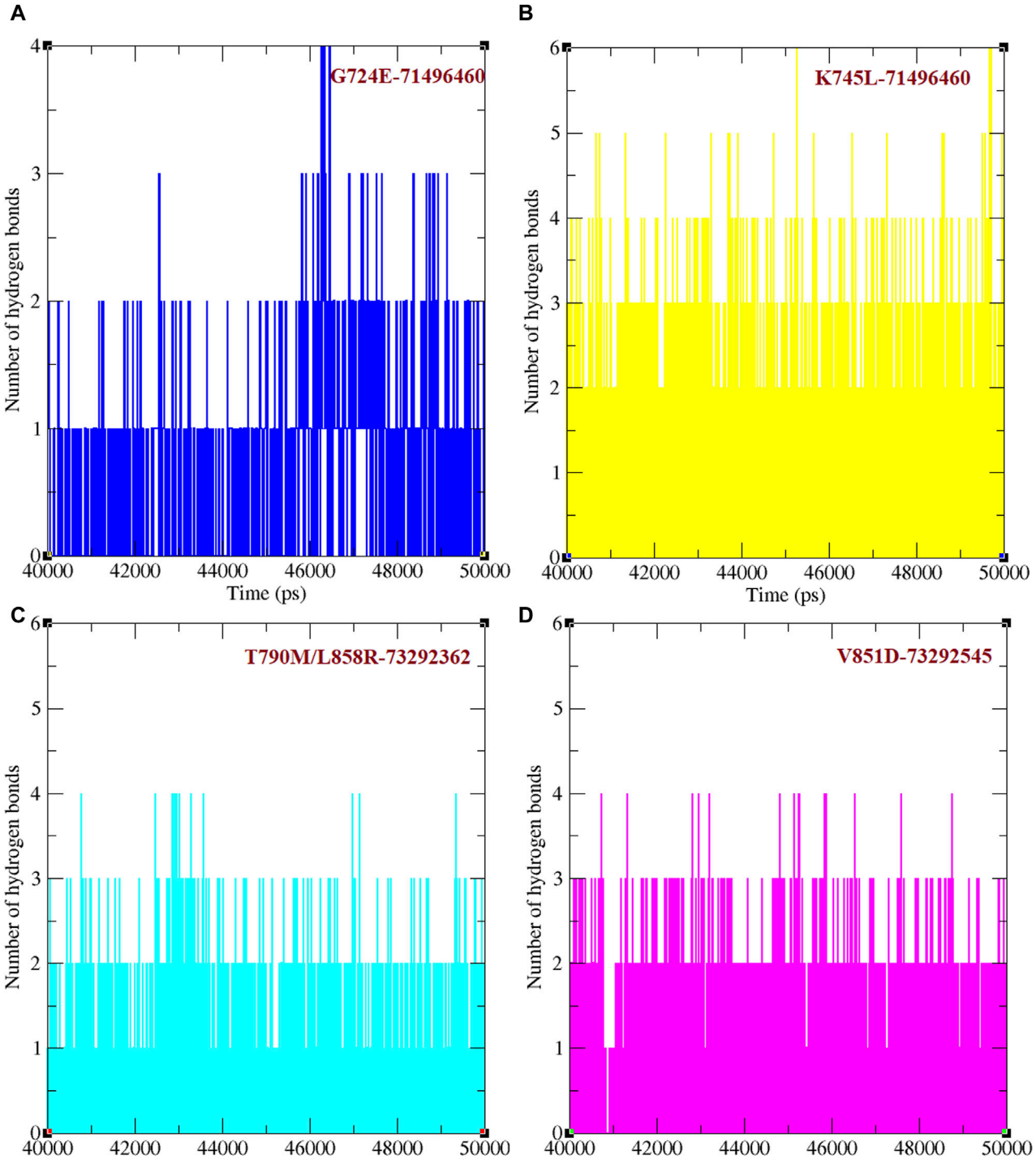

FIGURE 5
Total number of hydrogen bonds formed between mutant EGFRs with its respectively screened compounds. **(A)** The number of hydrogen bonds formed between G724E-71496460. **(B)** The number of hydrogen bonds formed between K745L-71496460. **(C)** The number of hydrogen bonds formed between T790M/L858R-732992362. **(D)** The number of hydrogen bonds formed between V851D-73292545.

substitutes leucine with alanine at position 718 (Zhang et al., 2019). This change alters the way the EGFR protein interacts with drugs. Leucine is a hydrophobic amino acid located in the extracellular domain of the EGFR protein, anchoring it to the cell membrane. In contrast, alanine is also hydrophobic but smaller, potentially affecting interactions with other molecules due to its smaller size.

The less common mutations, G724E, G724K, K745L, and V851D, were found in 1%–10% of NSCLC patients (Tu et al., 2017; Brindel et al., 2020). Both G724E and G724K mutations replace glycine at position 724 with glutamic acid and lysine, respectively, the G724 mutations leading to increased EGFR activity and responsiveness to Epidermal Growth Factor (EGF) (Oztan et al., 2017). These mutations are in the

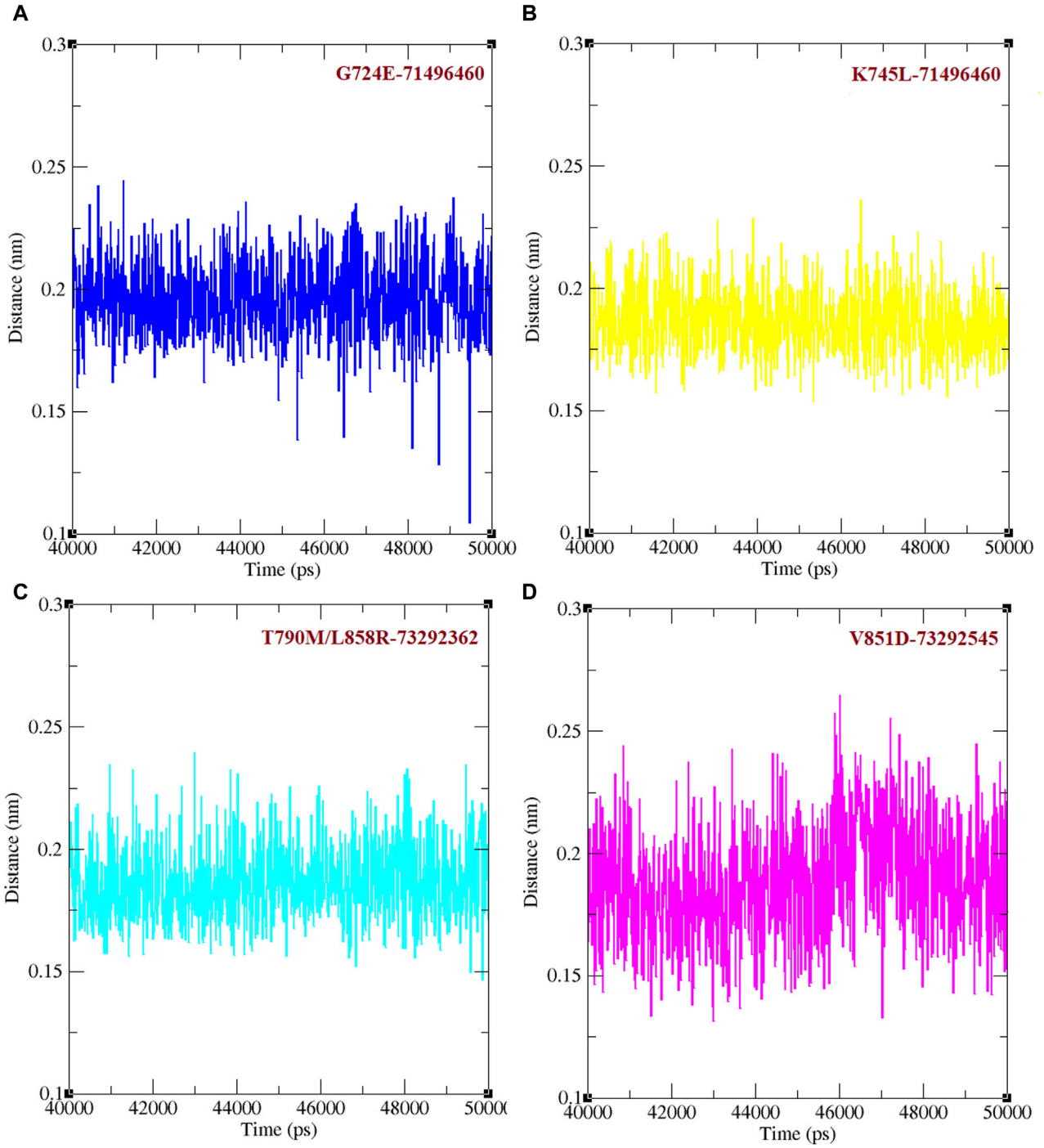

FIGURE 6
Minimum distance between mutant EGFR with its respectively screened compounds. **(A)** The minimum distance between G724E-71496460. **(B)** The minimum distance between K745L-71496460. **(C)** The minimum distance between T790M/L858R-732992362. **(D)** The minimum distance between V851D-73292545.

EGFR protein's extracellular domain that is responsible for drug molecule binding (Brindel et al., 2020). The K745L mutation alters the amino acid at position 745, where lysine plays a role in anchoring the EGFR protein to the cell membrane and activating it when bound to EGF (Bean et al., 2008). Lysine is a larger than leucine and a positively charged amino acid and this substitution can change the shape and solvent accessibility of the EGFR protein, which can affect its ability to interact with other molecules. The double mutation, T790M/L858R, occurs in exon 20 of the EGFR gene (Fujiwara et al., 2020). T790M mutation replaces threonine with methionine, while L858R replaces lysine with arginine. Both these mutations have the potential to alter EGFR's drug interactions as the substituting amino acids could affect the polarity and charge properties of the protein potentially obstructing drug binding.

To the best of our knowledge, this study is the first to report the V851D mutation in EGFR as drug resistant in NSCLC cases. Substitution of aspartic acid for valine at position 851 in the V851D mutant imparts additional negative charge potentially altering its folding as well as function. Moreover, position 851 falls in the tyrosine kinase domain of EGFR, which is responsible for binding to other molecules, and this mutation could negatively affect its binding to other proteins or drugs due to altered electrostatic interactions within the protein.

Among the six mutant structures considered for molecular docking analysis, K745L and V851D exhibited high binding energies and a slightly modified binding orientation when interacting with osimertinib. Similarly, G724E and T790M/L858R also showed high binding energy and a slightly modified orientation when interacting with afatinib. The higher the binding energy, the lower the binding affinity, and *vice versa*. Molecular docking analysis also elucidated mutations that impact the drug-binding abilities of EGFR as indicated by the elevated RMSD values due to significant conformational changes in the mutant EGFR proteins. Hydrogen bond analysis revealed fewer hydrogen bonds formed between the mutant structures with corresponding drugs compared to WT EGFR. Similarly, in the minimum distance analysis, it was observed that the mutant structures exhibited greater distances compared to WT EGFR when interacting with afatinib or osimertinib. The hydrogen bond and minimum distance analyses confirmed that all drug resistance mutations affected the conformation of the drug-binding pocket, consequently disrupting the usual non-bonded interactions with afatinib and osimertinib. The SASA measurement, reflecting the overall surface area of the protein structure, indicated the potential interaction areas with other molecules. WT EGFR exhibited a larger surface area than the mutant structures, indicating that drug-resistant mutations rendered the EGFR structures more compact. Collectively, these findings contribute to a comprehensive characterization of the WT and mutant complexes and their implications for drug binding.

Our next goal is to identify new drug compounds that could potentially inhibit the mutant EGFR activity. Using virtual screening, we screened for compounds that have structural similarity to FDA-approved afatinib and osimertinib to determine the most effective compound to block the mutant EGFR structures. A total of 7385 chemical compounds were screened against four mutant EGFR structures (G724E, K745L, V851D, and T790M/L858R) resulting in the identification of three compounds (CID 71496460, 73292362, and 73292545) that exhibited strong binding affinity with the EGFR mutant structures. CID 71496460 was identified to target both G724E and K745L mutants, while CID 73292362 and CID 73292545 were found to be good candidates for T790M/L858R and V851D mutants, respectively. These compounds demonstrated similar characteristics to osimertinib and established more hydrogen bonds with the mutant EGFR than afatinib and osimertinib. In this context, the drug resistance mutations within the binding site induced subtle conformational changes that affected the binding of afatinib and osimertinib. Conversely, compounds similar to these drugs might possess slight conformational variations that enable them to fit the newly acquired conformation of EGFR resulting from the mutations. Molecular dynamic simulations were performed to delve deeper into the efficacy of the screened compounds, analyzing crucial parameters such as hydrogen bond formation and minimum distance analysis. The analysis of hydrogen bonds revealed that the screened compounds formed more hydrogen bonds than the original drugs, while the minimum distance analysis demonstrated that the identified compounds exhibited reduced distances relative to the approved drugs. These analyses further confirm the suitability of using the three screened compounds as effective inhibitors of the mutant EGFR proteins, which should be further evaluated by experimental studies.

5 Conclusion

EGFR inhibitors have revolutionized cancer treatment, offering substantial benefits in managing various malignancies. However, the intricate nature of tumor biology, marked by heterogeneity and genomic instability, poses a significant challenge in the form of anticancer drug resistance, particularly with EGFR inhibitors. Our research has identified specific drug resistance mutations using WES data that hyperactivate the EGFR protein, leading to uncontrolled cell proliferation in NSCLC patients. This resistance to anti-cancer drugs highlights the urgent need for alternative approaches to effectively combat drug resistance in the EGFR-driven tumors. Through virtual screening, we have successfully identified lead compounds with the potential to inhibit EGFR activity in the presence of identified drug resistance mutations. This promising avenue offers hope for developing effective and personalized treatment options for patients with heterogeneous genetic backgrounds. By targeting drug-resistant EGFR mutations and leveraging the potential of NGS technologies, we aim to pave the way for more personalized and effective treatments, ultimately improving outcomes and quality of life for those affected by EGFR-driven NSCLC cancers.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: SRA ID PRJEB21459, PRJNA616048/dbGaP: phs002001, PDB ID: 3VJO.

Ethics statement

Ethical approval was not required for the study involving humans in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was not required from the participants or the participants'' legal guardians/next of kin in accordance with the national legislation and the institutional requirements.

Author contributions

NN: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Software, Validation, Visualization, Writing–original draft, Writing–review and editing. CG: Conceptualization, Funding acquisition, Investigation, Project administration, Resources, Supervision, Writing–review and editing.

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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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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2024.1428158/full#supplementary-material

SUPPLEMENTARY FIGURE S1
Interaction analysis between WT and mutant type with drug osimertinib. **(A)** Interaction analysis between wild-type EGFR with osimertinib. **(B)** Interaction analysis between G724K with osimertinib. **(C)**. Interaction analysis between mutant K745L with osimertinib. **(D)** Interaction analysis between mutant V851D with osimertinib.

SUPPLEMENTARY FIGURE S2
Interaction analysis between WT and mutant type with drug afatinib. **(A)** Interaction analysis between wild-type EGFR with afatinib. **(B)**. Interaction analysis between L718A with afatinib. **(C)** Interaction analysis between mutant G724E with afatinib. **(D)** Interaction analysis between mutant T790M/L858R with afatinib.

SUPPLEMENTARY FIGURE S3
Root mean square deviation analysis for WT and mutant EGFR structures interacts with **(A)** Osimertinib and **(B)** Afatinib.

SUPPLEMENTARY FIGURE S4
Solvent accessible surface analysis for WT and mutant EGFR structures interacts with **(A)** Osimertinib and **(B)** Afatinib.

SUPPLEMENTARY FIGURE S5
Virtually screened compounds against EGFR mutant structures: **(A)** CID: 71496460, **(B)** CID:73292362, and **(C)** CID: 73292545.

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Potential therapeutic option for EGFR-mutant small cell lung cancer transformation: a case report and literature review

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Transformation from non-small cell lung cancer (NSCLC) to small cell lung cancer (SCLC) is rare and is associated with poor prognosis. However, the standard treatment protocols for patients with SCLC transformation remain unknown. Here, we report the case of a patient with advanced EGFR exon 19 deletion (19del) NSCLC who underwent SCLC transformation during targeted therapy. Biopsies and genetic testing were performed to adjust treatment regimens accordingly. The patient responded favorably to a combined treatment regimen comprising etoposide plus cisplatin chemotherapy and adebrelimab plus osimertinib. This case highlights the critical importance of acknowledging tumor heterogeneity in clinical decision-making and identifying potentially effective treatment options for patients with SCLC transformation. Additionally, we reviewed cases of the transformation of NSCLC to SCLC from 2017 to 2023.

KEYWORDS

non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC), pathological transformation, EGFR exon 19 deletion (19 del), combination therapy, case report

Introduction

The management of non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) is a critical area of investigation in the field of oncology. NSCLC, which accounts for 80-85% of all lung cancers, plays a significant role in targeted therapy (1, 2). EGFR exon 19 deletion (19del) is a common genetic alteration observed in patients with advanced NSCLC (3). When treated with EGFR-tyrosine kinase inhibitor (TKI), some EGFR-mutated NSCLC patients may undergo rare pathological transformations to SCLC (4), which is an important mechanism for resistance to EGFR-TKI treatment. Several studies have reported that NSCLC-derived SCLCs exhibit clinical features similar to primary SCLCs (5). However, for patients who undergo transformation from NSCLC to SCLC, chemotherapy provides only short-term effectiveness and leads to poor prognosis, with a median overall survival (OS) of

less than 1 year (6). Therefore, the timely identification and development of effective treatment strategies are crucial. Although SCLC transformation in NSCLC patients has been documented in the literature (Table 1), there is no clear consensus on the optimal treatment regimen for these patients.

Here, we describe the case of a patient with advanced NSCLC with EGFR 19del who underwent pathological transformation from NSCLC to SCLC. Repeated biopsies and next-generation sequencing (NGS) tests, along with clinical disease evolution, have underscored tumor heterogeneity. These findings indicate that multimodal treatment, including chemotherapy, targeted therapy, and immunotherapy, may be a viable therapeutic strategy for this specific patient group.

Case presentation

Diagnosis and initial treatment response

A 68-year-old female was admitted to the hospital on July 12, 2021, because of cough and expectoration for 2 months. The patient had no history of smoking or cancer history. Contrast-enhanced chest computed tomography (CT) revealed a mass in the upper lobe of the left lung, along with multiple small nodules in both lower lobes and enlarged mediastinal and hilar lymph nodes. Moreover, pleural thickening and pleural effusion were observed (Figure 1A). Biopsy of the enlarged lesion in the left upper lobe (LUL) revealed poorly differentiated adenocarcinoma of the lung (Figure 2A). 14-gene panel testing identified an EGFR 19del mutation (Table 2). The patient was diagnosed with stage IV lung adenocarcinoma with EGFR 19del. The patient achieved partial response (PR) after first-line treatment with osimertinib (Figure 1B). Progression-free survival (PFS) after the first-line treatment was 24 months.

Disease progression and SCLC transformation

Subsequently, the patient experienced progressive disease (PD), with an increase in the size of the LUL lesion (Figure 1C) and emergence of cervical lymph node metastasis (Figure 3A). In June 2023, a second LUL biopsy was performed. Unexpectedly, hematoxylin and eosin (HE) staining showed mixed histology of adenocarcinoma and SCLC. Immunohistochemical (IHC) staining confirmed the presence of *thyroid transcription factor-1 (TTF-1)* (weakly +), *napsin A* (+), *synaptophysin* (+), *CD56* (+), and *CgA* (+) (Figure 2B). In addition to EGFR 19del, 1012-gene panel testing further demonstrated a TP53 missense mutation, RB1 truncating mutation, EGFR amplification, KIT amplification, and tumor mutational burden (TMB) of 11 mutations per megabase (mt/Mb) (Table 2).

Subsequent treatment regimen and treatment response

The patient declined the therapeutic option of chemotherapy and instead opted for second-line treatment with a combination of anlotinib and aumolertinib. However, 4 months later, follow-up enhanced CT and neck ultrasonography revealed PD of the LUL lesion (Figure 1D) and shrinkage of the cervical lymph nodes (Figure 3B). Therefore, the regimen was changed to etoposide plus cisplatin (EP) chemotherapy plus adebrelimab. Following two cycles of EP chemotherapy combined with immunotherapy, the primary lesion located in the LUL exhibited a significant reduction in size (Figure 1E), while enlargement of the right cervical lymph node was observed (Figures 3C, D). Fine-needle aspiration biopsy of the right cervical lymph node was performed to determine the underlying reasons for the inconsistent response in distinct lesions. Pathological examination revealed poorly differentiated adenocarcinoma originating in the lung (Figure 2C). IHC staining demonstrated *TTF-1* (+), *napsin A* (+), *CK7* (+), *synaptophysin* (-), *CD56* (-), and *CgA* (-). 1012-gene panel testing revealed multiple gene mutations, including EGFR 19del, TP53 missense mutation, RB1 truncating mutation, NDM4 amplification, and a TMB of 11 mt/Mb (Table 2). Considering the heterogeneity of lung cancer, we introduced osimertinib in addition to the existing chemotherapy and immunotherapy regimens from the third cycle onward. After two cycles of combined treatment, both the primary LUL lesion and metastatic lesion in the cervical lymph nodes showed a notable decrease (Figures 1F, 3E, F). Until the last follow-up in February 2024, no deaths occurred and the follow-up time was 32 months. The flowchart of the treatment process is shown in Figure 4.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the patient for publication of the case report and accompanying images. A copy of the written consent form is available for review by the journal's editorial office.

Discussion

For advanced NSCLC patients with EGFR mutation, the first-line treatment option is EGFR-TKIs, including gefitinib, erlotinib, afatinib, osimertinib, anlotinib, and aumolertinib (34). However, single-agent targeted therapies for NSCLC frequently fail because of the development of acquired drug resistance. Transformation into SCLC represents a rare mechanism of resistance to EGFR-TKIs in advanced lung adenocarcinoma harboring EGFR mutations, accounting for approximately 5-15% of resistance etiologies (35, 36). However, the precise mechanisms underlying this transformation remain unknown. The potential mechanisms of SCLC transformation include epithelial-to-mesenchymal transition (EMT); mutations that affect TP53, RB1, and PIK3CA; and acquired EGFR mutations (35, 37, 38). Patients with a triple-positive mutation profile of EGFR, TP53, and RB1 exhibited a 6-fold augmented susceptibility to SCLC conversion compared with patients without mutations in TP53 and RB1 (39, 40). Few cases of SCLC transformation have been reported in patients receiving immunotherapy, such as programmed death-1 inhibitors (41).

Patients with EGFR-mutated NSCLC who underwent transformation to SCLC exhibited a significantly unfavorable

TABLE 1 Summary of cases of small cell lung cancer transformed from non-small cell lung cancer (2017 to 2023).

Case Number	Report Year	Age (years)	Sex	Country	Smoking status	Mutational status of tumor sample	Medication taken before the transition	Medication taken after the transition	CNS metastasis	OS after transformation	OS	Reference
1	2017	75	Male	Japan	Smoker	Negative	Docetaxel and bevacizumab followed by nivolumab	Amurubicin	NM	About 2 months	About 8 months	(7)
2	2018	62	Male	Japan	Smoker	ALK rearrangement	PC, bevacizumab, followed by alectinib	Alectinib followed by EP and then AMR, nivolumab, and irinotecan	Yes	About 8 months	About 4 years	(8)
3	2018	65	Male	USA	Smoker	Negative	PC and then nivolumab	EC	NM	NA	NA	(9)
4	2018	68	Male	USA	NM	NM	TC and pembrolizumab	EC	NM	NA	NA	(9)
5	2018	38	Male	China	Never-smoker	EGFR exon 21 L858R	PP followed by erlotinib	EP	Yes	NA	NA	(10)
6	2018	69	Male	Japan	NM	EGFR 19del	Erlotinib and pemetrexed plus bevacizumab	IP followed by afatinib and then osimertinib	Yes	NA	NA	(11)
7	2019	67	Female	USA	Smoker	TP53, RB1	carboplatin and P TX and then nivolumab	EC and then paclitaxel	NM	About 11 months	About 4 years	(12)
8	2019	75	Female	USA	Smoker	KRAS G12C, TP53	Nivolumab	EC and then nivolumab and then ipilimumab and then irinotecan	NM	About 16 months	About 5.5 years	(12)
9	2019	66	Male	Japan	Smoker	EGFR	TC and bevacizumab and then pembrolizumab	EC and then amrubicin	NM	About 5 months	About 12 months	(13)
10	2019	70	Female	Israel	Smoker	TP53	Nivolumab	NM	NM	NA	NA	(14)
11	2019	75	Male	Israel	Smoker	TP53	Nivolumab	EC	NM	About 13 months	About 31 months	(14)
12	2020	65	Male	Japan	Smoker	Strongly positive for PD-L1	Pembrolizumab	IP and then Amrubicin	No	About 17 months	NM	(15)

(Continued)

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TABLE 1 Continued

Case Number	Report Year	Age (years)	Sex	Country	Smoking status	Mutational status of tumor sample	Medication taken before the transition	Medication taken after the transition	CNS metastasis	OS after transformation	OS	Reference
13	2020	69	Male	China	Smoker	TP53 mutation; R342* nonsense mutation	Pembrolizumab	EC	NM	NA	NA	(16)
14	2020	60	Female	USA	Smoker	TP53, CDKN2A R58, PIK3CA E545K mutation; SOX2 PIK3CA, CCND2, CCND3, MYCL1, CSF3R, FGF23, FGF6, C17orf39, KDM5A, PRKCI, TERC, VEGF amp	carboplatin and gemcitabine and then nivolumab	EC	NM	About 14 months	About 39 months	(17)
15	2020	62	Male	Japan	NM	High PD-L1 (70%) expression, TP53 inactivation and RB1 loss	IP and then pembrolizumab	EP	NM	NA	NA	(18)
16	2020	56	Male	China	Smoker	EGFR 19del, EGFR amp, RB1, TP53, MSH6, PMS2 amp; PD-L1 (–); TMB of 15.32 Muts/Mb; MSS	Icotinib	EC followed by docetaxel, sequential icotinib, irinotecan, anlotinib, and pabolizumab	NM	About 9 months	About 15 months	(19)
17	2020	68	Male	Japan	Smoker	EGFR 19 del, T790M	Osimertinib followed by erlotinib and then osimertinib and then carboplatin, paclitaxel, docetaxel, and pemetrexed and then S-1 monotherapy	EC	NM	NA	NA	(20)
18	2021	63	Female	Italy	Never-smoker	EGFR 19del and T790M, TP53	Gefitinib followed by osimertinib	Platinum–etoposide doublet followed by paclitaxel and whole-brain radiotherapy	Yes	NA	NA	(21)
19	2021	64	Male	Japan	Smoker	NM	CBDCA and docetaxel and then nivolumab	IC, AMR, nab-paclitaxel	NM	NA	NA	(22)
20	2021	70	Male	Japan	Smoker	NM	TC and then nivolumab	Etoposide	NM	NA	NA	(22)

(Continued)

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TABLE 1 Continued

Case Number	Report Year	Age (years)	Sex	Country	Smoking status	Mutational status of tumor sample	Medication taken before the transition	Medication taken after the transition	CNS metastasis	OS after transformation	OS	Reference
21	2021	74	Female	Japan	Never-smoker	NM	TC followed by vinorelbine and then nivolumab and then atezolizumab	AMR	NM	NA	NA	(22)
22	2021	43	Male	China	Never-smoker	EGFR 19del and high PD-L1 (80.9%) expression	Gefitinib followed by 8 cycles of pembrolizumab plus pemetrexed and then osimertinib	EP followed by anlotinib plus gefitinib and then EC plus durvalumab	NM	About 20 months	About 7 years	(23)
23	2021	57	Male	China	Smoker	EGFR 19 del, EGFR exon20p, MYC amp, RB1, TP53, T790M, EGFR amp	Gefitinib	EC followed by irinotecan and nedaplatin plus icotinib	Yes	NA	NA	(24)
24	2022	84	NM	China	Smoker	EGFR exon 21 L858R	Osimertinib	Durvalumab and EC	Yes	NA	NA	(25)
25	2022	63	Female	China	Never-smoker	EGFR	Gefitinib	Refuse treatment	NM	About 12 months	About 22 months	(26)
26	2022	50	Male	China	Smoker	EGFR 19del and T790M	Erlotinib followed by toripalimab plus PC	EC followed by osimertinib	Yes	NA	NA	(27)
27	2022	44	Male	China	NM	EGFR 19del, TP53 Y220H, RB1 F755V	Icotinib	Combined radioactive particle implantation and 6 cycles of IP chemotherapy followed by paclitaxel plus cisplatin and then apatinib followed by GP	Yes	NM	About 3 years	(28)
28	2023	56	Male	China	Smoker	Negative	Sugemalimab (neoadjuvant with chemotherapy); Sugemalimab (consolidation therapy)	EP	NM	About 6 months	About 14 months	(29)

(Continued)

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TABLE 1 Continued

Case Number	Report Year	Age (years)	Sex	Country	Smoking status	Mutational status of tumor sample	Medication taken before the transition	Medication taken after the transition	CNS metastasis	OS after transformation	OS	Reference
29	2023	58	Female	China	NM	EGFR L858R, T790M, TP53, RB1	Osimertinib	EP followed by osimertinib in combination with EP, and then osimertinib and anlotinib	Yes	About 11 months	About 35 months	(30)
30	2023	43	Female	France	Smoker	TP53	Alectinib	Pralsetinib followed by EC and then TC	Yes	NA	NA	(31)
31	2023	30	Female	China	Never-smoker	KIF5B-RET fusion	No treatment during pregnancy and then selpercatinib	HS-10365 followed by EC	Yes	NA	NA	(32)
32	2023	52	Male	China	Smoker	EML4-ALK fusion, KRAS G12D, TP53, RB1, PIK3CA, ALK V1180L; TMB of 11.3 muts/Mb; MSS	Ensartinib followed by alectinib	EP followed by lorlatinib	Yes	NA	NA	(2)
33	2023	77	Male	China	NM	EML4-ALK fusion, CRKL amp, VEGFR1 amp, loss of RB1; TMB of 2.23 muts/Mb; MSS	Alectinib followed by radiotherapy	Atezolizumab plus EC, remaining alectinib	Yes	About 9 months	About 21 months	(33)
Our case	2024	71	Female	China	Never-smoker	EGFR 19 del	Osimertinib	Anlotinib and aumolertinib followed by EP plus adebrelimab and then osimertinib, EP, plus adebrelimab	No	NA	NA	

*The asterisk means termination codon.

amp, amplification; AMR, ceritinib, alectinib, and amrubicin; CNS, central nervous system; EC, etoposide plus carboplatin; EP, etoposide plus cisplatin; GP, gemcitabine plus cisplatin; IC, irinotecan plus carboplatin; IP, irinotecan plus cisplatin; MSS, microsatellite stability; NA, not applicable; NM, Not mentioned; OS, overall survival; PC, pemetrexed plus carboplatin; PP, pemetrexed plus cisplatin; TC, paclitaxel plus carboplatin; TMB, tumor mutational burden; 19del, exon19 deletion.

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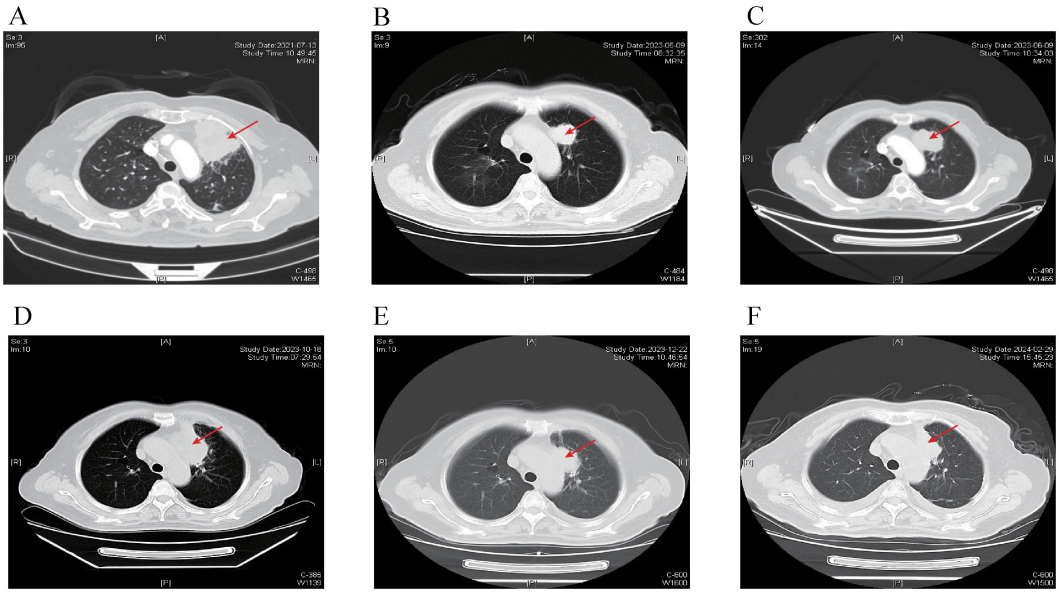

FIGURE 1
Chest CT scans at different time points. The red arrow indicates primary lesion in the left upper lobe of the lung. **(A)** Chest CT scan of baseline. **(B)** Chest CT scan of best response PR after first-line treatment with Osimertinib. **(C)** Chest CT scan showing progression after 24 months of Osimertinib. **(D)** Chest CT scan showing progression after 4 months of Anlotinib and Aumolertinib. **(E)** Chest CT scan showing reduction in the LUL lesion after 2 cycles of EP chemotherapy plus Adebrelimab. **(F)** Chest CT scan showing regression in the LUL lesion after fourth-line treatment with Osimertinib in addition to the existing chemotherapy and immunotherapy regimen. CT, computed tomography; PR, partial response; LUL, left upper lobe; EP, etoposide plus cisplatin.

prognosis in terms of survival. A study involving 39 patients reported an average survival duration of merely 6 months after SCLC conversion (42). An analysis of 67 patients revealed a median OS of 10.9 months after SCLC transformation (43). These data imply that timely recognition and efficient intervention play crucial roles in the management of patients undergoing SCLC transformation.

Due to the lack of established treatment guidelines for patients undergoing SCLC transformation, current therapeutic approaches

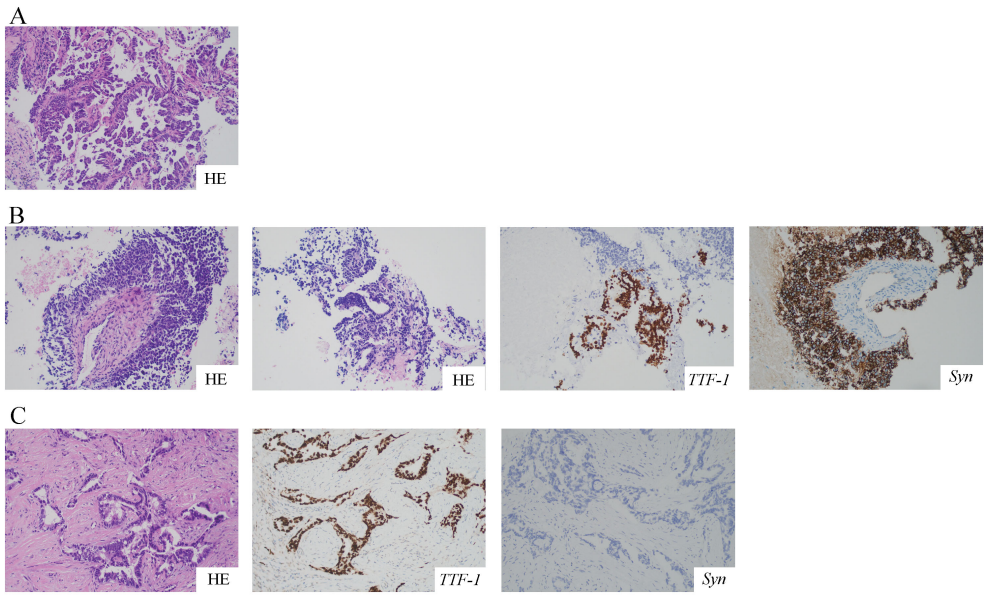

FIGURE 2
HE and IHC staining of the tumor at different time points. All pictures were taken at a 200-fold magnification using a light microscope. **(A)** Biopsy specimen of LUL revealed poorly differentiated lung adenocarcinoma with HE staining. **(B)** The second biopsy of LUL revealed mixed histology of adenocarcinoma and SCLC with HE and IHC staining for *TTF-1* and *Syn*. **(C)** The third biopsy of the right cervical lymph node revealed poorly differentiated adenocarcinoma with HE and IHC staining for *TTF-1* and *Syn*. HE, hematoxylin and eosin; IHC, immunohistochemistry; LUL, left upper lobe; SCLC, small cell lung cancer; *TTF-1*, thyroid transcription factor-1; *Syn*, synaptophysin.

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TABLE 2 Overview of patient's multiple next-generation sequencing results.

Gene name	Mutations	Mutation frequency/copy number		
		LUL before treatment	LUL after treatment	Right cervical lymph node
EGFR	p.L747_A755delinsSKD 19del	26.10%	45.85%	8.07%
TP53	p.P278T exon8 missense mutation		83.52%	33.48%
RB1	p.E464* exon15 nonsense mutation		80.16%	38.84%
EGFR	gene amplification		6.6-fold	NA
KIT	gene amplification		4.1-fold	NA
MDM4	gene amplification		NA	6.0-fold

19del, exon19 deletion; LUL, left upper lobe; NA, not applicable.

are based on retrospective studies and case reports (6). Platinum and etoposide-based chemotherapy remains the standard treatment for patients with SCLC transformation, with the median disease control time of approximately 3 months. A real-world study included 29 patients who developed SCLC transformation following EGFR-targeted therapy. The analysis indicated that compared to chemotherapy alone, the combination of chemotherapy and targeted therapy improved objective response rates and PFS, although it did not significantly extend OS. Anti-angiogenic therapy and local radiotherapy can prolong OS after transformation (44). A multicenter study involving 32 patients with EGFR-mutant NSCLC who experienced SCLC transformation after targeted therapy revealed that the most commonly used chemotherapy regimen post-transformation was etoposide combined with platinum (n=27), with a median PFS of 3.5 months. Additionally, 3 patients received irinotecan combined with platinum, achieving a median PFS of 7.6 months. Five patients were treated with anlotinib, and the anlotinib group showed a median PFS of 6.2 months (45). Although data suggest that irinotecan combined with platinum and anlotinib may yield better survival outcomes, the limited sample size makes this conclusion less convincing. Furthermore, a case report compared the outcomes of two patients with EGFR-mutant NSCLC who underwent SCLC transformation and received different treatment regimens. One patient received the EP regimen alone post-transformation, achieving a PFS of only 3 months. The other patient received erlotinib combined with the EP regimen, followed by long-term maintenance therapy with erlotinib and oral etoposide, ultimately achieving a PFS of 8 months (46). However, to date, there have been no reports on combined use of chemotherapy, targeted therapy, and immunotherapy for patients with SCLC transformation. In this case, the patient developed PD that transformed into SCLC after 24 months of osimertinib treatment. Further PD occurred following the dual-targeted therapy. Subsequent EP chemotherapy and immunotherapy led to a reduction in the size of the primary lesion and enlargement of

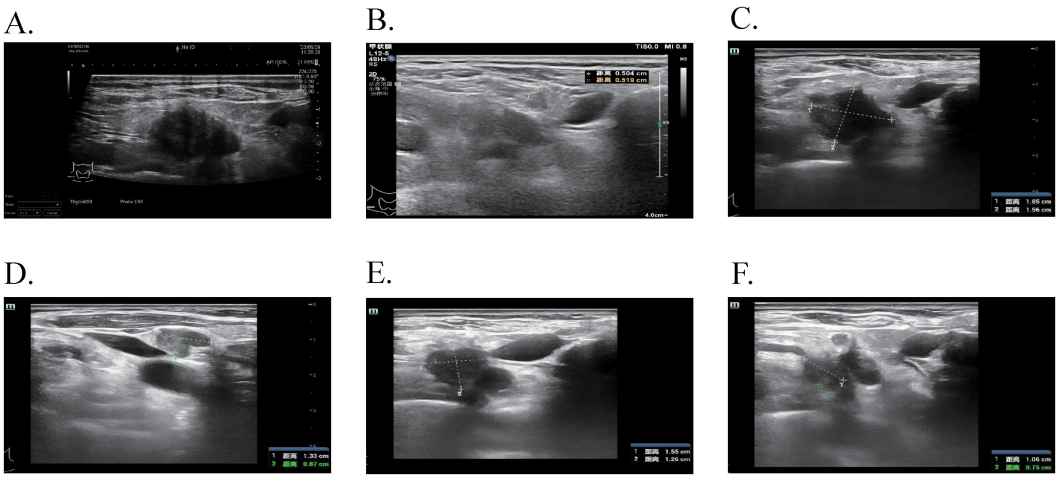

FIGURE 3
The ultrasound features of cervical lymph nodes at different time points. **(A)** After 24 months of Osimertinib, enlarged lymph nodes were observed in the IV region of the right neck, with a maximum size of 2.3 × 1.7 cm. **(B)** Following dual-targeted therapy, a previously enlarged lymph node in the IV region of the right neck reduced to 0.5 × 0.5 cm. **(C, D)** After 2 cycles of EP chemotherapy plus Adebrelimab, increased and enlarged lymph nodes were detected in the right neck IV area, with the largest measuring 1.9 × 1.6 cm and 1.3 × 0.9 cm. **(E, F)** With the addition of Osimertinib to the existing chemotherapy and immunotherapy regimen, the enlarged lymph nodes in the right neck IV area measured 1.6 × 1.3 cm and 1.1 × 0.8 cm.

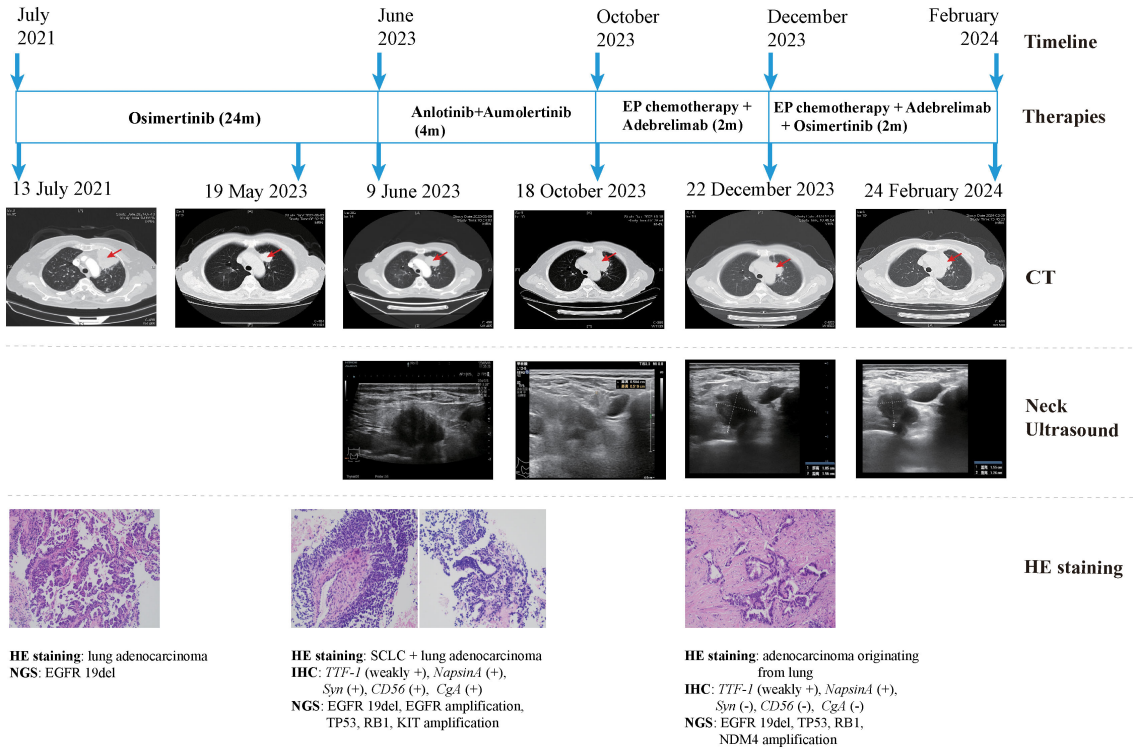

FIGURE 4
Case presentation of the 68-year-old female patient of SCLC transformation, including timeline, treatment details, chest CT images, neck ultrasound images, HE staining images and NGS findings. CT, computed tomography; HE, hematoxylin and eosin; SCLC, small cell lung cancer; NGS, next-generation sequencing; 19del, exon19 deletion; IHC, immunohistochemistry; *TTF-1*, thyroid transcription factor-1; *Syn*, synaptophysin.

cervical lymph nodes. The addition of osimertinib for two cycles resulted in a reduction in both the LUL and cervical lymph node lesions. This finding suggests that EGFR-TKIs only inhibit the EGFR-mutant NSCLC component, allowing the SCLC component to rapidly proliferate and reach PD. EP chemotherapy combined with adebrelimab is the standard treatment for SCLC; thus, simple inhibition of SCLC may lead to rapid regrowth of the NSCLC component. The combination of targeted therapy, chemotherapy, and immunotherapy resulted in a reduction in both primary and metastatic lesions, indicating that mixed histological components of SCLC and NSCLC should be considered. This suggests that for patients experiencing SCLC transformation who still harbor EGFR mutations, a combination of chemotherapy, immunotherapy, and targeted therapy may be an effective treatment approach. However, additional randomized controlled trials are required for further validation. Moreover, recognizing tumor heterogeneity and performing timely biopsies and genetic testing during changes in a patient's condition are pivotal for facilitating the rapid detection of pathological transformations, tailoring individualized treatment strategies, and enhancing the prognoses of patients.

EGFR-mutated lung adenocarcinoma accompanied by RB1 and TP53 mutations represents the highest-risk group for SCLC transformation during targeted therapy, with a transformation probability of up to 18%. Patients harboring EGFR, RB1, and TP53 mutations exhibit the poorest treatment outcomes, with median time to treatment discontinuation and OS of 9.5 months and 29.1 months, respectively (40). In our case, re-biopsy following disease progression on EGFR-TKIs revealed concurrent EGFR, RB1, and TP53 mutations. Unfortunately, due to the lack of comprehensive genetic analysis at the initial NSCLC diagnosis, only a 14-gene panel was performed, missing critical baseline information on TP53 and RB1 gene status. This underscores the importance of re-biopsy in EGFR/RB1/TP53-mutant lung adenocarcinoma, particularly in patients with poor response to EGFR-TKIs.

In a comprehensive systematic review by Roca et al., 39 patients who underwent SCLC transformation between 2006 and 2016 were systematically evaluated (42). To delve deep into the demographic characteristics, therapeutic interventions, and prognoses of patients experiencing SCLC transformation, we reviewed 33 cases of SCLC transformation from 2017 to 2023 and summarized their genetic mutations, treatment modalities, and patient outcomes in Table 1. Among the 33 reported cases, the majority were of Asian ethnicity and demonstrated a pronounced association with poor prognoses, frequently accompanied by central nervous system metastases. Notably, 13 out of 33 patients (39%) presented with central nervous system metastasis. Observational data suggest that male

patients (66%) may be more likely to undergo SCLC transformation. What's more, among the 33 cases, the majority of patients had either an unmentioned family history or no family history, and the patient presented in this case had no history of cancer. It was worth noting that 63% were smokers and 18% were non-smokers, suggesting that smoking may have a potential impact on transformation to SCLC. Disparities in the implementation of personalized medicine across different countries and regions underscore variations in treatment standards and medication accessibility, potentially impacting treatment efficacy and patient survival rates. For instance, Asian populations may prioritize the utilization of the EGFR-TKIs, while Western countries may prioritize the utilization of immunotherapy. EGFR, ALK, and TP53 mutations are commonly observed in patients undergoing SCLC transformation. Among them, EGFR mutations were reported in 13 cases (39%), including 8 cases with EGFR 19 del (62%) and 3 case with EGFR exon 21 L858R (23%). Therefore, we speculate that SCLC transformation is more likely to occur in patients with EGFR mutation and subsequent resistance to targeted therapy.

Surgical specimens were unattainable in patients with unresectable NSCLC at the initial diagnosis. The presence of two histological components could not be definitively excluded because of the inherent limitations of the existing examination methods and techniques. This highlights the importance of obtaining an ample number of tissue specimens from patients with advanced lung cancer to mitigate misdiagnoses resulting from limited sampling.

Despite multiple reported cases of SCLC transformation, treatment strategies remain inadequately explored. In our case report, we document the successful use of EP chemotherapy in combination with adebrelimab and osimertinib for the first time in the management of advanced SCLC transformation. Encouragingly, imaging results indicate a favorable therapeutic response. Nevertheless, the precise molecular mechanism underlying this transformation remains elusive, and consensus treatment guidelines are lacking. Future work should focus on unraveling the molecular mechanisms of this transformation and conducting prospective studies to establish evidence-based treatment protocols.

Conclusions

SCLC transformation is a rare but crucial cause of acquired EGFR-TKI resistance. It is essential to conduct repeated biopsies and employ NGS and IHC tests to identify alterations in histological types. We found that the combination of EP chemotherapy plus adebrelimab and osimertinib had a significant therapeutic effect in patients with NSCLC pathological transformed to SCLC. The multimodal treatment approach involving chemotherapy, targeted therapy and immunotherapy may be a promising strategy for this distinct patient cohort.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding authors.

Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

XXL: Writing – original draft, Writing – review & editing. XCL: Writing – original draft, Writing – review & editing. MZ: Writing – original draft. RW: Writing – review & editing. JG: Methodology, Writing – review & editing. JL: Investigation, Writing – review & editing. WQ: Supervision, Writing – review & editing. SZ: Supervision, Writing – review & editing.

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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.

Publisher's note

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Glossary

amp	amplification
AMR	Ceritinib, alectinib, amrubicin
CNS	central nervous system
CT	computed tomography
EMT	epithelial-to-mesenchymal transition
EC	etoposide plus carboplatin
EP	etoposide plus cisplatin
GP	gemcitabine plus cisplatin
HE	hematoxylin and eosin
IC	irinotecan plus carboplatin
IHC	immunohistochemistry
IP	irinotecan plus cisplatin
LUL	left upper lobe
MSS	microsatellite stability
mt/Mb	mutations per megabase
NA	not applicable
NGS	next-generation sequencing
NM	Not mentioned
NSCLC	non-small cell lung cancer
OS	overall survival
PC	pemetrexed plus carboplatin
PP	pemetrexed plus cisplatin
PD	progressive disease
PFS	progression-free survival
PR	partial response
SCLC	small cell lung cancer
Syn	synaptophysin
TC	paclitaxel plus carboplatin
TKI	tyrosine kinase inhibitors
TMB	tumor mutational burden
TTF-1	thyroid transcription factor-1
19del	exon 19 deletion.

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Efficacy and patient-reported outcomes in advanced non-small cell lung cancer patients receiving aumolertinib as first-line therapy: a real-world study

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Background: Aumolertinib demonstrated superior progression-free survival (PFS) and a well-tolerated toxicity profile compared to gefitinib in front-line treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC) in the AENEAS trial. However, patient-reported outcomes (PROs) of aumolertinib have not been published.

Methods: In this real-world study, the efficacy was evaluated by Response Evaluation Criteria in Solid Tumors (RECIST) 1.0. PROs were evaluated using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (QLQ-C30) and the EORTC Quality of Life lung cancer-specific module (QLQ-LC13) in advanced NSCLC patients receiving aumolertinib as initial therapy. Pre-specified key symptoms were cough, hemoptysis, dyspnea, sore mouth or tongue, dysphagia, hair loss, tingling in hands or feet, chest pain, arm or shoulder pain, and pain at other sites.

Results: A total of 33 patients were included, 23 of whom had efficacy information up to January 2024. The median follow-up time was 264 days (interval: 36–491 days). The objective response rate and disease control rate were 65.2% and 91.3%, respectively. The EORTC QLQ-LC30 general health status scale showed that functional scales increased and symptom scales decreased during aumolertinib treatment. Symptom scales assessed by the EORTC QLQ-LC13 showed that improvements in cough, sore mouth or tongue, tingling in hands or feet, chest pain, arm or shoulder pain, and other pain sites were both clinically and statistically significant after 6 months of aumolertinib treatment ($p < 0.05$).

Conclusion: In this real-world study, aumolertinib showed comparable disease control and objective response rates as reported in the AENEAS trial for advanced NSCLC patients with EGFR-sensitizing mutations. Aumolertinib treatment improved PROs, further supporting it in first-line clinical practice.

KEYWORDS

non-small cell lung cancer, epidermal growth factor receptor, aumolertinib, patient-reported outcomes, efficacy

1 Introduction

Worldwide, lung cancer ranks first in cancer-related deaths, of which non-small cell lung cancer (NSCLC) accounts for approximately 85% (Travis et al., 2015). The discovery of an epidermal growth factor receptor (EGFR)-sensitive mutation and the development of epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) pioneered targeted therapy for NSCLC. EGFR-TKIs, including the first, second, and third-generation drugs, significantly prolonged progression-free survival (PFS) and overall survival (OS) for advanced NSCLC patients with sensitive EGFR mutations as first-line treatment (Zhou et al., 2011; Maemondo et al., 2010; Fukuoka et al., 2011; Wu et al., 2014; Yang et al., 2015; Wu et al., 2017; Mok et al., 2017).

Advanced NSCLC is characterized by a high symptom burden (Iyer et al., 2014). At least 90% of patients experience fatigue, appetite loss, dyspnea, and pain, which significantly negatively impact disease-specific health-related quality of life (HRQoL) (Iyer et al., 2013; Polanski et al., 2016). Knowledge of the effects of new therapies on patient experiences, when combined with survival data, can provide crucial information to assist physicians and patients in making informed treatment decisions (Bottomley et al., 2005; Fallowfield and Fleissig, 2011). Compared with chemotherapy, the first-generation EGFR-TKIs, including gefitinib and erlotinib, significantly improved symptom control and HRQoL. Afatinib, a representative of the second generation EGFR-TKIs, exhibited similar results (Chen et al., 2013; Geater et al., 2015; Oizumi et al., 2012). In the ARCHER 1050 trial, dacomitinib, when used as first-line treatment for NSCLC, demonstrated superior survival compared to gefitinib. However, global HRQoL improvements were observed only with gefitinib (Wu et al., 2017). Osimertinib, a third-generation EGFR-TKI, demonstrated superior survival outcomes compared to first-generation EGFR-TKIs (Soria et al., 2018). Investigators sought to determine whether osimertinib provided better patient-reported outcomes (PROs) in addition to its longer survival benefits. However, PRO results from the FLAURA trial revealed that key symptoms improved significantly and were clinically relevant in both the osimertinib and erlotinib/gefitinib arms (Leighl et al., 2020). These findings suggest that the efficacy data reported by investigators may not fully align with PROs. It is, therefore, recommended that PROs and HRQoL be assessed in all prospective clinical comparative effectiveness research studies (Bottomley et al., 2005).

Aumolertinib (HS-10296) is a novel, irreversible, third-generation EGFR-TKI targeting both EGFR-sensitizing and T790M mutations while sparing wild-type EGFR. In the APOLLO registrational trial, patients with EGFR T790M-positive advanced NSCLC after disease progression on a first- or second-generation EGFR-TKI achieved a median PFS of 12.4 months, and the toxicity profile was tolerable (Lu et al., 2022a). ANEAS, a randomized, double-blind, phase-III trial, evaluated the efficacy and safety of aumolertinib compared with gefitinib as a first-line treatment of locally advanced or metastatic EGFR-mutated NSCLC. Aumolertinib achieved better survival than gefitinib, with a median PFS of 19.3 months *versus* 9.9 months (hazard ratio, 0.46; 95% CI, 0.36 to 0.60; $p < 0.0001$) (Lu et al., 2022b). Based on these results, aumolertinib was approved in China to treat advanced NSCLC with EGFR-sensitizing and T790M mutations.

Several studies also demonstrated the efficacy and safety profile of aumolertinib in real-world settings (Zhang et al., 2024; Ding et al., 2022; Zhang et al., 2022). However, all of these studies were retrospective, and some only reported individual cases. Importantly, PRO changes during aumolertinib treatment have not been reported. We prospectively collected European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire C30 (QLQ-C30) and EORTC Quality of Life lung cancer-specific module (QLQ-LC13) information and efficacy data. This showed that aumolertinib treatment significantly improved HRQoL.

2 Methods

2.1 Patients and study design

This prospective study was conducted between September 2022 and January 2024. Eligible patients were aged 18 years or older, with histologically/cytologically confirmed locally advanced or metastatic NSCLC, carrying an EGFR mutation, and having not received previous systemic anticancer therapy. The exclusion criteria were (i) previous receipt of any systemic therapy; (ii) concurrent presence of other malignancies requiring active treatment; and (iii) any other condition that, in the investigator's judgment, rendered the patient unsuitable for participation in this study. Enrolled patients received oral aumolertinib 110 mg once daily until disease progression, intolerable toxicity, or a request to discontinue by the patient or physician.

The treatment response was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0 based on computed tomography (CT) imaging. HRQoL was assessed with the use of the self-administered cancer-specific European Organization for Research and Treatment of Cancer (EORTC) quality-of-life questionnaire C30 (QLQ-C30) and its lung cancer-specific module, the QLQ-LC13. Patients were assessed monthly for the first half of the year from the start of

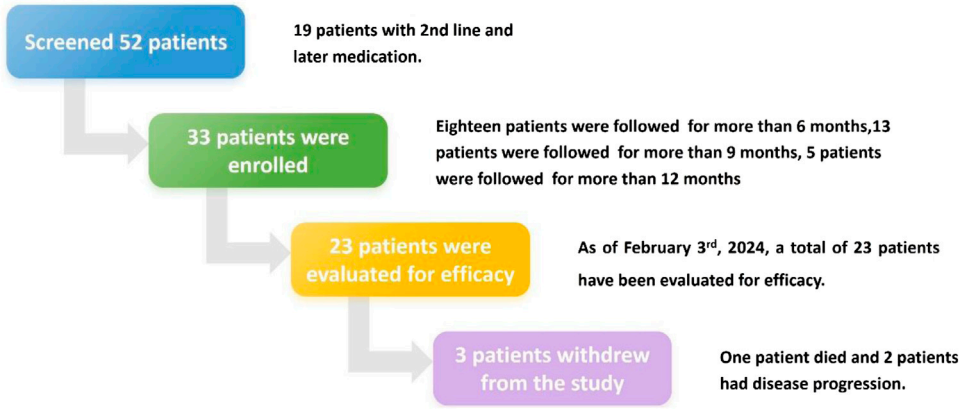


FIGURE 1
Flow chart of the research process.

treatment and then every 3 months until the 18th month. The primary endpoint was HRQoL. Secondary endpoints included objective tumor response (ORR) and disease control rate (DCR).

This study complied with the Ethical Guidelines for Medical and Health Research Involving Human Subjects. The study protocol received approval from the Ethical Review Boards and Institutional Review Boards of Qilu Hospital of Shandong University (KYLL-202308-041). All patients provided written, informed consent.

2.2 Assessment of tumor response and effectiveness

Tumor response was determined according to RECIST1.0 and was assessed every 2 months until disease progression. The objective response rate (ORR) was defined as the percentage of patients with a tumor-confirmed overall response of complete response (CR) or partial response (PR) in the total number of patients analyzed. The disease control rate (DCR) was defined as the percentage of patients with a tumor-confirmed overall response of complete CR, PR, or stable disease (SD). Progression-free survival (PFS) was followed up until the date of the first tumor progression or death for any reason, whichever occurred first. Overall survival (OS) was followed up until death for any reason.

2.3 EORTC QLQ-C30 and EORTC QLQ-LC13

The EORTC QLQ-C30 included five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, nausea, and vomiting), and the general health status scale. Multiple individual items on other common symptoms of cancer (dyspnea, loss of appetite, insomnia, constipation, and diarrhea) were also assessed, as were individual items measuring the economic impact of the disease. The majority of items were reported on verbal response scales of 1–4 with response options of "not at all," "a little bit," "quite a bit", and "very much," while the two general health status items were reported on numeric response scales of 1–7 with endings of "very poor" and "excellent".

The EORTC QLQ-LC13 consists of 13 questions on a multi-item scale, including questions measuring lung-cancer-related symptoms (coughing, hemoptysis, and dyspnea) and treatment-related adverse effects (sore mouth or tongue, dysphagia, hair loss, tingling in the hands or feet, chest pain, arm or shoulder pain, other pain, and the usefulness of pain medication). The QLQ-LC 13 item uses the same 1–4 verbal response scale as the QLQ-C30 item.

For each scale or item, a linear transformation was applied to normalize the raw score to 0–100. Higher scores on the functional and general health status scales represented better health status, while the opposite was true for the symptom scales. Any score change of 10 points from baseline was considered to be clinically meaningful. Improvement in health status was defined as an increase of ≥10 points from baseline in functional scale scores and a decrease of ≥10 points in symptom scales/items. Deterioration was defined as a decrease of ≥10 points in functional scales and an increase of ≥10 points in symptom scales/items. Otherwise, they were considered stable.

2.4 Statistical analyses

Descriptive statistical analysis of demographic information and clinical characteristics was performed, and chi-square testing was used to verify whether the distribution of the parameters conformed to a normal distribution. Differences between groups were assessed by ANOVA and Kruskal–Wallis's test. The Kaplan–Meier method was used to estimate the median PFS and OS with 95% confidence intervals (CIs). The questionnaire scales/items were scored according to the EORTC-published algorithm. Mean QLQ-C30 or QLQ-LC 13 scales or individual item scores and criteria were calculated at all time points to characterize patient efficacy after amitriptyline treatment (a 10-point difference between the score at each time point; the first month's score was considered clinically significant). Statistical analysis and plotting were performed using SPSS version 27 (IBM, Chicago, IL, United States) and GraphPad Prism version 9.5.1 (San Diego, California, United States).

TABLE 1 Patient demographics and baseline characteristics.

Characteristics	N (%)
Patients	33 (100)
Men	12 (36.4)
Women	21 (63.6)
Age (years), median (range)	63 (38–83)
Stage	
IV	33 (100)
Smoking history	
Ever Never	6 (18.2) 27 (81.8)
ECOG PS	
0–1 2 Unknown	27 (81.8) 5 (15.2) 1 (3.0)
Genetic mutation	
EGFR L858R EGFR 19Del EGFR G719X Unknown	13 (39.4) 14 (42.4) 1 (3.0) 5 (15.2)
Metastasis locations	
Liver Brain Bone	5 (15.2) 10 (30.3) 17 (51.5)
Response to aumolertinib (N = 23)	
CR PR SD PD ORR DCR	0 (0) 15 (69.6) 6 (26.1) 2 (8.7) (65.2) (91.3)

Abbreviations: ECOG PS, eastern cooperative oncology group performance status; EGFR, epidermal growth factor receptor; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate.

3 Results

3.1 Patient characteristics

A total of 52 patients diagnosed with EGFR-mutated (Exon 19 deletion or Exon 21 L858R) locally advanced or metastatic NSCLC and receiving aumolertinib treatment were successively screened from September 2022 (Figure 1). Of the 52 patients screened, 19 received aumolertinib as second- or later-line treatment; finally, 33 patients were enrolled. During the course of the study, three cases dropped out. Of these, one patient passed away after 10 months of medication (it is unclear whether the death was related to the illness), and two withdrew from the study due to disease progression and switched to alternative treatments.

Patient demographics and clinicopathological characteristics are presented in Table 1. The median age at diagnosis was 63 years (range: 38–83). The cohort included 21 female patients (63.6%) and 12 males (36.4%). Among the patients, six (18.2%) were former smokers, while 27 (81.8%) had never smoked. The majority of patients (81.8%) had an ECOG-PS of 0 or 1. The proportions of EGFR L858R and EGFR 19DEL mutations were 42.4% and 39.4%, respectively. Liver metastasis, brain metastasis, and bone metastasis were observed in 15.2%, 30.3%, and 51.5% of patients, respectively.

3.2 Efficacy evaluation and safety profile

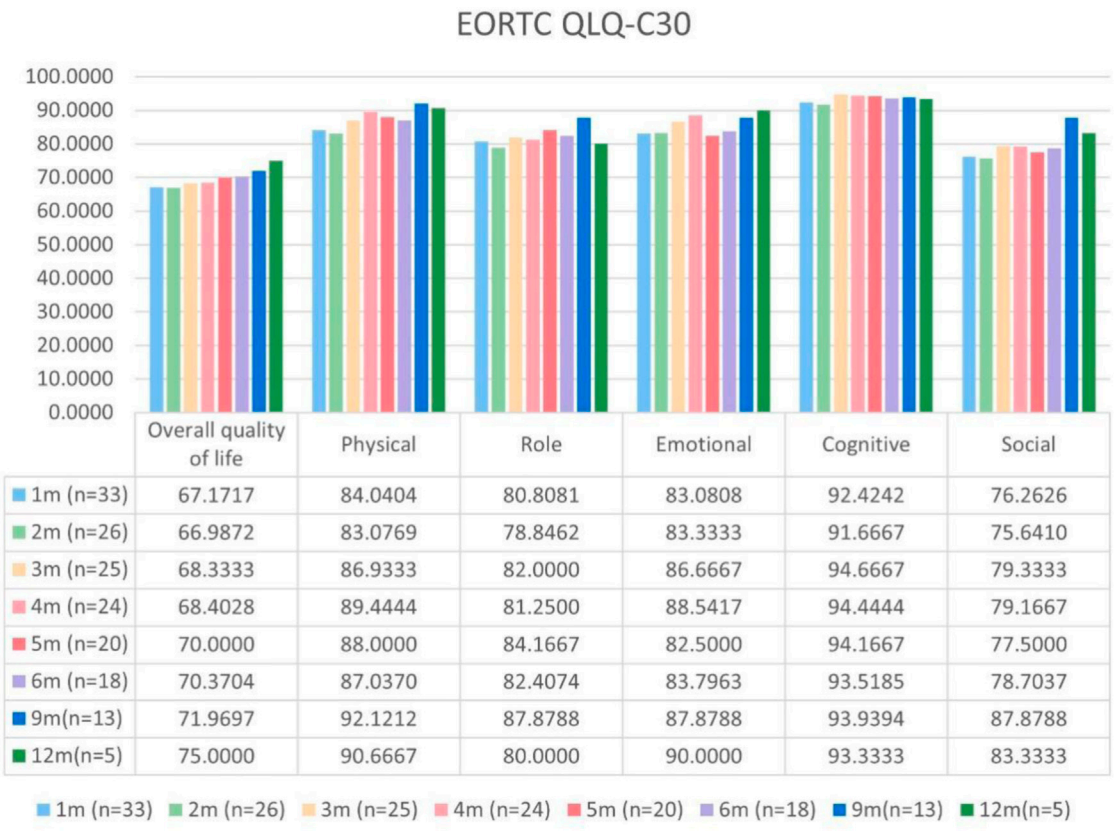
Before February 2024, 23 patients could be evaluated for treatment efficacy. The median follow-up time was 264 days (interval: 36–491 days). ORR and DCR were 65.2% and 91.3%, respectively. There was no significant difference in ORR between the major subgroups (Supplementary Table 1). In detail, 15 patients (65.2%) achieved PR, six (26.1%) achieved SD, and two patients (8.7%) experienced PD (Table 1). Due to the short follow-up period, median OS and PFS have not yet been reached (Supplementary Figure 1). The rate of treatment-related adverse events (TRAEs) and grade 3 or larger TRAEs was 87.9% and 12.1%, respectively. Detailed information is summarized in Supplementary Table 2.

3.3 PROs

Patients with at least one quality-of-life questionnaire were included in this analysis, and 54.5% of patients completed the first half-year follow-up. Patients reported a tendency toward higher functional scale scores, indicating good physical, role, emotional, cognitive, and social functioning after aumolertinib treatment (Figure 2). The overall quality of life score increased from 67.17 at baseline to 70.37 at the 6-month follow-up and 75.0 at the 12-month follow-up (Figure 2). The mean scores of the symptom scales and items also showed decreasing trends (Figure 3), indicating that aumolertinib treatment controlled symptoms. The mean scores of the first-month symptom scores in the aumolertinib arm were 21.21 for fatigue, 21.72 for pain, 7.07 for nausea and vomiting, 30.3 for dyspnea, 20.2 for insomnia, 12.12 for appetite loss, 9.09 for constipation, 6.06 for diarrhea, and 31.31 for financial difficulties (Figure 3). Compared to baseline scores, aumolertinib showed a clinically meaningful improvement in mean scores for pain and dyspnea after 6 months of treatment (Figure 3). However, only a decrease in pain scores was statistically significantly meaningful (Figure 4). QLQ-LC13 showed that lung-cancer-related symptoms also improved a lot, of which coughing, sore mouth or tongue, tingling in the hands or feet, chest pain, arm or shoulder pain, and other pain improvements were clinically meaningful at 6 months (Figure 5). Coughing, sore mouth or tongue, chest pain, arm or shoulder pain, and other pain improvements were statistically significantly meaningful (Figure 6).

4 Discussion

In the AENEAS trial, first-line treatment with aumolertinib demonstrated superior efficacy to gefitinib in advanced NSCLC patients with an activating EGFR mutation (Lu et al., 2022b). However, PROs have not been reported until now. In this real-world study, we evaluated the efficacy of aumolertinib with a particular focus on PROs. Our findings were consistent with



	Overall quality of life	Physical	Role	Emotional	Cognitive	Social
1m (n=33)	67.1717	84.0404	80.8081	83.0808	92.4242	76.2626
2m (n=26)	66.9872	83.0769	78.8462	83.3333	91.6667	75.6410
3m (n=25)	68.3333	86.9333	82.0000	86.6667	94.6667	79.3333
4m (n=24)	68.4028	89.4444	81.2500	88.5417	94.4444	79.1667
5m (n=20)	70.0000	88.0000	84.1667	82.5000	94.1667	77.5000
6m (n=18)	70.3704	87.0370	82.4074	83.7963	93.5185	78.7037
9m(n=13)	71.9697	92.1212	87.8788	87.8788	93.9394	87.8788
12m(n=5)	75.0000	90.6667	80.0000	90.0000	93.3333	83.3333

FIGURE 2
Mean scores of the general health status scale and functional scales from the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire C30 (QLQ-C30) with various time points.

those of the results reported in the AENEAS trial; importantly, we observed improvements in key lung cancer symptoms from baseline. Improvements in symptoms such as cough, sore mouth or tongue, tingling in the hands or feet, chest pain, arm or shoulder pain, and other types of pain were both clinically and statistically significant.

In the management of advanced NSCLC patients, incremental gains in PFS or OS are thought of as clinically meaningful only if they are achieved without a marked negative effect on HRQoL (Yang et al., 2015). Therefore, it is of great significance to record PROs in trials and real-world studies. The AENEAS trial showed a significant improvement in PFS of aumolertinib compared with gefitinib (19.3 months vs. 9.9 months) and a similar ORR of aumolertinib compared with gefitinib (73.8% vs. 72.1%) (Lu et al., 2022b). In this real-world study, the ORR of aumolertinib was 65.2%, which is comparable to that reported in clinical trials. The median PFS and OS were not reached because of a relatively shorter follow-up, and we will continue to track them. The similar short-term efficacy and demographics in our study support the following PRO analysis and may also reflect the results in AENEAS.

The EORTC QLQ-LC13 and QLQ-C30 questionnaires are well-established and are widely used in advanced NSCLC treatment trials (Geater et al., 2015; Bezjak et al., 2006; Blackhall et al., 2014; Brahmer et al., 2017; Yang et al., 2013), and have been thoroughly validated (Bergman et al., 1994; Aaronson et al., 1993; Sprangers et al., 1996). In this prospective and real-world study, questionnaire completion rates were high, with 54.5% of patients completing it during the first half year of aumolertinib treatment. Patients receiving first-line EGFR-TKI treatment usually have good performance status and low symptom burden, resulting in low symptom scores at baseline and difficulty in improvement measures. In practice, a score change equal to or greater than 10 points on the EORTC QLQ-LC13 and QLQ-C30 questionnaires is commonly deemed clinically significant (Fiteni et al., 2016). However, it has been shown that a lower, 5-point cut-off could also be clinically relevant. When the 5-point cut-off was administered here, fatigue, nausea and vomiting, dyspnea, appetite loss, and constipation score improvement at 6 months were clinically relevant.

There were several limitations in this real-world study. Firstly, it was a single-center study and the sample size was relatively small. With the development of EGFR-TKIs, advanced NSCLC patients with sensitive EGFR mutations have many choices, including gefitinib, erlotinib, afatinib, dacomitinib, osimertinib, furmonertinib, and befotertinib, which restricts the number of people receiving a specific drug. Secondly, the mPFS and mOS were not reached, and these patients are still in follow-up.

In conclusion, the PRO results from this real-world study showed improvements from baseline in key lung cancer symptoms in advanced NSCLC patients receiving aumolertinib as first-line therapy. Further follow-up of survival and symptom scores is ongoing.

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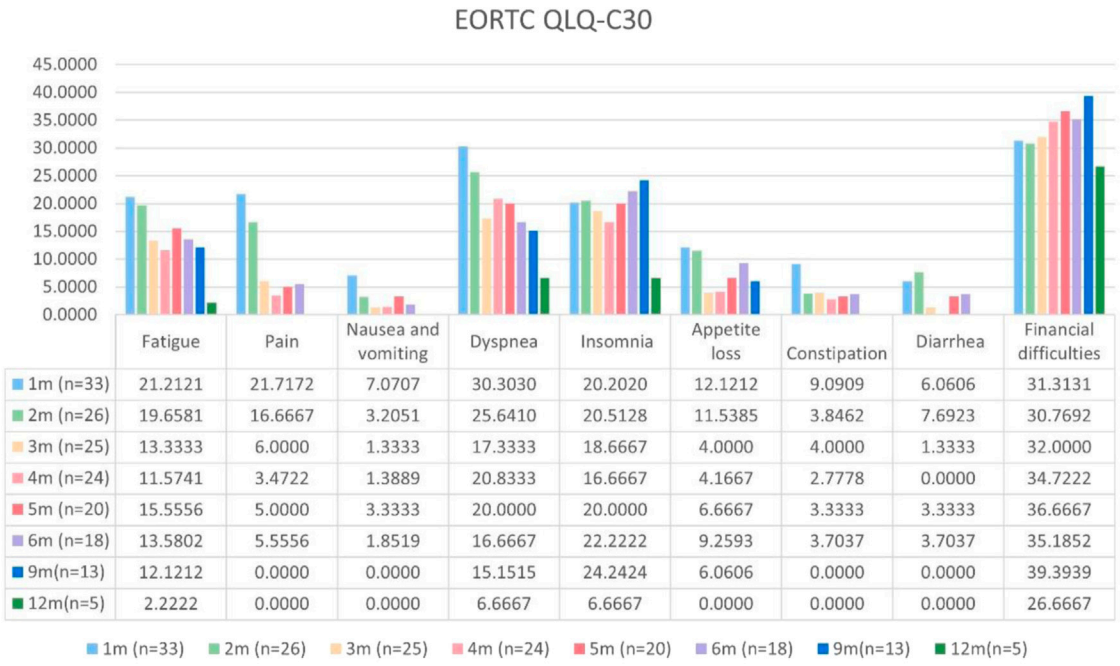
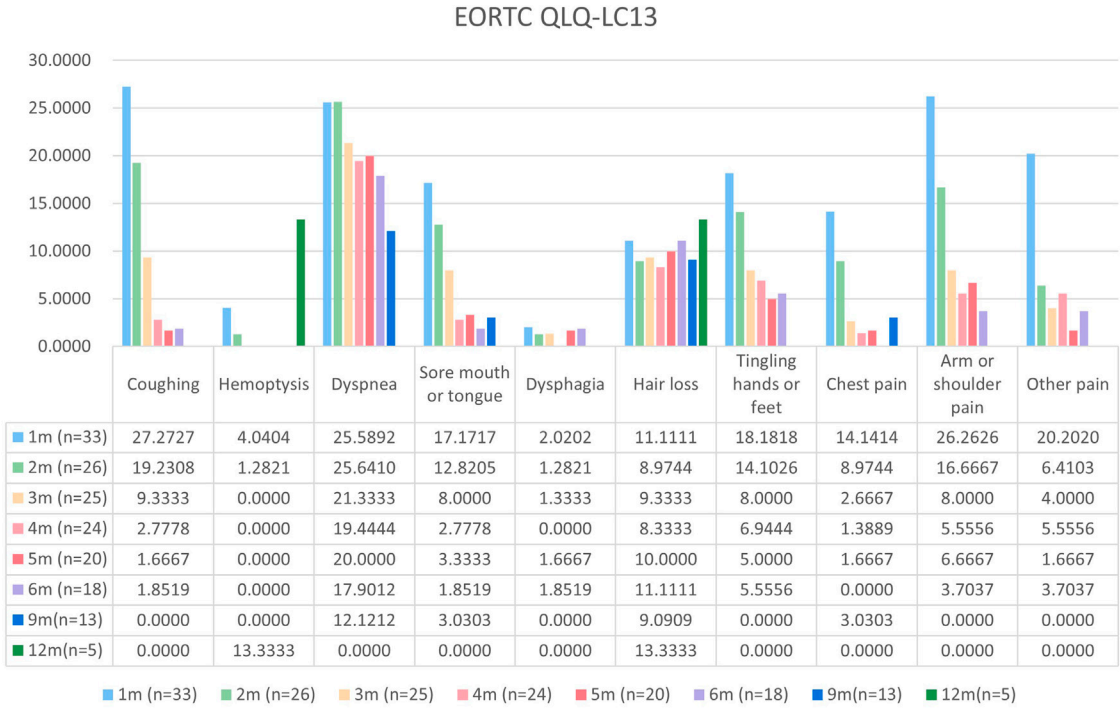


	Fatigue	Pain	Nausea and vomiting	Dyspnea	Insomnia	Appetite loss	Constipation	Diarrhea	Financial difficulties
1m (n=33)	21.2121	21.7172	7.0707	30.3030	20.2020	12.1212	9.0909	6.0606	31.3131
2m (n=26)	19.6581	16.6667	3.2051	25.6410	20.5128	11.5385	3.8462	7.6923	30.7692
3m (n=25)	13.3333	6.0000	1.3333	17.3333	18.6667	4.0000	4.0000	1.3333	32.0000
4m (n=24)	11.5741	3.4722	1.3889	20.8333	16.6667	4.1667	2.7778	0.0000	34.7222
5m (n=20)	15.5556	5.0000	3.3333	20.0000	20.0000	6.6667	3.3333	3.3333	36.6667
6m (n=18)	13.5802	5.5556	1.8519	16.6667	22.2222	9.2593	3.7037	3.7037	35.1852
9m(n=13)	12.1212	0.0000	0.0000	15.1515	24.2424	6.0606	0.0000	0.0000	39.3939
12m(n=5)	2.2222	0.0000	0.0000	6.6667	6.6667	0.0000	0.0000	0.0000	26.6667

FIGURE 3
Mean scores of the symptom scales and items from the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire C30 (QLQ-C30) with various time points.



	Coughing	Hemoptysis	Dyspnea	Sore mouth or tongue	Dysphagia	Hair loss	Tingling hands or feet	Chest pain	Arm or shoulder pain	Other pain
1m (n=33)	27.2727	4.0404	25.5892	17.1717	2.0202	11.1111	18.1818	14.1414	26.2626	20.2020
2m (n=26)	19.2308	1.2821	25.6410	12.8205	1.2821	8.9744	14.1026	8.9744	16.6667	6.4103
3m (n=25)	9.3333	0.0000	21.3333	8.0000	1.3333	9.3333	8.0000	2.6667	8.0000	4.0000
4m (n=24)	2.7778	0.0000	19.4444	2.7778	0.0000	8.3333	6.9444	1.3889	5.5556	5.5556
5m (n=20)	1.6667	0.0000	20.0000	3.3333	1.6667	10.0000	5.0000	1.6667	6.6667	1.6667
6m (n=18)	1.8519	0.0000	17.9012	1.8519	1.8519	11.1111	5.5556	0.0000	3.7037	3.7037
9m(n=13)	0.0000	0.0000	12.1212	3.0303	0.0000	9.0909	0.0000	3.0303	0.0000	0.0000
12m(n=5)	0.0000	13.3333	0.0000	0.0000	0.0000	13.3333	0.0000	0.0000	0.0000	0.0000

FIGURE 4
Mean scores of the symptom scales and items from the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life lung cancer-specific module QLQ-LC13 with various time points.

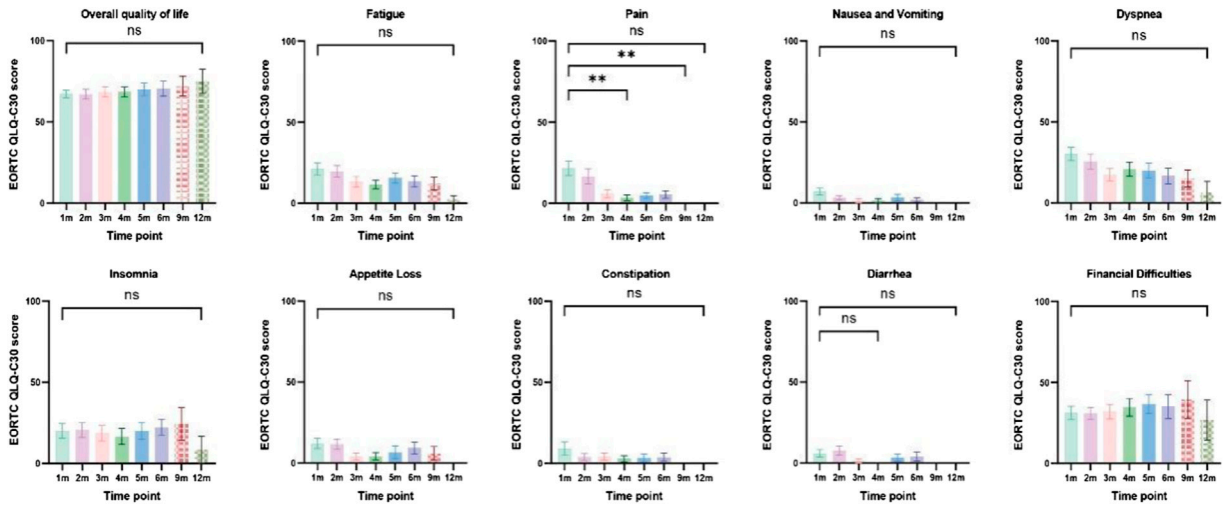


FIGURE 5
Column charts of general health status, three symptom scales, and multiple individual items. Statistical information: ns: non-significant, $p > 0.05$; "**", $p < 0.01$.

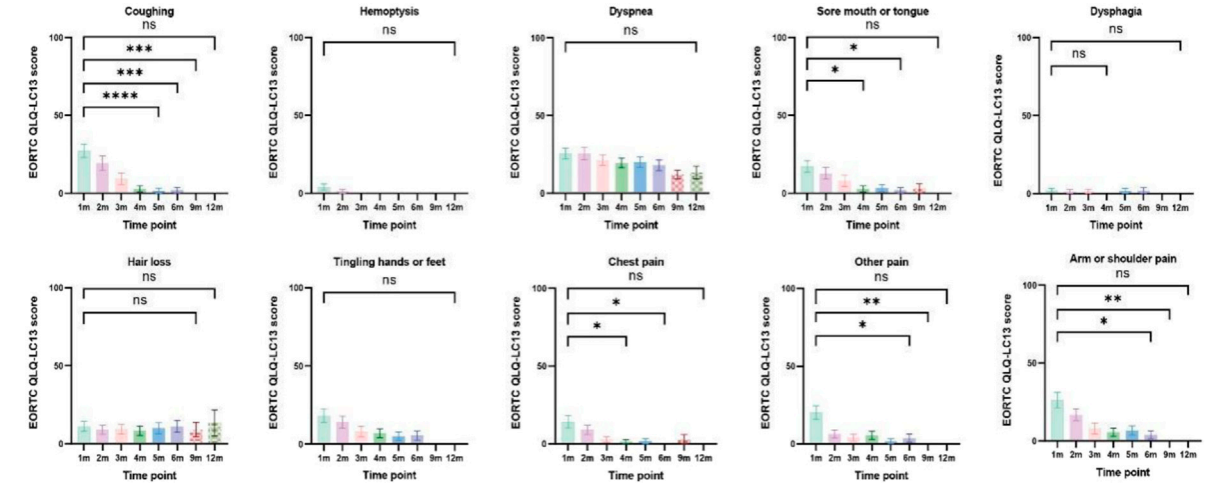


FIGURE 6
Column charts of lung-cancer-related symptoms and treatment-related adverse effects. Statistical information: ns: non-significant, $p > 0.05$; "*", $p < 0.05$; "**", $p < 0.01$; "***", $p < 0.001$; "****", and $p < 0.0001$.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material; further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving humans were approved by the Ethical Review Boards and Institutional Review Boards of Qilu Hospital of Shandong University. The studies were conducted in accordance with local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

HL: data curation, formal analysis, investigation, methodology, software, and writing–original draft. WZ: data curation, formal analysis, funding acquisition, investigation, methodology, software, and writing–original draft. CC: data curation, resources, validation, and writing–original draft. TX: formal analysis, methodology, validation, and writing–original draft. CW: data curation, formal analysis, investigation, and writing–original draft. RZ: data curation,

formal analysis, investigation, and writing–original draft. ChY: data curation, formal analysis, investigation, and writing–original draft. JW: formal analysis, methodology, validation, and writing–original draft. CuY: formal analysis, methodology, validation, and writing–original draft. XW: methodology, resources, validation, and writing–original draft. SY: conceptualization, project administration, resources, supervision, and writing–review and editing. JL: conceptualization, funding acquisition, methodology, project administration, resources, supervision, validation, and writing–review and editing.

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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.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2024.1444707/full#supplementary-material

SUPPLEMENTARY FIGURE S1
Kaplan–Meier survival curves of **(A)** overall survival in all evaluated patients and **(B)** progression-free survival in all evaluated patients.

SUPPLEMENTARY FIGURE S2
Subgroup analysis of significantly changed factors in EORTC QLQ-C30 and EORTC QLQ-LC13.

SUPPLEMENTARY TABLE S1
Subgroup analysis of ORR.

SUPPLEMENTARY TABLE S2
Summary of safety profiles in all patients receiving aumolertinib.

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Application of disitamab vedotin in the multiline treatment of EGFR mutation-positive lung adenocarcinoma with Her-2 overexpression

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Objective: To explore the efficacy of c in the multiline treatment of late-stage lung adenocarcinoma with Her-2 overexpression and epidermal growth factor receptor (EGFR) mutations.

Methods: We summarize the diagnosis and treatment of a female patient with EGFR 21L858R mutation combined with Her-2 overexpression in advanced lung adenocarcinoma, and analyze the effect of c in her treatment process.

Results: The patient was diagnosed with lung adenocarcinoma 8 years ago. After first-line treatment, the lung lesions enlarged. Following second-line treatment 5 years ago, intracranial metastasis occurred. After third-line treatment 3 years ago, intracranial and lung lesions enlarged. New lesions in the lungs, liver, and spleen appeared after fourth-line treatment 32 months ago. Lung progression occurred after fifth-line treatment 29 months ago. Liver and lung progression occurred after sixth-line treatment 22 months ago. Lung progression occurred after seventh-line treatment 19 months ago. The patient underwent eighth-line treatment with disitamab vedotin (RC48) + lung radiotherapy + liver intervention 13 months ago. Currently, the patient's condition is stable, with a good quality of life, and the efficacy assessment is stable disease (SD). Conclusion: Her-2 overexpression can occur in late-stage EGFR-mutant lung adenocarcinoma after multiline treatment. RC48 can achieve sustained remission in these patients.

KEYWORDS

HER-2 overexpression, epidermal growth factor receptor, lung adenocarcinoma, disitamab vedotin, efficacy, multiline treatment, conservative treatment

1 Introduction

Lung cancer is the most common malignant tumour, with non-small cell lung cancer (NSCLC) accounting for 80% to 85% of all lung cancers (1). Targeted therapies against specific molecular mutations, such as epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), and other driver genes, have rapidly advanced, improving the prognosis and quality of life of NSCLC patients (2). Compared to chemotherapy, targeted therapy has prolonged progression-free survival (PFS) and overall survival (OS) times. However, due to tumour heterogeneity and genomic instability, the widespread occurrence of secondary resistance, such as secondary gene mutations and activation of alternative signalling pathways, has greatly reduced the cure rate of non-small cell lung cancer, leading to the emergence of corresponding drug resistance issues (3). The emergence of immunotherapy has changed the treatment landscape for advanced NSCLC; however, research has mainly focused on NSCLC patients who are negative for driver genes (4, 5). For patients who are resistant to EGFR-tyrosine kinase inhibitors (TKIs) and have no standard targeted therapy, clinical studies have further explored the efficacy of immunotherapy in patients after EGFR-TKIs resistance, providing new treatment options for patients resistant to EGFR-TKIs (6, 7). Currently, immunotherapy combined with chemotherapy has shown initial effectiveness (8, 9), and the combination of immunotherapy with doublet chemotherapy and anti-angiogenesis quadruple therapy has shown remarkable efficacy (6). The frequency of Her-2 gene abnormalities in NSCLC is lower than that of EGFR, but its tumour driving mechanism is clear, and it is sensitive to some targeted drugs, making it a current research hotspot. This article summarizes the diagnosis and treatment of a patient with late-stage lung adenocarcinoma with Her-2 overexpression and EGFR mutation, aiming to explore the treatment efficacy of the antibody-drug conjugate (ADC) disitamab vedotin. The report is as follows.

2 Materials and methods

2.1 General information

The patient, a 52-year-old female, was admitted to the hospital on September 8, 2021, due to "shortness of breath and increased fatigue after activity for 1 week." The patient was diagnosed with lung adenocarcinoma at an outside hospital 8 years ago due to "persistent cough and shortness of breath for over 2 months." After 38 months of first-line treatment, lung lesions enlarged. Twenty months into second-line treatment 5 years ago, intracranial metastasis occurred. Five months into third-line treatment 3 years ago, intracranial and lung lesions enlarged. Four months into fourth-line treatment 2.5 years ago, new lesions appeared in the lungs, liver, and spleen. Seven months into fifth-line treatment 2.2 years ago, lung progression occurred. Three months into sixth-line treatment, liver and lung progression occurred. Five months into seventh-line treatment, lung progression occurred. Thirteen months ago, the patient underwent eighth-line treatment with RC48, combined with lung radiotherapy and liver local interventional therapy. Currently, the patient's condition is stable, with a good quality of life. This study was approved by the hospital's ethics committee (Approval No: Coren Trial No. (4) of 2024), adhering to the principles of the Helsinki Declaration, and informed consent was obtained from the patient.

2.2 methods

2.2.1 Genetic testing

Pathological paraffin-embedded (FFPE) tissue and blood samples from the patient were used for genetic testing. DNA was extracted using the Magnetic Bead-based FFPE DNA Extraction Kit (Guangzhou Meiji Biotechnology Co., Ltd., Guangzhou, China) and the Magnetic Bead-based Blood Genomic DNA Extraction Kit-T5C (Tiangen Biochemical Technology (Beijing) Co., Ltd., Beijing, China). Next-generation sequencing (NGS) was performed using a gene capture panel to detect mutations in 122 genes related to solid tumors (Wuxi Zhenhe Biotechnology Co., Ltd.).

2.2.2 Immunohistochemistry

Specimens were fixed in 10% neutral buffered formalin for 24 hours, routinely dehydrated, embedded in paraffin, and sectioned at 3 μm. Hematoxylin and eosin (HE) staining was performed for microscopic observation. Immunohistochemistry staining was performed using an automated immunohistochemistry staining machine (Roche, Switzerland) and the UltraView Universal DAB Detection Kit (Ventana), purchased from Roche Diagnostics Products (Shanghai) Co., Ltd.

2.3 Statistical analysis

Count data were expressed as frequencies or percentages.

3 Results

3.1 Patient's multiline treatment course

The patient's multiline treatment course is shown in Table 1.

3.2 Genetic testing results

On 18 January 2016, genetic testing (tissue) showed an EGFR 21 L858R mutation. On 22 April 2019, genetic testing (peripheral blood) was negative for T790M mutation, with no relevant driver gene mutations detected. On 2 April 2020, genetic testing (peripheral blood) confirmed the EGFR 21 L858R mutation with a mutation abundance of 0.29%. On 14 September 2021, genetic testing (tissue and blood) showed an EGFR p.L858R mutation with a mutation frequency of 56.43%, and ERBB2 gene amplification with a copy number change of 26.07.

TABLE 1 Patient's Multiline Treatment Course.

Stage	Time	Treatment Regimen	Treatment Efficacy	PFS(months)
1st Line	2016.2-2019.4	Gefitinib 250mg po qd	Lung PD	38
2nd Line	2019.4-2020.12	Osimertinib 80mg po qd	Brain PD	20
3rd Line	2020.12-2021.5	Osimertinib 80mg po qd + (Pemetrexed Disodium 745 mg iv d1 + Cisplatin 30 mg iv d1-3) x 4 cycles	Brain, lung PD	5
4th Line	2021.6-2021.9	Osimertinib 80mg po qd + (Bevacizumab 400mg iv d1 + Pemetrexed Disodium 750mg iv d1) x 3 cycles	Lung, liver, spleen PD	4
5th Line	2021-9.2022.4	Afatinib 30mg po qd + (Paclitaxel Liposome 180mg iv d1 + Nedaplatin 50mg iv d1-2) x 3 cycles. Liver local radiotherapy PGTV 69Gy/30F, Whole-brain radiotherapy PGTV 50Gy/20F, PTV 40Gy/20F	Lung PD	7
6th Line	2022.4-2022.7	Pyrotinib 400mg po qd	Lung, liver PD	3
7th Line	2022.7-2022.12	Anlotinib 12mg po d1-14 + Toripalimab 240 mg iv q3w	Lung PD	5
8th Line	2022.12-present	Disitamab vedotin 120mg iv q3w x 13 cycles. Lung radiotherapy PGTV 69Gy/30F, Liver local interventional therapy 2 times	PR	13

(PD, Progressive Disease; PR, Partial Response; PGTV, Planning Gross Target Volume; PTV, Planning Target Volume; Gy, Gray).

3.3 Pathology and Her-2 testing results

On 18 January 2016, a percutaneous lung biopsy (left upper lung) revealed adenocarcinoma. Immunohistochemistry did not detect Her-2. On 14 September 2021, a percutaneous lung biopsy (left lung) again showed adenocarcinoma. Immunohistochemistry did not detect Her-2. On 7 December 2022, a percutaneous lung biopsy (left lung tissue) confirmed adenocarcinoma. Immunohistochemistry showed Her-2 (3+).

3.4 Imaging results

The pathology and imaging results at the initial diagnosis on 18 January 2016 are shown in Figure 1. The lung imaging results during the treatment period are shown in Figure 2. The imaging results of extracorporeal organs (brain, liver, spleen) before and most recently during RC48 treatment are shown in Figure 3.

3.5 Efficacy

Since the start of eighth-line treatment, the patient has achieved 13 months of sustained remission. As of 20 January 2024, the patient's overall survival (OS) time has reached 8 years.

4 Discussion

Most patients with non-small cell lung cancer (NSCLC) are diagnosed at an advanced stage and have a poor prognosis (10). In

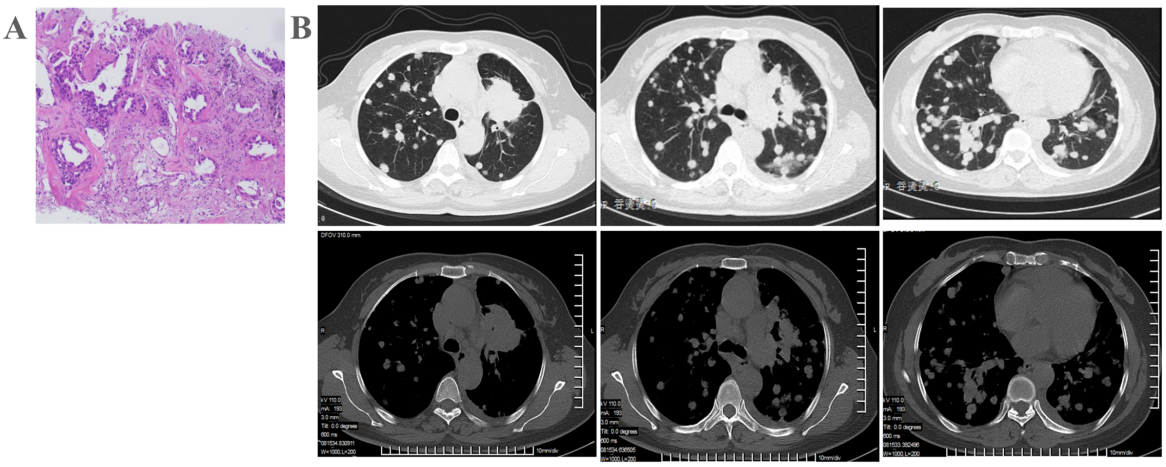

FIGURE 1
Patient examination before treatment. **(A)** Chest CT indicates left upper lung cancer with a high likelihood of bilateral lung metastasis, and multiple enlarged mediastinal lymph nodes. **(B)** Pathological biopsy confirms lung adenocarcinoma.

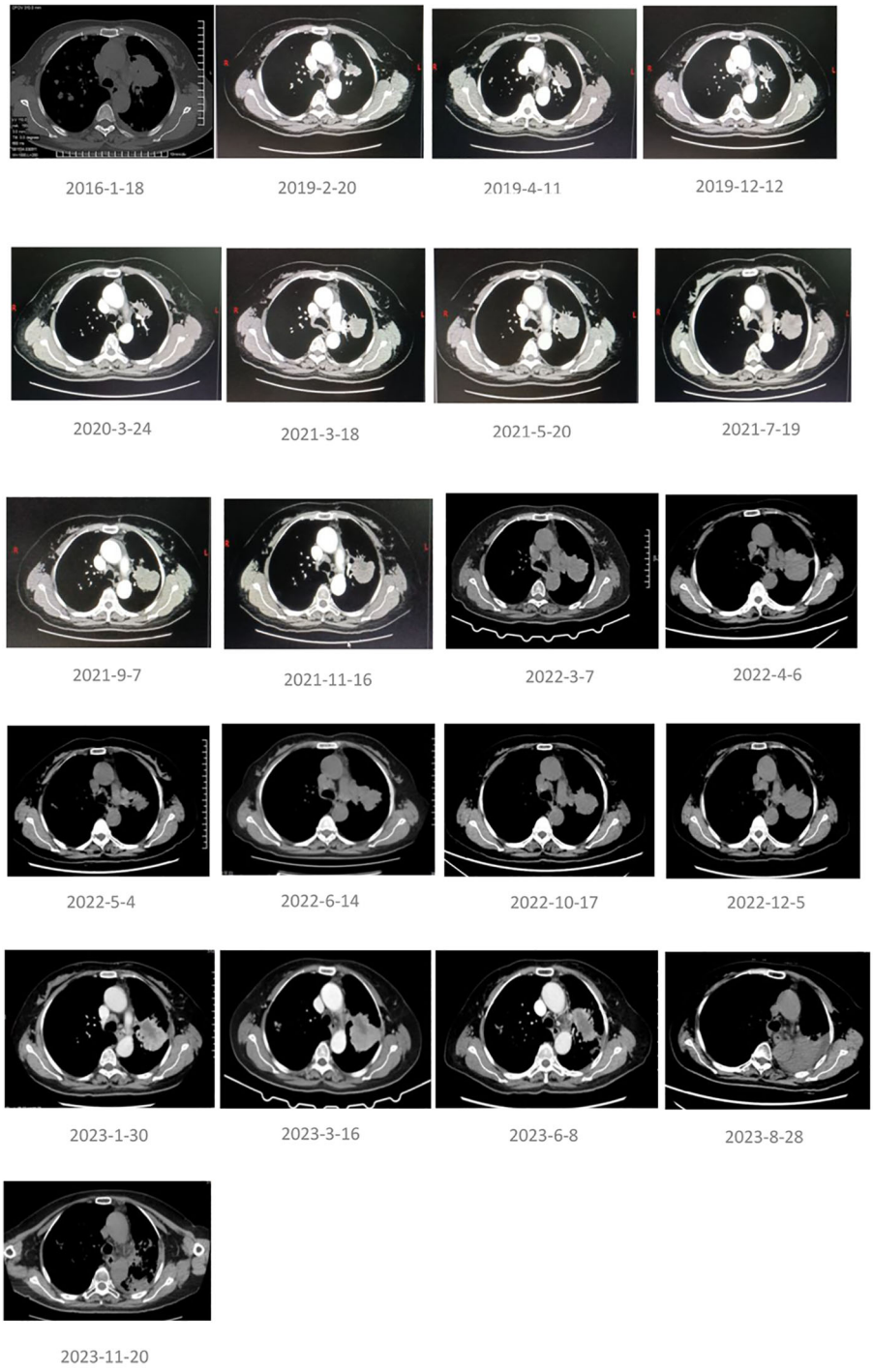

FIGURE 2
Chest CT images at key points during the patient's treatment process.

recent years, with the discovery of driver genes in NSCLC, especially adenocarcinoma, and advances in drug development, the survival of patients with advanced NSCLC has significantly improved, marking the advent of the targeted therapy era and providing new treatment options for NSCLC (11). Drugs such as gefitinib, dacomitinib, and osimertinib, EGFR-TKIs, have been approved by the FDA for the treatment of NSCLC with positive driver genes. However, the clinical efficacy of EGFR-TKIs is greatly limited by inevitable resistance, with resistance mechanisms including Her-2/Her-3/c-Met amplification and receptor tyrosine kinase-related bypass mechanisms, with Her-2 being the most representative (12).

Her-2 is a tyrosine kinase receptor in the ERBB/Her family and, together with other family members like EGFR, activates downstream signal transduction. Abnormalities in the Her-2 gene are closely related to the severity of many epithelial cell cancers, with tumours exhibiting strong metastatic and invasive capabilities,

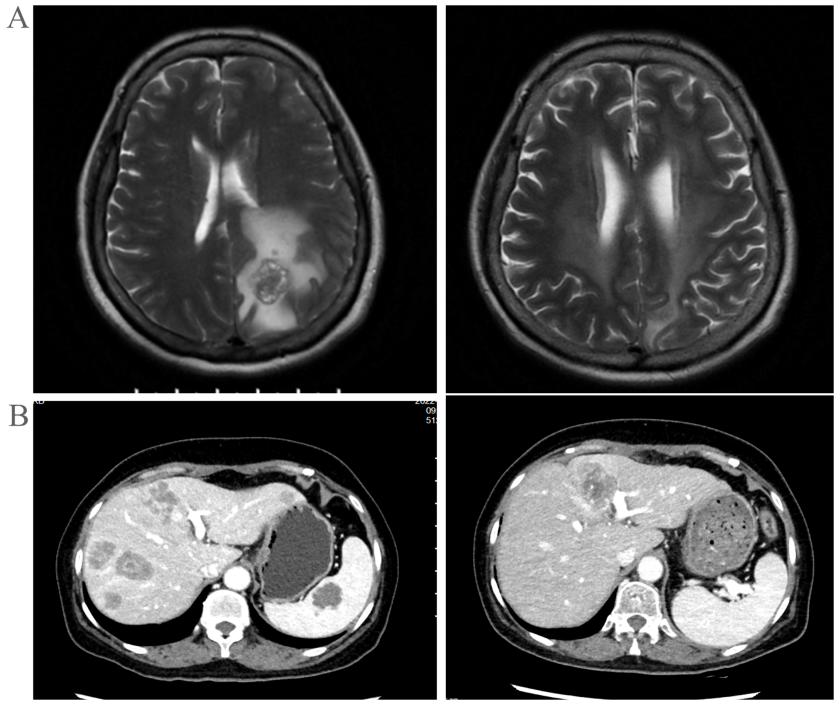

FIGURE 3
(A) Extra-pulmonary organs: head, MRI images before and after treatment. **(B)** Extra-pulmonary organs: liver, CT images at key points during the treatment process.

poor sensitivity to chemotherapy, and a high tendency for recurrence. Her-2 mutations and amplifications are associated with female gender, Asian ethnicity, non-smoking status, and poorly differentiated adenocarcinoma histology. In NSCLC, patients with Her-2 positivity have a shorter survival period compared to the general population (13). The forms of Her-2 variations in NSCLC primarily include mutations (2%–4%), amplifications (10%–20%), and overexpression (6%–35%). NSCLC resulting from Her-2 mutations, amplifications, or overexpression is referred to as Her-2 positive NSCLC (14).

In this study, the patient underwent a fourth genetic test (tissue and blood), which revealed an EGFR p.L858R mutation with a mutation frequency of 56.43% and ERBB2 gene amplification with a copy number change of 26.07. Afatinib, a pan-Her (EGFR/Her-1, Her-2, and Her-4) inhibitor, selectively and irreversibly binds to its HER family receptor targets, providing long-lasting inhibition. According to the LUX-Lung5 study (15), the progression-free survival (PFS) and objective response rate (ORR) in the afatinib plus paclitaxel group were significantly higher than those in the monotherapy chemotherapy group, with PFS (5.6 months vs. 2.8 months, HR=0.60, P=0.003) and ORR (32.1% vs. 13.2%, P=0.005) showing marked improvement. After multidisciplinary discussion and considering the patient's financial situation, the fifth-line treatment was chosen as afatinib combined with paclitaxel liposome and nedaplatin for three cycles, followed by liver and brain radiotherapy for further tumour control. After seven months, the efficacy evaluation indicated disease progression.

Her-2 antibodies such as trastuzumab have not significantly improved efficacy compared to traditional chemotherapy, and pan-HER inhibitors like dacomitinib and afatinib have shown unsatisfactory results. However, some new TKIs have shown initial advantages. A phase II prospective clinical study (ChiCTR180000262) indicated that pyrotinib treatment for Her-2 amplified populations had an ORR of 22.2%, a median PFS of 6.3 months, and a median OS of 12.5 months. Additionally, 30.8% of cases with progression on EGFR-TKIs responded to pyrotinib, and the ORR for patients with brain metastases was 40% (16). After one month of pyrotinib treatment, the tumour size was significantly reduced, with the efficacy evaluated as partial response, but after three months, liver and lung progression recurred.

According to the 2022 Chinese Expert Consensus on Immunotherapy for Advanced NSCLC with Driver Genes, for patients with extensive progression after resistance to EGFR-TKIs and in the absence of effective targeted treatments, the use of immune checkpoint inhibitors (ICIs) is recommended. Among the recommended regimens, ICIs combined with chemotherapy and anti-angiogenesis treatment, and ICIs combined with platinum-based chemotherapy, have substantial clinical evidence.For patients similar to those in this study, who have undergone multiple lines of treatment and cannot tolerate high-intensity therapy, ICIs combined with anti-angiogenic treatment is recommended (16). A real-world study in China (17) demonstrated that in second-line and subsequent treatments for recurrent NSCLC patients, the combination of toripalimab and anlotinib showed synergistic effects, significantly prolonging PFS compared to immunotherapy alone or single-agent chemotherapy. Therefore, the seventh-line treatment employed toripalimab combined with anlotinib. After five months, the efficacy assessment indicated disease progression. A repeat lung biopsy and immunohistochemistry revealed Her-2 (3+) status.

Antibody-drug conjugates (ADCs) have emerged as one of the fastest-growing areas in lung cancer treatment in recent years. Combining tumour cell-specific monoclonal antibodies (mAbs) with cytotoxic drugs, ADCs achieve both tumour cell targeting and cell-killing capabilities, positioning them as a promising future direction in cancer therapy. For Her-2 mutant NSCLC, ADCs have shown outstanding performance. In a phase II basket trial of T-DM1 (18), the ORR was 44%, with a PFS of 5.0 months, although the sample size was relatively small. T-DM1 demonstrated some clinical efficacy in NSCLC patients with Her-2 mutations and amplifications, but its effectiveness in Her-2 overexpressing NSCLC did not meet expectations. Trastuzumab deruxtecan (T-DXd) has shown remarkable results in treating Her-2 mutant NSCLC. Initial data from a phase I study reported an ORR of 72.7% and a PFS of 11.3 months (19). The phase II study (DESTINY-Lung01) showed an ORR of 55% and a PFS of 8.2 months (20). In the DESTINY-Lung01 study, for the Her-2 overexpressing (3+ or 2+) cohort, results presented at the 2022 ESMO conference indicated that the ORR assessed by ICR was 26.5% (cohort 1, 6.4 mg/kg) and 34.1% (cohort 1a, 5.4 mg/kg); the median PFS was 5.7 and 6.7 months, respectively, and the median OS was 12.4 and 11.2 months, respectively (21). While T-DXd shows significant promise in Her-2 mutant NSCLC, its efficacy in Her-2 overexpressing NSCLC is limited.

RC48 is a novel humanised anti-Her-2 ADC. It uses a Her-2 antibody as a targeting carrier, covalently conjugated to a small molecule toxin (MMAE) via a cleavable linker. In a phase II study of third-line treatment for locally advanced or metastatic Her-2 overexpressing gastric cancer or gastroesophageal junction cancer (22), the results showed an ORR of 24.4%, a median PFS of 4.1 months, and a median OS of 7.6 months. In patients with previously failed chemotherapy for Her-2 overexpressing locally advanced or metastatic urothelial carcinoma, the ORR with RC48 treatment was 50.0% (23). RC48 has demonstrated clinical benefits in the treatment of gastric cancer and urothelial carcinoma.A real-world retrospective study (24) included 23 patients with advanced solid tumours such as breast cancer, gastric cancer, colorectal cancer, and bladder cancer, with at least Her-2 immunohistochemistry 1+ expression and failure after at least one systemic chemotherapy. All patients received RC48 treatment (as monotherapy, combined with immunotherapy, or combined with radiotherapy). The ORR was 43.5%, and the median PFS was 6.0 months. Further stratified analysis showed that the ORR for the HER-2 low/medium expression (1+ or 2+) group was 37.5%, with a median PFS of 5.75 months. For the HER-2 high expression (3+) group, the ORR was 57.1%, with a median PFS of 7 months. In the RC48 combined with PD-1 inhibitor group, the ORR was 53.8%, with a median PFS of 8 months. In the group combined with local radiotherapy, the ORR was 40.0%, with a median PFS of 6.0 months. Current phase II/III clinical studies of RC48-ADC are ongoing for indications such as breast cancer, lung cancer, and cholangiocarcinoma. Considering the availability of the drug, the patient opted for RC48 treatment, during which the lesion assessment indicated partial response.

Considering that radiotherapy can reduce the tumour burden of local lesions and release tumour antigens, RC48-ADC targets Her-2 antigens on the surface of tumour cells, precisely identifying and destroying tumour cells. This can also lead to extensive antigen release from other metastatic lesions, thereby activating T-cell immunity and forming a "point-to-surface" treatment strategy. Therefore, RC48-ADC and radiotherapy may have a synergistic effect, achieving better therapeutic outcomes (25). Consequently, to better reduce the tumour, the patient underwent palliative radiotherapy of the left lung and received two sessions of liver interventional therapy. During treatment, the patient experienced mild adverse events, including grade II leukopenia and grade I anaemia, which improved after symptomatic treatment. No other treatment-related adverse events such as skin toxicity, neurotoxicity, cardiotoxicity, pulmonary toxicity, gastrointestinal toxicity and hepatic toxicity occurred during treatment. Currently, the patient's PFS is 13 months, with an OS of 8 years.

In summary, the patient achieved long-term survival through multiple lines of treatment, including targeted therapy, chemotherapy, radiotherapy, immunotherapy, and antibody-drug conjugates, indicating that lung cancer treatment is progressing towards a chronic disease management approach. This study highlights that Her-2 positivity in NSCLC presents a challenging therapeutic target, with current clinical needs not yet fully met. ADCs show great potential in the standard treatment pathway for Her-2 mutant NSCLC patients. However, further exploration is needed regarding the biological nature, treatment strategies, and diagnostic standards of Her-2 amplification/overexpression in lung cancer.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving humans were approved by the hospital's ethics committee (Approval No: Coren Trial No. (4) of 2024), adhering to the principles of the Helsinki Declaration, and informed consent was obtained from the patient. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

ML: Data curation, Funding acquisition, Investigation, Project administration, Supervision, Writing – original draft. TW: Conceptualization, Data curation, Project administration,

Visualization, Writing – review & editing. DL: Formal analysis, Visualization, Writing – original draft. YC: Methodology, Resources, Writing – original draft. WL: Conceptualization, Methodology, Project administration, Resources, Writing – original draft. RK: Conceptualization, Formal analysis, Writing – original draft. QX: Conceptualization, Data curation, Validation, Writing – original draft.

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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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A good response to furmonertinib fourth-line treatment of an advanced lung adenocarcinoma patient with EGFR exon20in and PIK3CA mutation: a case report and literature review

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Background: Lung cancer, including small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), is the most prevalent cancer globally and remains the leading cause of cancer-related mortality. Epidermal growth factor receptor (EGFR) mutations, frequently observed in female NSCLC patients, have revolutionized treatment strategies with the advent of tyrosine kinase inhibitors (TKIs). These therapies significantly improve survival and are considered the standard of care for patients harboring EGFR mutations. However, most patients eventually develop resistance to EGFR-TKIs, leading to disease progression. Resistance mechanisms are classified as either EGFR-dependent or EGFR-independent, the latter involving bypass pathway activation, including dysregulation of downstream signaling cascades. EGFR-independent resistance often renders all EGFR-TKIs ineffective, necessitating further investigation into resistance mechanisms.

Case summary: We report the case of a 63-year-old Chinese woman diagnosed with synchronous lung adenocarcinoma harboring an EGFR exon 21 far-loop insertion mutation and clear cell renal cell carcinoma (ccRCC). A multidisciplinary team recommended systemic therapy for the lung adenocarcinoma and clinical observation for ccRCC. First-line treatment with bevacizumab plus pemetrexed-carboplatin achieved a progression-free survival (PFS) of 7 months. Second-line treatment with sintilimab and nedaplatin resulted in a PFS of 4.9 months. Third-line therapy with sintilimab and anlotinib proved ineffective. In the fourth line, the patient received furmonertinib, a third-generation EGFR-TKI, based on the FAVOUR trial. This treatment achieved durable disease control with excellent tolerability, yielding a PFS of 27 months and ongoing clinical benefit.

Conclusion: This case demonstrates that furmonertinib can provide significant clinical benefit to NSCLC patients with complex resistance mechanisms, including those involving the PIK3CA/mTOR pathway. These findings support its potential to overcome EGFR-TKI resistance and warrant further investigation in similar clinical contexts.

KEYWORDS

EGFR-TKI, PIK3CA mutant, furmonertinib, synchronous cancer, EGFR-TKI acquired resistance

Introduction

The epidermal growth factor receptor (EGFR) plays a pivotal role in regulating cellular processes such as proliferation, differentiation, division, and survival, and is intricately linked to the development of cancer (1). Recognized as a key therapeutic target in oncology, EGFR is frequently mutated in non-small-cell lung cancer (NSCLC) (2, 3). EGFR-tyrosine kinase inhibitors (TKIs) have demonstrated significant efficacy in eliciting tumor responses, particularly in NSCLC patients with EGFR mutations, surpassing traditional cytotoxic chemotherapy regimens.

Despite the efficacy of EGFR-TKIs, emerging evidence suggests that patients with advanced NSCLC and EGFR Exon 20 insertions (Exon 20ins) exhibit significant resistance to these inhibitors (4). Studies conducted across Asia, encompassing populations from China, Taiwan, and India, have consistently reported that metastatic NSCLC patients with EGFR Exon 20ins mutations show the worst progression-free survival (PFS) and overall survival (OS) when treated with first-generation EGFR TKIs as either first-line or subsequent therapy (5, 6). Structural analyses have implicated mutations in the EGFR drug-binding pocket, which may reduce the binding affinity of TKIs to the receptor.

Among the available third-generation EGFR-TKIs, osimertinib has emerged as a potential countermeasure, demonstrating its ability to overcome the reduced sensitivity to EGFR-TKIs observed in certain EGFR exon 20ins variants, both *in vitro* and *in vivo*. Nevertheless, the challenge of resistance to EGFR TKI therapy in EGFR exon 20ins remains formidable.

Furmonertinib, a novel third-generation EGFR-TKI, has shown promise in overcoming drug resistance mediated by the ATP-binding cassette transporters ABCB1 and ABCG2, which are central to the development of multidrug resistance in cancer patients receiving conventional chemotherapy. The mechanism of action of furmonertinib was characterized through ATPase assays, revealing its interaction with ABCB1 and ABCG2,suggesting a potential strategy to overcome resistance in EGFR exon 20ins-mutated cancers.

We herein report a case of the use of furmonertinib, to treat lung cancer with EGFR exon 20ins. Furmonertinib was effective in treating lung cancer as subsequent therapy even the exist of PIK3CA mutant.

Chief complaints

A 63-year-old Chinese woman was referred to our hospital presenting with a cough and right-sided lumbar pain lasting for four months.

History of present illness

The patient presented with cough, expectoration, and dull pain in the right side of the waist for more than four months. Symptomatic treatment outside the hospital was ineffective.

History of past illness

The patient was previously healthy, with no significant history of illness, trauma, or surgery.

Personal and family history

The patient's personal and family medical histories were unremarkable, with no familial history of cancer and generally good health.

Physical examination

No palpable enlargement of the superficial lymph nodes was observed. No dry or moist rales were heard on auscultation of both lungs. The heart rhythm was regular, with no murmurs auscultated. The abdomen was soft, non-tender, with no rebound tenderness or palpable masses. Additionally, no percussion tenderness was noted over the liver and kidneys.

Imaging examinations

Contrast-enhanced chest CT(CCT) revealed clear lung fields and a prominent mass with significant contrast enhancement in the

upper lobe of the right lung, near the mediastinum. The lesion was 6.3 cm in its longest diameter and showed features typical of cancer, including pleural indentation, lobulation, and spiculation. Numerous small metastatic nodes were seen in both lungs, suggesting widespread metastasis. Additionally, multiple enlarged lymph nodes were identified in the mediastinum (Figure 1A). Unexpectedly, a distinct lesion was also detected in the right kidney. Neck ultrasound identified further swollen lymph nodes. The patient then underwent an enhanced MRI to exclude additional brain tumors.

Pathology examinations

The patient may have synchronous malignancies, as it is extremely rare for lung cancer to metastasize from kidney cancer

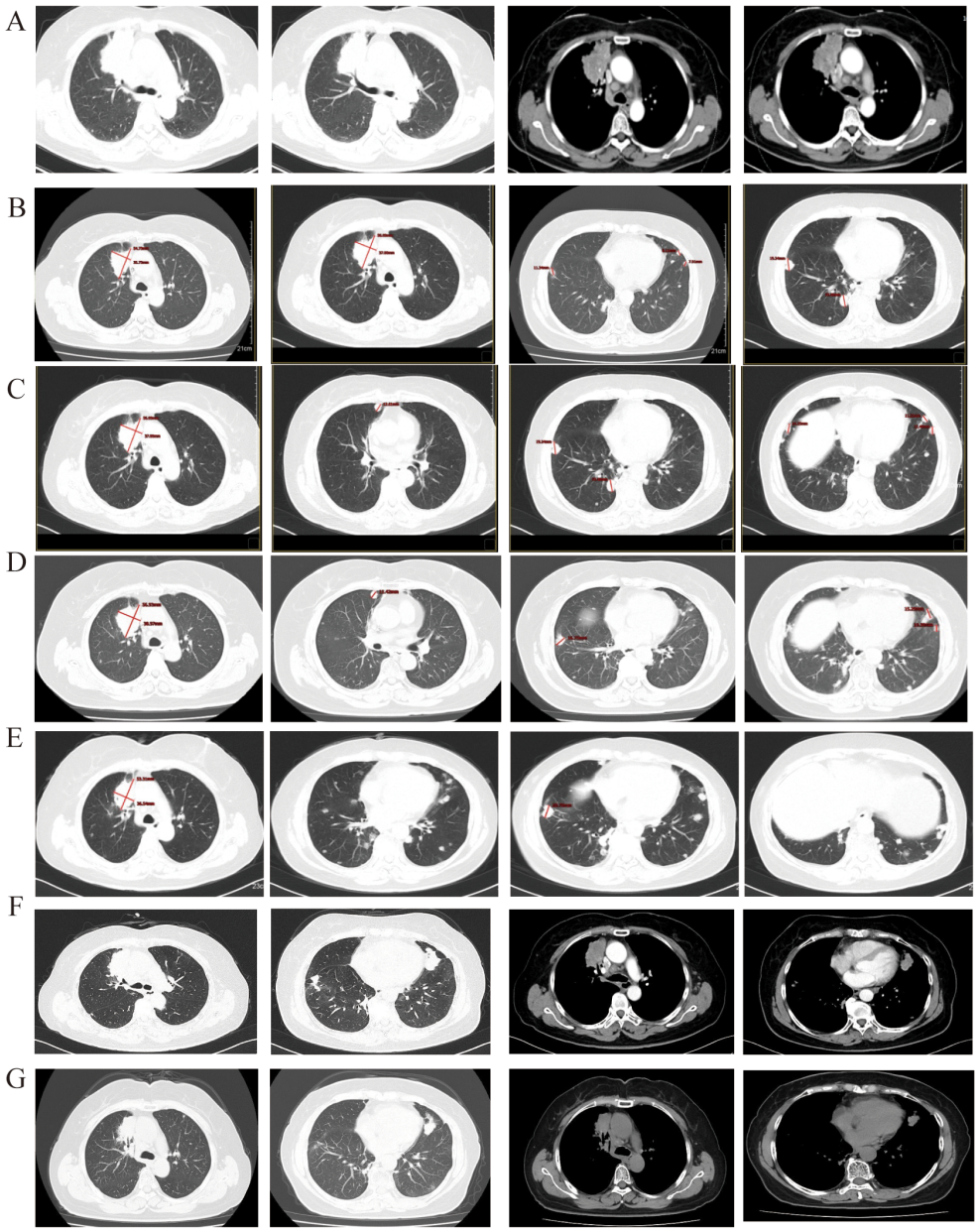

FIGURE 1
(A) Before treatment, the longest diameter of the target lesion is 6.3 cm + 1.6 cm to lung adenocarcinoma; **(B)** After 2 cycle of treatment, the primary lesion in the right lung has reduced compared to before, the efficacy evaluation was SD. **(C)** The size of the primary lung lesion shows no significant change compared to before, with multiple nodules of varying sizes seen in both lungs, some of which have increased in size compared to the previous observation. The efficacy evaluation was PD. **(D)** The primary lung lesion shows no significant change compared to before, while the metastatic lesions in both lungs have increased and enlarged compared to before. The efficacy evaluation was PD. **(E)** The primary lung lesion and the metastatic lesions in both lungs show no significant change compared to before and there is a trend of reduction. **(F)** The primary lung lesion and the metastatic lesions in both lungs show significant progression compared to before. **(G)** After 2 cycle threefold dosage furmonertinib treatment, the primary lung lesion and the metastatic lesions in both lungs show significant reduce.

or vice versa. Both tumors were identified through needle biopsies. Histopathological and immunohistochemical analyses confirmed lung adenocarcinoma (LUAD) (Figure 2A) and clear cell renal carcinoma (ccRCC) (Figure 2B). Genome sequencing of the LUAD tissue identified two significant genetic mutations: an EGFR exon20ins and a PIK3CA H1047R mutation, with allele fractions of 28.85% and 18.66%, respectively (Table 1). According to the Fuhrman classification, the ccRCC is classified as Grade 1, indicating a low risk of progression and well-differentiated features.

Final diagnosis

Based on pathological, imaging, and laboratory findings, both LUAD and ccRCC were diagnosed. "LUAD was staged as IVa (cT4N3M1a) with EGFR and PIK3CA mutations, according to the eighth edition of the TNM staging system. Similarly, ccRCC was staged as I (cT1bN0M0), also according to the eighth edition of the TNM staging system, and classified as Grade 1 by Fuhrman classification.

Treatment and follow Up

First-line

According to the 2020 CSCO guidelines for non-small-cell lung cancer (7), the first-line treatment for LUAD with EGFR exon 20 mutation is chemotherapy plus bevacizumab. Similarly, the CSCO guidelines for kidney cancer recommend bevacizumab plus IFNα-2b for ccRCC. Due to overlapping treatment protocols, the patient received combined therapy with bevacizumab and pemetrexed-carboplatin. After two cycles of combined therapy, the patient's condition was assessed as stable disease (SD) according to RECIST 1.1 criteria, with a 21.5% reduction in the maximum diameter of the lung's target lesion and significant shrinkage of non-target lesions (Figure 1B). The ccRCC also remained SD. After six cycles of combined treatment and subsequent maintenance therapy with bevacizumab and pemetrexed, the LUAD progressed locally (Figure 1C), while the ccRCC continued to exhibit sustained SD. The PFS from the first-line treatment was 7 months.

Second-line

The patient received sintilimab, a PD-L1 inhibitor, combined with nedaplatin and paclitaxel as a second-line treatment. After the first four cycles, she showed SD for 4.9 months, with a slight reduction in the maximum diameter of the target lesion. Following six cycles of treatment, the disease locally advanced again (Figure 1D). However, the ccRCC remained stable. The PFS for this second-line treatment was 4.9 months.

Third-line

According to the 2021 CSCO guidelines for NSCLC treatment (8), the patient received sintilimab combined with anlotinib, an anti-angiogenic agent. The third-line treatment was ineffective, as the disease rapidly progressed due to new lung metastases (Figure 1E). However, the ccRCC remained stable.

Fourth-line

The patient commenced furmonertinib, an EGFR-mutant targeted therapy, as fourth-line treatment following the publication of the FAVOUR study. This drug has provided sustained benefits. After two months of treatment with furmonertinib, the disease achieved a partial response (PR). The ccRCC remained stable. The PFS for the fourth-line treatment has reached 24 months. Recently, the disease was progressed again due to locally advancement (Figure 1F). The patient underwent genome sequencing again. The second genome sequencing result was similar to the first time: an EGFR exon20ins and a PIK3CA H1047R mutation, with allele fractions of 51.07% and 13.66%, respectively (Table 2). Due to prolonged cancer control and the recurrence of the same gene mutation, the patient was administered a threefold dose of furmonertinib (240mg QD).After two cycles treatment, the patient underwent another CCT to assess treatment efficacy. The lung lesion had significantly reduced compared to prior scans (Figure 1G). The patient has achieved a total of 27 months of PFS with furmonertinib, and the PFS continues to extend (Figure 3).

The patient tolerated the dose escalation well, with manageable side effects. During high-dose therapy, the primary side effect was Grade 1 oral mucositis classified as per the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. The patient reported mild oral pain, occurring occasionally while chewing, which was tolerable and

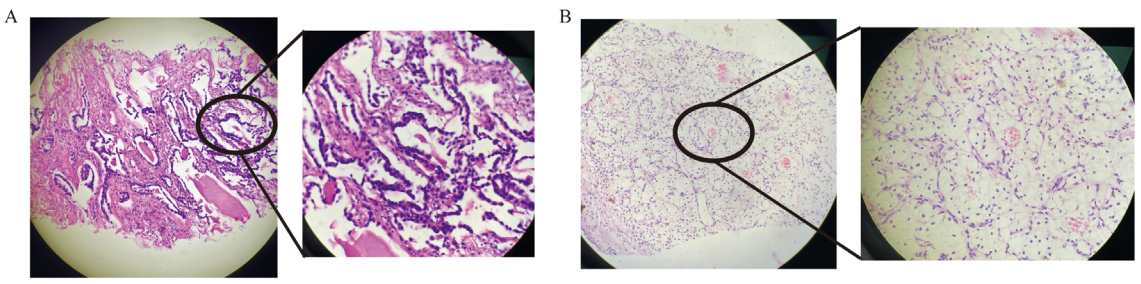

FIGURE 2
HE staining of lung adenocarcinoma diagnosis **(A)** and HE staining of renal clear cell carcinoma diagnosis **(B)**.

TABLE 1 The patient's first genome sequencing results.

Gene	Mutation	Fraction
EGFR	exon20 c2303_2311dup p.S768_D770dup	28.85%
KRAS	No significant mutation	/
ALK	No significant mutation	/
ROS1	No significant mutation	/
MET	No significant mutation	/
BRAF	No significant mutation	/
FGFR1	No significant mutation	/
FGFR2	No significant mutation	/
HER2	No significant mutation	/
NRAS	No significant mutation	/
HRAS	No significant mutation	/
RET	No significant mutation	/
TSC1	No significant mutation	/
AKT1	No significant mutation	/
PIK3CA	exon21 c3140A>G p.H1047R	18.66%
NTRK1	No significant mutation	/
NTRK2	No significant mutation	/
NTRK3	No significant mutation	/

TABLE 2 The patient's second genome sequencing results.

Gene	Mutation	Fraction
EGFR	exon20 c2303_2311dup p.S768_D770dup	51.07%
KRAS	No significant mutation	/
ALK	No significant mutation	/
ROS1	No significant mutation	/
MET	No significant mutation	/
BRAF	No significant mutation	/
FGFR1	No significant mutation	/
FGFR2	No significant mutation	/
HER2	No significant mutation	/
NRAS	No significant mutation	/
HRAS	No significant mutation	/
RET	No significant mutation	/
TSC1	No significant mutation	/
AKT1	No significant mutation	/
PIK3CA	exon21 c3140A>G p.H1047R	13.66%
NTRK1	No significant mutation	/
NTRK2	No significant mutation	/
NTRK3	No significant mutation	/

did not significantly impact daily activities or quality of life. No medical intervention was required, and the treatment dose of furmonertinib was maintained without adjustment.

Discussion

Lung cancer, classified into small cell lung cancer (SCLC) and Non-small cell lung cancer (NSCLC), is the most prevalent cancer globally and is the predominant contributor to mortality attributed to cancer (9, 10).

EGFR mutations are commonly observed in most female NSCLC patients. The use of TKIs in patients who harbor EGFR mutations significantly improves overall survival (11–13).

Developing treatment plan

This patient has synchronous primary cancers: LUAD and ccRCC. According to the Fuhrman classification, this patient is classified within the low-risk subgroup for ccRCC, which is likely to remain stable even without treatment. Therefore, clinical observation can be a viable option for managing low-risk ccRCC. However, LUAD requires timely treatment. Given the patient's synchronous cancers, treatment decisions should require a multidisciplinary team approach to address both conditions effectively. The 2020 CSCO treatment guidelines for NSCLC (7) recommend bevacizumab combined with chemotherapy for LUAD with an EGFR mutation, which can also provide therapeutic benefits for ccRCC. A real-world study (14) demonstrated that chemotherapy is more effective than EGFR-TKIs for LUAD with an EGFR exon20ins. This is because the mutation alters the conformation at the kinase active site, reducing the efficacy of early-generation EGFR-TKIs. Combining chemotherapy with bevacizumab has been shown to improve overall survival, and this approach resulted in a PFS of 7 months. The second-line treatment, based on the Orient-11 study (15), combines immunotherapy with chemotherapy, providing a longer PFS for non-squamous cell carcinoma NSCLC patients. This plan resulted in a 4.9-month PFS. As the cancer advanced, the efficacy of anti-cancer therapies diminished. The third-line treatment involved anti-angiogenic therapy, a standard choice for subsequent treatment in LUAD, which sometimes leads to favorable clinical outcomes. Due to drug marketing policies, the patient received sintilimab for free, combining anti-angiogenic therapy with immunotherapy. Despite this combination, no significant PFS improvement was observed. When the LUAD advanced again, the FAVOUR study was published, indicating that patients with an Exon 20 insertion could benefit from furmonertinib, which demonstrates a favorable safety profile. According to the study, the patient achieved a long-term PFS.

After 24 months of treatment with furmonertinib at a standard dose of 80 mg daily, the patient experienced disease progression, as evidenced by an increase in the size of the pulmonary lesion. The second genome sequencing revealed that the EGFR exon20ins mutation persisted and demonstrated an increased mutant allele frequency compared to baseline, without the emergence of any new resistance-associated genetic alterations. This finding suggested that

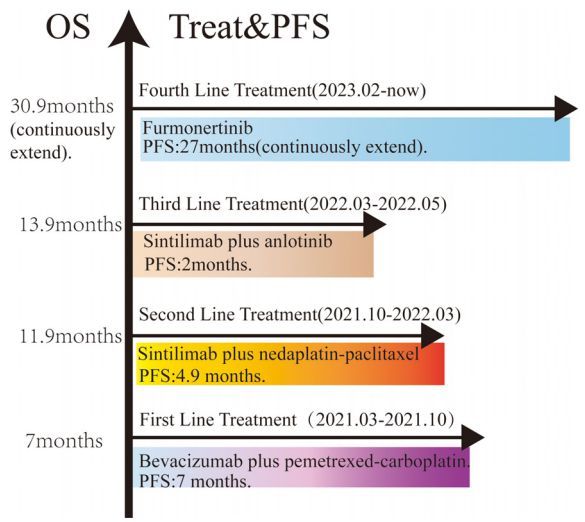

FIGURE 3
An overall review of the efficacy evaluation and treatment duration for this patient.

the resistance mechanism remained EGFR-dependent, likely due to increased mutant EGFR burden, which rendered the standard dose insufficient to suppress tumor progression effectively. In response, the treatment regimen was adjusted to a higher dose of furmonertinib at 240 mg daily to enhance EGFR inhibition. After two cycles of high-dose furmonertinib, a follow-up imaging assessment demonstrated a significant reduction in the size of the pulmonary lesion, suggesting effective disease control.

EGFR exon20 insertion mutation in NSCLC

EGFR is a glycoprotein composed of three principal domains: an extracellular EGF-binding domain, a transmembrane region and a cytoplasmic tyrosine kinase domain essential for regulating catalytic activity. The cytoplasmic domain includes a smaller N-terminal lobe and a larger C-terminal lobe, separated by the ATP-binding cleft. Ligand binding to EGFR triggers dimerization, activating the kinase domain and initiating downstream signaling pathways (Figure 4A). Common EGFR mutations in NSCLC include exon 19 deletions (exon19del) and the L858R substitution in exon 21, together accounting for 85% of EGFR mutations observed in NSCLC (11, 16, 17).

EGFR exon20ins account for approximately 4% to 12% of all EGFR mutations, making them the third most frequent (18, 19). These mutations are predominantly found in women, non-smokers, and Asians (10, 18). EGFR ex20ins mutations occur primarily in the C-terminal loop of the αC-helix (ex20ins-L) and within the αC-helix itself, and can be further classified into near-loop (AA767–772) and far-loop (AA773–775) subtypes. Far-loop mutations are notably resistant to first- and second-generation EGFR-TKIs. The effectiveness of EGFR-TKI is always insufficient in the patients with EGFR exon21 far-loop insertion (14, 20) (Figure 4B).

Osimertinib, a third-generation EGFR-TKI, exhibits limited efficacy in NSCLC patients with EGFR exon20ins. Studies reveal low ORR (5% to 6.5%) and short mPFS (2.3 to 3.6 months). A phase II trial doubling the recommended dose of osimertinib in such patients did not reach 30% ORR, recording a 24% ORR and a median PFS of 9.6 months (21). Hence, osimertinib may offer only modest benefits at higher doses.

Furmonertinib has shown effectiveness as a first-line treatment in advanced NSCLC patients with EGFR exon20ins, achieving mPFS of 8.13 to 10.90 months (22). It and its main metabolite effectively target cancers with sensitive EGFR mutations and the T790M resistance mutation, while minimally affecting wild-type cells. The FURLONG study demonstrated that furmonertinib significantly prolongs mPFS compared to gefitinib in Chinese patients with EGFR mutation-positive advanced NSCLC (22). Ongoing clinical trials also report favorable outcomes and tolerability for furmonertinib in patients with these specific mutations.

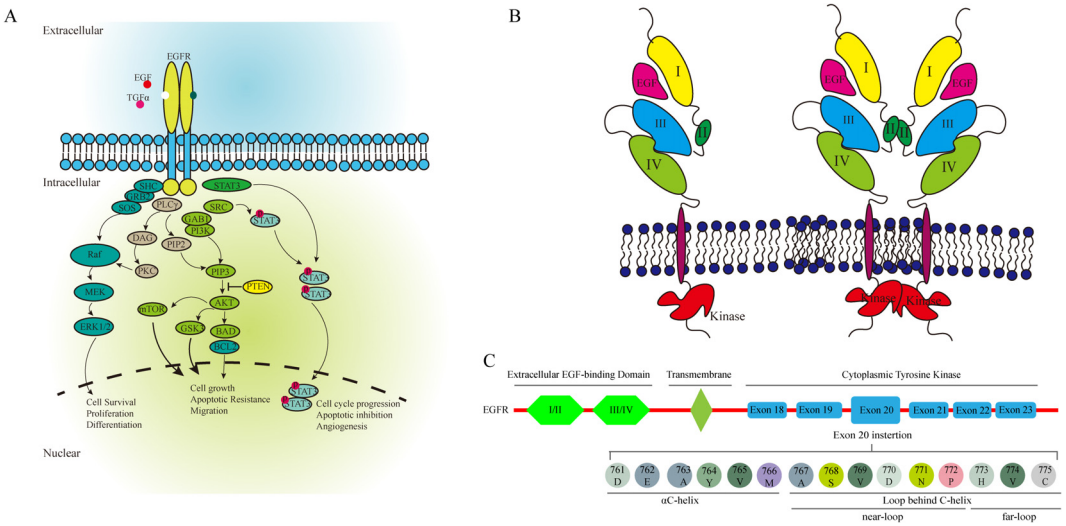

FIGURE 4
The EGFR associated pathway **(A)**, the activation of EGFR **(B)**, and the structure of EGFR **(C)**.

Novel Ex20ins inhibitors

Recent advancements have led to the development of novel targeted therapies for NSCLC patients with EGFR ex20ins. Drugs such as mobocertinib, amivantamab, CLN-081, and sunvozertinib have demonstrated promising therapeutic effects in clinical trials (23). Mobocertinib, a small molecule EGFR/HER2 TKI, is designed to specifically target EGFR exon20ins (18, 24, 25). It achieves enhanced selectivity by irreversibly binding to the cysteine-797 (c-797) residue of EGFR, with clinical studies reporting an investigator-confirmed response rate of 43% and a median PFS of 7.3 months in NSCLC patients. Amivantamab (26–29), an innovative bispecific monoclonal antibody targeting EGFR and c-MET, has shown antitumor efficacy through multiple mechanisms, including disruption of ligand binding and receptor phosphorylation, and immune cells engagement. In the CHRYSALIS phase I clinical trial, previously treated NSCLC patients with ex20ins mutations exhibited an ORR of 40% and a median PFS of 8.3 months (26). CLN-081, an oral irreversible EGFR-TKI, selectively targets exon20ins mutations and has demonstrated efficacy in preclinical studies by inhibiting various exon 20 insertion mutations. Clinical trials of CLN-081 have shown a PR rate of 40% and stable disease in 56% of NSCLC patients with ex20ins mutations. Sunvozertinib, a selective small molecule inhibitor of EGFR exon20ins, has exhibited remarkable antitumor activity in a pivotal study, with a confirmed ORR of 60.8% among Chinese NSCLC patients harboring these mutations (30, 31).

EGFR-dependent mechanisms of resistance to third-generation EGFR-TKIs

Acquired resistance to third-generation EGFR-TKIs represents a significant clinical challenge in the treatment of EGFR-mutant lung adenocarcinoma. Among EGFR-dependent resistance mechanisms, secondary mutations within the EGFR kinase domain are predominant. The C797S mutation, which disrupts the covalent binding of third-generation EGFR-TKIs, is the most frequently observed, often typically emerging following prolonged therapy (32). Additional mutations, including T790M, L792H, G796R, M766Q, and L798I, can modify the kinase domain and reduce drug efficacy (33–36). Furthermore, the formation of EGFR heterodimers, such as EGFR-HER2 or EGFR-HER3, initiates compensatory signaling pathways that bypass EGFR inhibition. This dimerization drives oncogenic downstream signaling, thereby sustaining tumor cell proliferation and survival. An additional key mechanism is the activation of the PKCδ signaling pathway, which leads to the nuclear translocation of PKCδ and subsequent activation of AKT and NF-κB signaling, promoting cell survival and therapeutic resistance. Together, these mechanisms highlight the complexity of EGFR-dependent resistance and underscore the need for therapeutic strategies that target both the EGFR kinase domain and its downstream effectors. Combination therapies, integrating EGFR inhibitors with agents targeting HER2/3 or the PKCδ pathway, may represent a promising approach to overcoming resistance. Further investigations are warranted to develop strategies that prevent or delay the emergence of these resistance mechanisms, ultimately improving outcomes for patients with EGFR-mutant lung adenocarcinoma.

PIK3CA mutation in NSCLC

The PIK3CA gene encodes the alpha isoform of the catalytic subunit of phosphatidylinositol 3-kinase (PI3K) and plays a key role in the activation of the PI3K/AKT/mTOR signaling pathway, which is critical for regulating cancer-associated cellular processes (37). PIK3CA mutations occur in various cancers, at frequencies of 5% to 8% in NSCLC cases and have been identified in approximately 6.33% of Chinese pan-cancer samples. Key mutation hotspots include E545K/Q/A/V/D/G, E542K, and H1047R/L/Y. These mutations promote cellular survival and proliferation by activating the PI3K/AKT/mTOR pathway. Notably, the H1047R mutation, one of the most common, is located in the kinase domain and plays a significant role in promoting cell growth and survival. This mutation also contributes to resistance to EGFR-TKIs in lung cancer by activating downstream effectors such as AKT and mTOR (38). Furthermore, studies suggest that NSCLC patients with concurrent EGFR and PIK3CA mutations experience significantly shorter progression times and reduced overall survival when treated with EGFR-TKI therapy, compared to those with only EGFR mutations (17, 38).

PIK3CA inhibitors in cancer

In recent years, many PI3K/AKT pathway specific TKIs were developed, such as pan-AKT inhibitors, dual PI3K/mTOR inhibitor, PI3K subtype inhibitor and mTOR inhibitors. Alpelisib, a selective PI3Kα inhibitor, has demonstrated a notable efficacy in targeting PIK3CA-mutated tumors, a significant genetic subgroup within breast cancer. The phase III SOLAR-1 trial provided evidence that the therapeutic synergy of alpelisib with fulvestrant in endocrine therapy significantly enhanced PFS in patients with PIK3CA-mutated, ER+ metastatic breast cancer who had previously undergone antiestrogen treatment (39). Alpelisib emerges as a beacon of promise as a PI3Kα-specific inhibitor. Taselisib, a PI3Kα-specific inhibitor, has been scrutinized in clinical trials for its potential role in breast cancer treatment (40, 41). The phase III SANDPIPER trial demonstrated a modest, but statistically significant, enhancement in PFS with the taselisib and fulvestrant combination, as opposed to fulvestrant monotherapy, in ER+ advanced breast cancer patients who had encountered progression during or subsequent to aromatase inhibitor (AI) therapy (41). This improvement, though not substantial, was notable, with a median PFS of 7.4 months versus 5.4 months (p=0.0037), irrespective of the PIK3CA mutation status. Conversely, the phase II LORELEI trial did not reveal a significant divergence in pathologic complete response (pCR) rates between the taselisib and letrozole combination and letrozole alone in the neoadjuvant treatment of early-stage, ER+/HER2- breast cancer patients, whether they harbored PIK3CA

mutations or not (40). Both the SANDPIPER and LORELEI trials reported high incidences of severe adverse effects associated with taselisib treatment, resulting in a significant rate of treatment discontinuation—17% and 11%, respectively. These safety concerns have overshadowed the drug's potential benefits and have impeded its progression in clinical development.

This patient was tested out two gene mutants, EGFR exon20ins and PIK3CA H1047R. As a previous study, EGFR-TKIs might not benefit this patient. But furmonertinib resulted in a long PFS, even as fourth line treatment. The reasons of EGFR-TKIs working in this patient are complicated. This patients was subjected with a history of multi-line therapy, including chemotherapy, immunotherapy and anti-angiogenic therapy. Polytherapy is one of the key points for this patient. It might change the gene expression profile, the EGFR mutant might be more in allele fraction, or the PIK3CA/AKT/mTOR pathway might not be primary pathway in cancer cell proliferation for this patient. Another reason might be the drug, furmonertinib. Furmonertinib could irreversibly inhibits EGFR with resistance (T790M mutation) or activating mutations. Previous study demonstrated that furmonertinib may be suitable as a first-line treatment option for patients with EGFR exon20 ins, as it can significantly improve symptoms and prolong survival, with fewer and manageable side effects.

This case study has several limitations. When diagnosing LUAD and ccRCC, additional examinations, such as bone scans and positron emission tomography-computed tomography (PET/CT), should be completed. The genetic status of the thoracic lesions must be confirmed by comprehensive Gene Testing Methods, such as Whole-Genome Sequencing (WGS) or Transcriptome Sequencing (RNA-Seq), to test for both known and unknown genetic mutations. Regarding this patient, three critical questions need addressing: What is the next treatment plan after the fourth progression? Is PD-L1 detection necessary in lung tissue? When is it appropriate to operate on ccRCC? Our research group is committed to augmenting the scope of our study by broadening the sample cohort, thereby facilitating a more definitive assessment of the clinical efficacy of furmonertinib as an effective therapeutic treatment for individuals afflicted with NSCLC that exhibit EGFR exon20 ins and other gene mutant. We will also explore the potential clinical benefit by which furmonertinib has effects against NSCLC with EGFR ex20ins mutation combined other treatment.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Written informed consent was obtained from the individual(s), and minor(s)' legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article.

Author contributions

KS: Visualization, Writing – original draft. PW: Funding acquisition, Resources, Writing – review & editing.

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Conflict of interest

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Publisher's note

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Efficacy and safety of immune checkpoint inhibitors for EGFR mutated non-small cell lung cancer: a network meta-analysis

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Introduction: Non-small cell lung cancer (NSCLC) constitutes approximately 80–85% of cancer-related fatalities globally, and direct and indirect comparisons of various therapies for NSCLC are lacking. In this study, we aimed to compare the efficacy and safety of immune checkpoint inhibitors (ICIs) in patients with epidermal growth factor receptor (EGFR)-mutated NSCLC.

Methods: The electronic databases were systematically searched from inception until March 18, 2024. Studies comparing two or more treatments involving ICIs in patients with EGFR-mutated NSCLC were included. The primary endpoints were overall survival (OS) and progression-free survival (PFS), and the secondary endpoints were overall response rate (ORR), any grade adverse events (AEs), grade ≥3 AEs, and AEs requiring treatment discontinuation. The R software with the gemtc package was used to compare the outcomes of the different treatments.

Results: In 11 eligible studies involving 1462 patients and 5 regimens (chemotherapy [chemo], ICI, ICI+chemo, antiangiogenesis+chemo, and ICI +antiangiogenesis+chemo), ICI+antiangiogenesis+chemo achieved the most favorable OS compared to chemo (HR=0.74, 95% CI 0.41–1.23), ICI+chemo (HR=0.94, 95% CI 0.57–1.46), and ICI (HR=0.58, 95% CI 0.27–1.08) and a nearly equivalent effect to antiangiogenesis+chemo (HR=1.01, 95% CI 0.52–1.92). The PFS and ORR results were similar to those of OS. ICI monotherapy exhibited the lowest toxicity profile.

Conclusions: These findings indicate that ICI+antiangiogenesis+chemo may be potentially beneficial for patients with EGFR-mutated NSCLC. However, the observed difference was not significant; thus, more studies are needed to confirm the efficacy and safety of the combined ICI treatment strategy.

Systematic Review Registration: https://www.crd.york.ac.uk/PROSPERO/, identifier CRD42023424781.

KEYWORDS

treatment strategy, immunotherapy, overall survival, progression-free survival, adverse events

1 Introduction

Lung cancer is the most prevalent type of cancer and the primary cause of cancer-related mortality globally (1, 2), with non-small cell lung cancer (NSCLC) accounting for approximately 80–85% of cases (3). Most NSCLCs are locally advanced or metastatic at diagnosis, reducing opportunities for surgery (4, 5), thereby resulting in a diminished overall 5-year relative survival rate and an unfavorable prognosis (6, 7).

Epidermal growth factor receptor (EGFR) mutations occur in many patients with NSCLC (8). Currently, EGFR tyrosine kinase inhibitors (TKI) are widely used clinically owing to their inhibitory effects on neovascularization, invasion, metastasis, and tumor cell growth (9, 10). Presently, three generations (gens) of EGFR-TKIs exist as follows: gefitinib, erlotinib and icotinib (1st gen), afatinib and dacomitinib (2nd gen), and osimertinib (3rd gen). However, most patients eventually experience disease progression and develop resistance within 9–12 months, limiting the long-term efficacy of EGFR-TKIs (11, 12).

In the last decade, immune checkpoint inhibitors (ICIs) targeting programmed death 1 (PD-1), programmed death ligand 1 (PD-L1), and cytotoxic T lymphocyte antigen 4 have dramatically changed the prognosis of patients with advanced NSCLC (13); however, their clinical benefits are constrained in individuals with EGFR-mutated NSCLC (14). KEYNOTE-001 indicated that the objective response rate (ORR), progression-free survival (PFS), and median overall survival (OS) were only 4%, 56 days, and 120 days, respectively, for 26 patients on pembrolizumab in a phase I study, and none of the patients had an objective response in subsequent phase II trials (15). CheckMate 012 also revealed lower ORR and PFS in patients with EGFR mutations than in those with wild-type mutations on first-line nivolumab monotherapy (ORR: 14% versus 30%; PFS: 1.8 versus 8.8 months) (16). In the ORIENT-31 study, Lu et al. (17) reported that sintilimab in combination with chemo significantly improved PFS compared to chemo alone (median PFS 5.5 months [95% CI 4.5–6.1] vs. 4.3 months [4.1–5.3]; hazard ratio [HR] 0.72 [95% CI 0.55–0.94]; two-sided p=0.016). These results demonstrate the potential benefit of ICIs in patients with EGFR-mutated NSCLC who had previously progressed on treatment with tyrosine kinase inhibitors. However, in a retrospective study, immunotherapy with platinum doublet chemo post-osimertinib was associated with a worse OS than platinum doublet chemo alone (18).

The efficacy and safety of ICIs remain controversial in patients with EGFR-mutated NSCLC, particularly in those with EGFR-TKI progression. Despite numerous ICI regimens for treating EGFR-mutated NSCLC, direct and indirect comparisons among these agents are lacking. Therefore, using a well-designed and comparative synthesis, we performed a systematic review and network meta-analysis (NMA) to directly and indirectly compare the advantages of these treatments and assess the efficacy and safety of ICIs in patients with EGFR-mutated NSCLC.

2 Materials and methods

2.1 Study selection

Two investigators independently screened the titles and abstracts to eliminate irrelevant articles and further screened dissertations by reading the full text. Disagreements were resolved through a group discussion.

The inclusion criteria were as follows:

- Studies that enrolled patients with histologically or cytologically confirmed NSCLC with EGFR mutations.
- Studies with reported outcomes of at least one of the following:

  OS, defined as the time from randomization to death from any cause; PFS, defined as the time from randomization to the first disease progression (locoregional or distant) or all-cause mortality; ORR, defined as the rate at which patients achieve an objective response; toxicity, characterizing as adverse events (AEs) of any grade, grade 3 or higher (grade ≥3 AEs), or requiring treatment discontinuation.

- The study design included randomized controlled trials (RCTs) and real-world studies (RWSs).

The exclusion criteria were as follows:

- Conferences, abstracts, protocols, single-arm studies, nonhuman research, systematic reviews, and case reports.
- For studies based on the same trial, only the most recent trial was included.

We conducted this meta-analysis according to the preferred reporting items for systematic reviews and meta-analysis extension statements for NMA (19). This study protocol was registered in the Prospective Register of Systematic Reviews (PROSPERO CRD42023424781). Institutional Review Board exemption was granted due to the innocuousness of this review study.

Two investigators systematically searched PubMed, Web of Science, and Cochrane Library databases for relevant articles from inception to March 18, 2024, with no language limits, using a combination of the main search terms, including "ICI," "NSCLC," and "EGFR." The reference lists of relevant articles were examined for additional articles, and the detailed search strategies are listed in Supplementary Table S1.

2.2 Data extraction and quality assessment

Extracted publication details included the first author's name, year of publication, country, study design, phase of the trial, setting,

diagnostic criteria, treatment regimens of the intervention and control groups, the number of participants in each arm, follow-up duration, patient characteristics (age and male ratio), primary clinical outcomes (OS and PFS), and secondary clinical outcomes (ORR, any grade AEs, grade ≥3 AEs, and AEs requiring treatment discontinuation). For primary clinical outcomes, we extracted the hazard ratios (HRs) and 95% confidence intervals (CIs) published in each study. When HRs could not be extracted directly, we used GetData software to capture data from Kaplan–Meier curves and calculated them using the digital computation chart developed by Tierney et al. (20). If the HRs and Kaplan–Meier curves could not be obtained, we extracted data using Cox univariate analysis. For secondary clinical outcomes, we directly extracted the corresponding number of cases from each study. The relative ratio (RR) and 95% CIs were used to evaluate the ORR and AEs, respectively. Data from six studies (17, 21–25) were extracted from original articles, whereas data from four studies (18, 26–28) were extracted from Kaplan–Meier curves. PFS data were extracted from original articles, and OS data were extracted from the Kaplan–Meier curves in Chen et al. (29).

The RWS quality was assessed using the Newcastle–Ottawa Scale (NOS), which comprises the following three major parameters: selection, comparability, and exposure or outcome. Scores >6 points indicate high-quality studies (30). RCTs were evaluated using the Cochrane risk of bias (ROB) Tool in Review Manager 5.3 software. Six aspects were evaluated as follows: random sequence generation, allocation concealment, blinding of participants and personnel or outcome assessment, incomplete outcome data, selective reporting, and other sources of bias. Each study was graded into low, high, or unclear (moderate) bias (31).

Two investigators independently extracted data and assessed the quality of the included studies. Discrepancies were resolved through consensus and arbitration within groups.

2.3 Statistical analysis

We synthesized evidence and compared the efficacy and safety. Efficacy was reported as PFS, OS, ORR, and safety was reported as any grade AEs, grade ≥3 AEs, and AEs requiring treatment discontinuation. Network plots were generated for the different outcomes of the regimens to illustrate the comparisons between different treatments in the included studies using Stata 14.0. We performed Bayesian NMA using the R software 4.3.2 (R Project for Statistical Computing; gemtc package) (32). For efficacy and safety outcomes, 20,000 sample iterations were generated with 5,000 burn-ins and a thinning interval of 1 (33). The two fundamental assumptions underlying the NMA are transitivity (the exchangeability across studies to compare two treatments via a third one) and consistency (the direct and indirect estimates are statistically similar) (34). Heterogeneity was assessed using the Q test and I^2 statistic within a visual forest plot, and the heterogeneity was considered low, moderate, and high when I^2 <25%, 25%≦I^2 <50%, and I^2≧50%, respectively (30). Inconsistency was calculated using the node splitting approach, where direct and indirect evidence were separately contrasted for a particular comparison (node). Moreover, for each outcome, we estimated the probability of each agent at each possible rank, and the surface under the cumulative ranking (SUCRA) curve was used to rank the safety and clinical outcomes of various regimens, with a higher SUCRA value indicating a better outcome ranking (35). A regimen with an HR <1 for OS and PFS or an RR >1 for ORR was deemed preferable, whereas an RR >1 for AEs indicated a greater likelihood of toxic effects. The risk of inconsistency was low (95% CI: 1). A funnel plot was constructed to further detect publication bias in the included studies, and significant asymmetry was defined as the presence of publication bias. Statistical significance was set at p<0.05.

3 Results

3.1 Systematic review and characteristics

We initially screened 4108 articles from the databases according to the search strategy, and 56 articles were retrieved and reviewed for their full text. Eventually, 11 articles met the inclusion criteria for this NMA, comprising two RCTs (17, 23) and nine RWSs (18, 21, 22, 24–29) with 1462 patients. Figure 1 illustrates the process of the study selection process. These patients received the following five regimens: ICI+chemo, chemo, ICI, antiangiogenesis +chemo, and ICI+antiangiogenesis+chemo. ICIs included atezolizumab, nivolumab, pembrolizumab, and sintilimab. Chemo included carboplatin, paclitaxel, pemetrexed, cisplatin, and platinum. Antiangiogenesis included bevacizumab and its biosimilar agent (IBI305). The networks are presented in Figure 2, with nodes representing regimens and edges indicating RCTs or RWSs for pairs of treatments. All primary features are detailed in Table 1.

3.2 NMA in EGFR-mutated NSCLC for efficacy

For OS (Table 2A; Supplementary Figure S2A), ICI +antiangiogenesis+chemo (HR=0.74, 95% CI 0.72–2.32), antiangiogenesis+chemo (HR=0.73, 95% CI 0.38–1.32), and ICI +chemo (HR=0.78, 95% CI 0.50–1.19) prolonged OS compared to chemo, albeit without significant difference, whereas ICI reduced OS compared to chemo (HR=1.26, 95% CI 0.72–2.32). No significant differences were observed between combination treatments.

The results of PFS (Table 2B; Supplementary Figure S2B) were similar to those of the OS. ICI+antiangiogenesis+chemo (HR=0.55, 95% CI 0.28–1.14), antiangiogenesis+chemo (HR=0.84, 95% CI 0.29–2.56), and ICI+chemo (HR=0.74, 95% CI 0.44–1.28) showed prolonged PFS compared to chemo, with no significant difference, whereas ICI reduced PFS compared to chemo (HR=1.44, 95% CI 0.79–2.76). ICI+antiangiogenesis+chemo yielded a better benefit in PFS than any other treatment (antiangiogenesis+chemo: HR=0.65, 95% CI, 0.21–2.04; ICI+chemo: HR=0.74, 95% CI 0.40–1.40).

For ORR (Table 2C; Supplementary Figure S2C), ICI +antiangiogenesis+chemo exhibited a tendency toward a higher ORR than chemo (HR=1.64, 95% CI 0.32–8.54) and any other

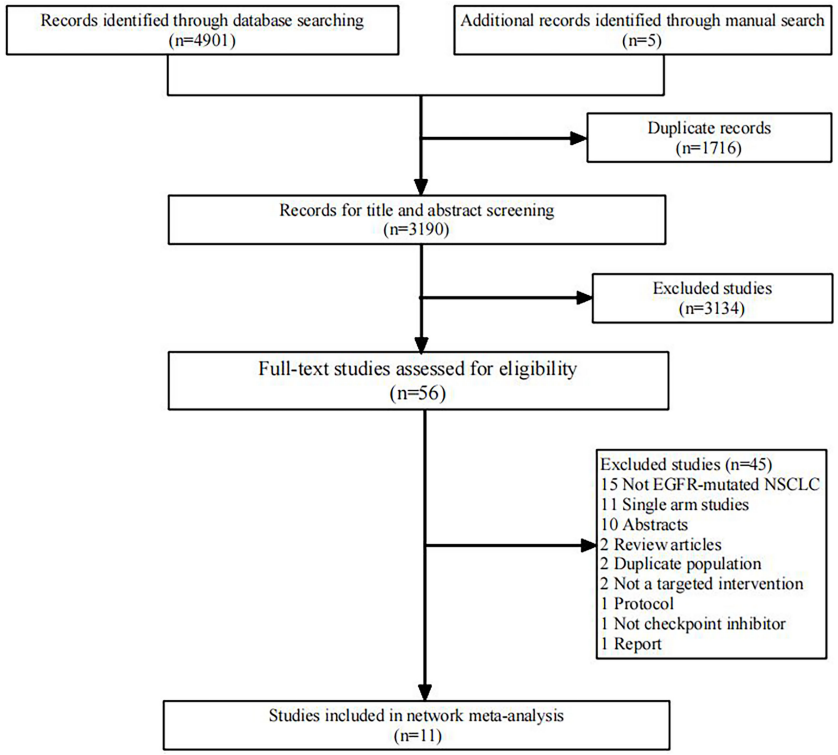

FIGURE 1
Flowchart of literature search and selection followed the preferred reporting items for systematic reviews and meta-analysis guidelines. EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer.

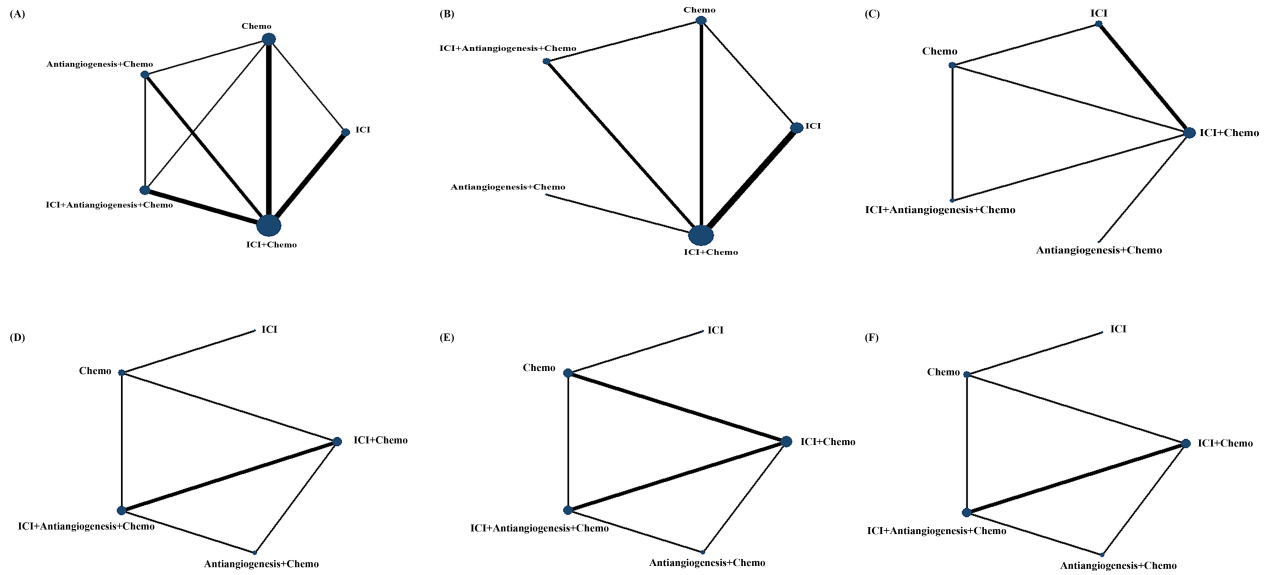

FIGURE 2
Comparative network plots for efficacy and safety of ICI for patients with EGFR-mutated NSCLC. Circular nodes represent the different types of treatments, while lines depict head-to-head comparison. The size of the node and the width of the line are proportional to the number of patients and comparisons, respectively. Comparisons were conducted using the Bayesian framework on **(A)** OS. **(B)** PFS. **(C)** ORR. **(D)** Safety assessed according to AEs of any grade. **(E)** Safety assessed according to grade ≥3 AEs. **(F)** Safety assessed according to AEs of any grade leading to treatment discontinuation occurred. AEs, adverse events; Chemo, chemotherapy; ICI, immune checkpoint inhibitor; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; ORR, objective response rate.

TABLE 1 Main characteristics of the studies included in the network meta-analysis.

Author	Year	Country	Study design, Phase	Setting	Diagnostic criteria	Treatment arm	Sample size (No.)	Age (Range)	Male ratio (%)	Follow-up (months)
Hayashi et al.	2022	Japan	prospective, randomized, II	37 sites of West Japan Oncology Group	locally advanced, metastatic, or recurrent non-squamous NSCLC positive for an activating mutation of EGFR	nivolumab	52	70.5 (51–84)	46.2	25.5 (0.1-46.1)
						carboplatin+pemetrexed	50	67 (45–83)	38	23.4 (1.6-48)
White et al.	2021	US	retrospective, NR	Stanford Cancer Institute and Massachusetts General Hospital	stage IV or recurrent metastatic NSCLC with a sensitizing EGFR mutation	chemotherapy+immunotherapy	12	56.5	50	NR
						chemotherapy	57	62.9	37	
						chemotherapy+immunotherapy	12	56.5	50	
						chemotherapy+bevacizumab	35	60.9	29	
Chen et al.	2022	China	retrospective, NR	Peking Union Medical College Hospital	NSCLC with sensitive EGFR mutations	chemotherapy+pembrolizumab	82	65.5 (32-82)	40.2	12.5
						chemotherapy	82	59 (36-80)	39.0	13.1
Nogami et al.	2021	Japan	randomized,open-label, III	240 study centers in 26 countries	chemotherapy-naive, metastatic, non-squamous NSCLC with EGFR mutations	atezolizumab+bevacizumab +carboplatin+paclitaxel	34	64.0 (37–76)	52.9	39.3
						atezolizumab +carboplatin+paclitaxel	45	63.0 (38–82)	37.8	
						bevacizumab +carboplatin+paclitaxel	44	61.5 (31–81)	45.5	
Lu et al.	2023	China	randomized, double-blind, III	52 centers across China	locally advanced or metastatic EGFR-mutated non-squamous NSCLC	sintilimab+IBI305 +pemetrexed+cisplatin	158	58.5 (52.0–65.0)	41	12.9
						sintilimab+pemetrexed+cisplatin	158	57.5 (52.0–65.0)	41	15.1
						pemetrexed+cisplatin	160	56.0 (51.0–64.5)	40	14.4
Yu et al.	2021	China	retrospective, NR	Shanghai Pulmonary Hospital and Shanghai Chest Hospital	EGFR-TKI resistance in patients with EGFR-mutant advanced NSCLC	chemotherapy+immunotherapy	44	63.5 (19–76)	52.3	8.9
						chemotherapy+antiangiogenesis	100	58.5 (36–75)	45	
Kuo et al.	2019	China	retrospective, NR	Chang Gung Memorial Hospital	advanced or metastatic lung cancer who were administered at least one cycle of ICI treatment	immune checkpoint inhibitor+chemotherapy	5	NR	NR	NR
						immune checkpoint inhibitor	16			

(Continued)

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TABLE 1 Continued

Author	Year	Country	Study design, Phase	Setting	Diagnostic criteria	Treatment arm	Sample size (No.)	Age (Range)	Male ratio (%)	Follow-up (months)
Morimoto et al.	2022	Japan	retrospective, NR	12 institutions in Japan	histologically confirmed NSCLC, confirmed EGFR-activating mutation	immune checkpoint inhibitor	42	68 (43-85)	50.0	25.6
						immune checkpoint inhibitor+ chemotherapy	38	66 (39-79)	57.9	15.3
Shen et al.	2021	China	retrospective, observational, NR	a tertiary medical center	stage IV EGFR-mutant NSCLC	immune checkpoint inhibitor	22	65.5 (45-78)	45.5	16.76
						immune checkpoint inhibitor+ chemotherapy	8	67.5 (55-85)	37.5	
Bylicki et al.	2023	France	multicenter, open-label, non-randomized, II	27 centers	stage IIIB/IV non-squamous NSCLC patients with EGFR mutation or ALK/ ROS1 fusion	platinum+ pemetrexed+ atezolizumab+ bevacizumab	62	NR	NR	14.8
						platinum+ pemetrexed+ atezolizumab	70			13.1
Chen et al.	2021	China	retrospective, NR	Shanghai Chest Hospital	stage IV NSCLC with positive EGFR mutation	Pembrolizumab	32	61 (39-80)	59.4	NR
						pembrolizumab+chemotherapy	26	66 (54-78)	50	
						pembrolizumab+anlotinib	28	59 (41-78)	57.1	

EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; TKI, tyrosine kinase inhibitors; NR, not report.

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TABLE 2 Pooled estimates of the network meta-analysis for patients with EGFR-mutated NSCLC.

A. Hazard ratios (HR) with 95% confidence interval (CI) for OS				
Antiangiogenesis+Chemo	1.38 (0.76, 2.65)	1.73 (0.85, 3.94)	1.01 (0.52, 1.92)	1.08 (0.61, 1.97)
0.73 (0.38, 1.32)	**Chemo**	1.26 (0.72, 2.32)	0.74 (0.41, 1.23)	0.78 (0.50, 1.19)
0.58 (0.25, 1.17)	0.80 (0.43, 1.38)	**ICI**	0.58 (0.27, 1.08)	0.62 (0.35, 1.02)
0.99 (0.52, 1.92)	1.36 (0.82, 2.45)	1.71 (0.92, 3.64)	**ICI+Antiangiogenesis+Chemo**	1.06 (0.68, 1.75)
0.93 (0.51, 1.64)	1.28 (0.84, 1.98)	1.61 (0.98, 2.83)	0.94 (0.57, 1.46)	**ICI+Chemo**
B. HR with 95% CI for PFS				
Antiangiogenesis+Chemo	1.18 (0.39, 3.47)	1.70 (0.59, 5.05)	0.65 (0.21, 2.04)	0.88 (0.34, 2.26)
0.84 (0.29, 2.56)	**Chemo**	1.44 (0.79, 2.76)	0.55 (0.28, 1.14)	0.74 (0.44, 1.28)
0.59 (0.20, 1.68)	0.70 (0.36, 1.26)	**ICI**	**0.38 (0.18, 0.82)**	**0.52 (0.31, 0.84)**
1.53 (0.49, 4.74)	1.82 (0.88, 3.63)	**2.61 (1.22, 5.69)**	**ICI+Antiangiogenesis+Chemo**	1.35 (0.71, 2.48)
1.14 (0.44, 2.95)	1.35 (0.78, 2.29)	**1.93 (1.20, 3.26)**	0.74 (0.40, 1.40)	**ICI+Chemo**
C. Relative risk (RR) with 95% CI for ORR				
Antiangiogenesis+Chemo	1.90 (0.19, 18.34)	0.48 (0.05, 4.45)	3.11 (0.28, 35.65)	2.25 (0.37, 13.51)
0.53 (0.05, 5.30)	**Chemo**	0.26 (0.05, 1.06)	1.64 (0.32, 8.54)	1.18 (0.29, 4.90)
2.06 (0.22, 21.61)	3.90 (0.94, 18.22)	**ICI**	6.41 (0.97, 47.19)	**4.63 (1.21, 20.90)**
0.32 (0.03, 3.62)	0.61 (0.12, 3.13)	0.16 (0.02, 1.03)	**ICI+Antiangiogenesis+Chemo**	0.72 (0.14, 3.75)
0.44 (0.07, 2.67)	0.85 (0.20, 3.40)	**0.22 (0.05, 0.83)**	1.39 (0.27, 7.14)	**ICI+Chemo**
D. RR with 95% CI for safety assessed according to any grade AEs				
Antiangiogenesis+Chemo	1.07 (0.68, 1.88)	0.81 (0.43, 1.67)	1.12 (0.79, 1.91)	1.00 (0.69, 1.49)
0.93 (0.53, 1.47)	**Chemo**	0.75 (0.47, 1.18)	1.04 (0.75, 1.56)	0.93 (0.62, 1.30)
1.24 (0.60, 2.35)	1.33 (0.85, 2.11)	**ICI**	1.40 (0.80, 2.59)	1.23 (0.67, 2.17)
0.89 (0.52, 1.26)	0.96 (0.64, 1.34)	0.71 (0.39, 1.25)	**ICI+Antiangiogenesis+Chemo**	0.89 (0.60, 1.14)
1.00 (0.67, 1.45)	1.07 (0.77, 1.61)	0.81 (0.46, 1.50)	1.13 (0.88, 1.66)	**ICI+Chemo**
E. RR with 95% CI for safety assessed according to grade ≥3 AEs				
Antiangiogenesis+Chemo	1.08 (0.68, 1.71)	0.85 (0.23, 2.98)	1.16 (0.78, 1.77)	0.96 (0.64, 1.48)
0.93 (0.58, 1.48)	**Chemo**	0.80 (0.24, 2.53)	1.08 (0.81, 1.46)	0.89 (0.70, 1.17)
1.17 (0.34, 4.26)	1.26 (0.40, 4.23)	**ICI**	1.36 (0.42, 4.72)	1.12 (0.35, 3.87)
0.86 (0.56, 1.29)	0.92 (0.69, 1.23)	0.73 (0.21, 2.40)	**ICI+Antiangiogenesis+Chemo**	0.83 (0.64, 1.08)
1.04 (0.68, 1.56)	1.12 (0.85, 1.43)	0.89 (0.26, 2.88)	1.21 (0.93, 1.56)	**ICI+Chemo**
F. RR with 95% CI for safety assessed according to AEs of any grade leading to treatment discontinuation occurred				
Antiangiogenesis+Chemo	0.81 (0.13, 4.68)	0.31 (0.02, 3.53)	2.35 (0.59, 9.53)	1.06 (0.24, 4.33)
1.24 (0.21, 7.80)	**Chemo**	0.38 (0.06, 2.13)	2.90 (0.82, 11.30)	1.31 (0.35, 5.01)
3.27 (0.28, 45.90)	2.61 (0.47, 17.80)	**ICI**	7.72 (0.92, 80.36)	3.46 (0.39, 35.13)
0.43 (0.10, 1.70)	0.34 (0.09, 1.21)	0.13 (0.01, 1.08)	**ICI+Antiangiogenesis+Chemo**	0.45 (0.16, 1.17)
0.95 (0.23, 4.10)	0.76 (0.20, 2.88)	0.29 (0.03, 2.55)	2.22 (0.86, 6.25)	**ICI+Chemo**

AEs, adverse events; Chemo, chemotherapy; ICI, immune checkpoint inhibitor; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; ORR, objective response rate. Bold indicates different regimens, and colored represents significant differences.

treatment (antiangiogenesis+chemo: HR=3.11, 95% CI 0.28–35.65; ICI+chemo: HR=1.39, 95% CI 0.27–7.14; ICI: HR=6.41, 95% CI 0.97–47.19).

3.3 NMA in EGFR-mutated NSCLC for safety

For any grade AEs (Table 2D; Supplementary Figure S2D), each point estimates of the combined RRs exceeded 1 in ICI +antiangiogenesis+chemo treatment, indicating that ICI +antiangiogenesis+chemo may increase the incidence more than any other treatment (antiangiogenesis+chemo: HR=1.12, 95% CI 0.79–1.91; ICI+chemo: HR=1.13, 95% CI 0.88–1.66; chemo: HR=1.04, 95% CI 0.75–1.56; and ICI: HR=1.40, 95% CI 0.80–2.59). In contrast, all point estimates of the pooled RRs were lower than 1 in the ICI treatment, indicating that ICI yielded the lowest incidence compared to any other treatment (ICI+antiangiogenesis +chemo: HR=0.71, 95% CI 0.39–1.25; antiangiogenesis+chemo: HR=0.81, 95% CI 0.43–1.67; ICI+chemo: HR=0.81, 95% CI 0.46–1.50; and chemo: HR=0.75, 95% CI 0.47–1.18).

Regarding grade ≥3 AEs (Table 2E; Supplementary Figure S2E) and AEs leading to treatment discontinuation (Table 2F; Supplementary Figure S2F), the results were similar to those of any grade AEs.

3.4 Rank probabilities

Figure 3 shows the Bayesian ranking profiles of various comparable treatments. Among EGFR-mutated NSCLC, ICI +antiangiogenesis+chemo was most likely to be ranked first for OS (74%), PFS (92%), ORR (87%), ICI for any grade AEs (84%) and any grade AEs leading to treatment discontinuation (89%), and ICI +chemo for grade ≥3 AEs (68%).

3.5 Quality assessment

During the literature quality assessment, all RWSs were assessed as high quality with NOS scores >6 points. However, one study (Supplementary Table S2) was evaluated as low risk, whereas two

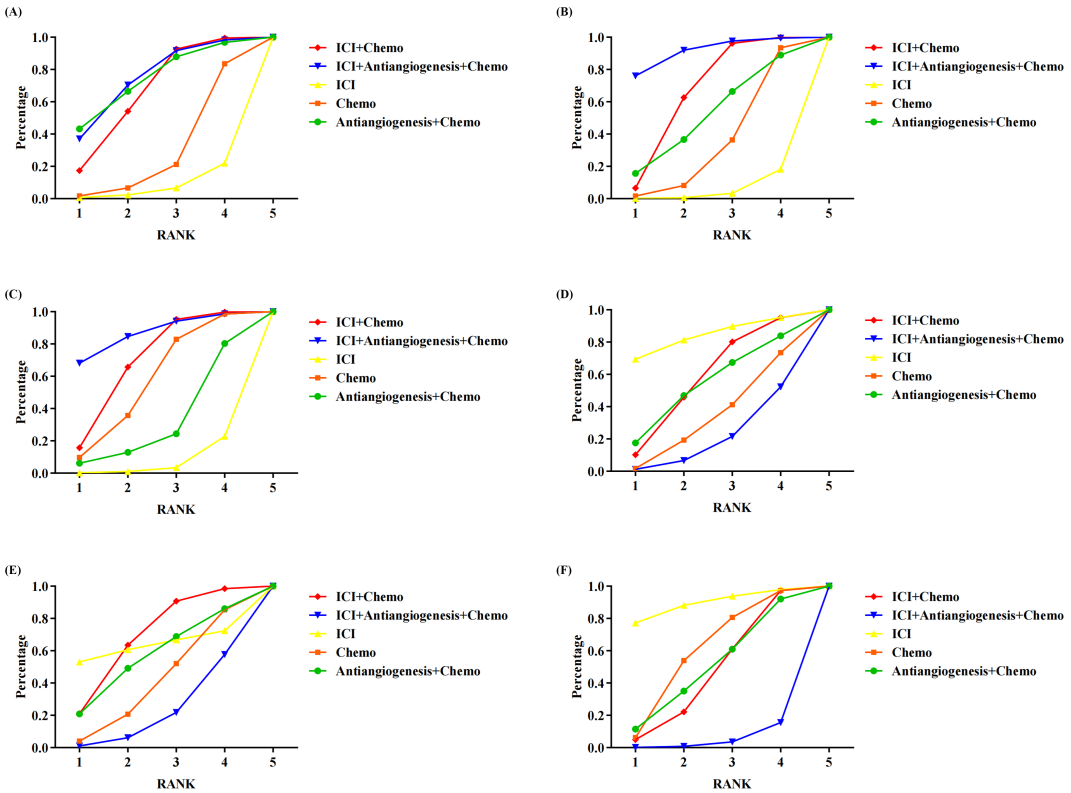

FIGURE 3
Bayesian ranking profiles assessing the efficacy and safety of ICI for patients with EGFR-mutated NSCLC. The profiles indicate the probability of each treatment being ranked from first to last on **(A)** OS. **(B)** PFS. **(C)** ORR. **(D)** safety assessed according to any grade AEs. **(E)** Safety assessed according to grade ≥3 AEs. **(F)** Safety assessed according to AEs of any grade leading to treatment discontinuation occurred. Different colored lines represent different interventions. The position of each line on the graph corresponds to the ranking probability of each intervention. AEs, adverse events; Chemo, chemotherapy; ICI, immune checkpoint inhibitor; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; ORR, objective response rateTables.

were classified as moderate risk using the ROB tool owing to concerns regarding blinding (Supplementary Figure S1).

3.6 Heterogeneity and inconsistency assessment

Forest plots with heterogeneity estimates are shown in Supplementary Figure S3. These results suggest low or moderate heterogeneity across most of the outcomes. An analysis of inconsistency among the direct, indirect, and overall effects showed low inconsistency with $p>0.05$ (Supplementary Figure S4). The funnel plot for all outcomes was almost symmetric, confirming the absence of publication bias (Supplementary Figure S5).

4 Discussion

This NMA included 11 articles, comprising two RCTs and nine RWSs, involving 1462 patients and evaluating five regimens. It summarized the comparative efficacy and safety of ICIs and combination therapies for patients with EGFR-mutated NSCLC using R software with the gemtc package. The results of this study indicated that ICI+antiangiogenesis+chemo achieved greater survival benefits than the other treatments regarding OS, PFS, and ORR. However, it was associated with a higher incidence of AEs, although this difference was not significant.

EGFR-TKIs are recommended as the standard first-line treatment for patients with advanced EGFR-mutated NSCLC (36). However, long-term EGFR-TKI resistance is inevitable. Currently, the main indication for first-line therapy with ICIs is in patients with wild-type EGFR because the PD-L1 expression level in EGFR mutations is lower than that in the wild-type (37–39). Tumor cells often exhibit high PD-L1 expression under the influence of various cytokines. When T cells recognize tumor cells, PD-L1 on the tumor cell surface binds to PD-1 on T cells, thereby inhibiting T cell proliferation and their cytotoxic effects on tumor cells, leading to immune evasion by the tumor (40, 41). ICIs block the interaction between PD-1 and PD-L1, thereby restoring the antitumor activity of T cells. Consequently, PD-L1 expression is currently the most widely used ICI predictive marker. This is not only because ICIs target PD-1 receptor-ligand interactions but also because PD-L1 expression correlates with parameters associated with immune activation in the tumor, such as activated $CD8^+$ T cells and antigen presentation. Therefore, patients who are PD-L1 negative or have low expression are more prone to developing resistance to ICIs (42). Kuo et al. (25) conducted a study comparing the efficacy of ICI combined with chemo versus chemo alone in EGFR-mutated NSCLC with PD-L1 expression levels of <50% and ≥50%. The results indicated that patients in the ICI plus chemo group experienced improved PFS compared to those receiving chemo alone. Notably, the lower the PD-L1 expression level, the greater the improvement observed (for PD-L1 TPS≥50%, PFS: ICI +Chemo vs Chemo HR=0.93, 95% CI 0.37-2.36; for PD-L1 TPS<50%, PFS: ICI+Chemo vs Chemo HR=0.86, 95% CI 0.39-1.92). In contrast, Hayashi et al. (21) compared the efficacy of ICI and chemo in EGFR-mutated NSCLC with PD-L1 TPS between 1% and 49% and PD-L1≥50%. Their findings showed that patients in the ICI group had improved PFS compared to those in the chemo group, with the benefit being more pronounced at higher PD-L1 expression levels (for 1%≤ PD-L1 TPS ≤ 49%, PFS: ICI vs Chemo HR=2.10, 95% CI 0.83-5.29; for PD-L1 TPS≥50%, PFS: ICI+Chemo vs Chemo HR=1.49, 95% CI 0.31-7.24). These findings suggest the need for further research to explore the relationship between PD-L1 expression levels and the efficacy of ICI in EGFR-mutated NSCLC.

EGFR mutation may reduce $CD8^+$ T cell infiltration by activating transforming growth factor-β (TGFβ), leading to immunosuppression and lymphocyte depletion within the tumor (43). Additionally, under TGFβ induction, stromal cells can form a physical muscle fiber barrier around tumor cells, preventing T cell infiltration and migration (44). Patients with EGFR-mutated NSCLC and high CD73 expression can hydrolyze ATP into adenosine, exerting immunosuppressive effects by acting on A2a/A2b receptors. It can activate regulatory T cells and myeloid-derived suppressor cells, weaken the anti-tumor functions of dendritic and natural killer cells, polarize macrophages towards the M2 phenotype, and suppress T cell-mediated anti-tumor responses, thereby mediating the immune escape of tumors (45–47). The lack of effective tumor-killing effector cells in the tumor microenvironment of EGFR-mutated NSCLC and the dysfunction of effector cells are potential causes of poor immunotherapy outcomes in patients with EGFR-mutated NSCLC.

Vascular endothelial growth factor (VEGF) is a key factor in fostering angiogenesis and tumor growth (48). However, this neovascularization is structurally disorganized and dysfunctional, lacks pericellular and basement membrane wrapping, and has loose connections with the endothelium, resulting in reduced infiltration of cytotoxic T cells (49). Studies have shown that VEGF inhibitors can "normalize" tumor blood vessels, increase pericyte coverage, improve tumor vessel perfusion, and destroy the physical and chemical barriers of endothelial cells, resulting in an increased inflow of $CD4^+$ and $CD8^+$ T cells into the tumor parenchyma (50). Therefore, antiangiogenesis therapy can improve VEGF-induced tumor vascular system dysfunction, promote effector cell infiltration, and eliminate obstacles in tumor immunotherapy. ICIs induce $CD4^{+/}CD8^+$ T cells to produce interferonγ, increase lymphocyte infiltration and activation, promote tumor vascular normalization, and produce synergistic effects (51).

White et al. (18), Chen et al. (22), and Lu et al. (17) all compared the effects of ICI+chemo versus chemo alone on OS in EGFR-mutated NSCLC. The results indicated that, except for White's study, all showed that ICI+chemo could improve OS in patients with EGFR-mutated NSCLC compared to chemo alone. There are two possible reasons for this: 1. In Lu's study, the investigational drugs included 200 mg sintilimab, 15 mg/kg IBI305, 500 mg/m² pemetrexed, and 75 mg/m² cisplatin; in Chen's study, the investigational drugs included pembrolizumab and platinum-based doublet chemotherapy; in White's study, 54 patients received carboplatin/pemetrexed; 1 received carboplatin/paclitaxel; 1 received carboplatin/albumin-bound paclitaxel; 1 received carboplatin/gemcitabine, 12 patients received chemotherapy plus immunotherapy (carboplatin/pemetrexed/pembrolizumab), and 35

patients received chemotherapy plus bevacizumab (carboplatin/pemetrexed/bevacizumab). White's study involved a wider variety of chemotherapy drugs, with significant differences between the different chemotherapy regimens. 2. It is possible that in White's study, the HR was derived from points taken on the Kaplan-Meier curve, which may have introduced some errors. While, Chen and Lu both confirmed that ICI+chemo could improve PFS in patients with EGFR-mutated NSCLC compared to chemo alone.

Recently, a network meta-analysis on the efficacy and safety of ICIs for individuals with advanced EGFR-mutated NSCLC who progressed on EGFR tyrosine kinase inhibitors was published in *Lancet Oncology* (52). Our study differs from the recent study in *Lancet Oncology*. To clarify the study population, we focused specifically on EGFR-mutant NSCLC, excluding metastatic nonsquamous EGFR-mutant NSCLC. In terms of OS, PFS, and ORR, our conclusions align with those of the Lancet Oncology study. We found that ICI+antiangiogenesis+chemotherapy yielded the best OS, PFS, and ORR compared to any other treatment. However, due to the limited number of original studies in our analysis, we did not observe significant differences between ICI +antiangiogenesis+chemo and other treatment strategies, except for the benefit of ICI+antiangiogenesis+chemo over ICI alone in terms of PFS. In contrast, Zhao et al. (52) demonstrated significant differences between ICI+antiangiogenesis+chemo and other treatment strategies for both PFS and ORR, based on a larger number of original studies. Regarding safety, both studies found that ICI+antiangiogenesis+chemo was associated with a higher risk of any-grade adverse events compared to ICI+chemo and chemo alone.

This NMA has some limitations. First, the number of studies included was limited. Therefore, this study lacked a subgroup analysis based on smoking status, sex, or other associated factors, which might compromise the credibility and veracity of this assessment. Therefore, future studies should investigate these clinical characteristics using NMA. Second, variations in mechanisms and toxicities among ICIs (e.g., atezolizumab, nivolumab, pembrolizumab, and sintilimab), chemo drugs (carboplatin, paclitaxel, pemetrexed, cisplatin, and platinum), and anti-angiogenic drugs (bevacizumab, IBI305) incorporated into treatment regimens introduce heterogeneity. Third, data extraction from several studies in this NMA involved digitizing Kaplan–Meier curves from clinical trials rather than being based on exact PFS and OS for each patient. This approach may have resulted in minor deviations in our results.

To conclude, based on our results, it is inferred that combination therapy of ICI, antiangiogenesis, and chemotherapy holds potential benefits for patients with EGFR-mutated NSCLC, although without significant differences. Further studies are warranted to validate the efficacy and safety of combined ICI treatments.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding authors.

Author contributions

LZ: Conceptualization, Methodology, Writing – original draft. WH: Software, Writing – original draft. CX: Data curation, Validation, Writing – original draft. YS: Data curation, Validation, Writing – original draft. CZ: Supervision, Writing – review & editing. YZ: Supervision, Writing – review & editing.

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Comparative safety profile of tyrosine kinase inhibitors in NSCLC: a network meta-analysis of hypertension and thrombotic risks

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Background: This study examines the risks of hypertension and thrombotic events in NSCLC patients treated with Tyrosine Kinase Inhibitors (TKIs).

Objective: To compare the safety profiles of TKIs used in NSCLC treatment, focusing on hypertension and thrombotic risks.

Methods: A comprehensive search identified randomized controlled trials evaluating the effects of TKIs in NSCLC patients. Bayesian network meta-analysis was employed to construct a comparative network of treatments.

Results: Thirty studies involving 11,375 patients were included. Erlotinib had the lowest incidence of hypertension (SUCRA: 91.1%), followed by chemotherapy (88.8%). For thrombotic events, Erlotinib had the lowest risk (SUCRA: 66.1%), while Anlotinib and Cabozantinib had the highest thrombotic risks (SUCRA: 26.9%).

Conclusion: Erlotinib presents the lowest risk for hypertension and thrombotic events, making it a preferred choice for NSCLC patients with cardiovascular concerns.

Systematic review registration: https://www.crd.york.ac.uk/prospero, identifier CRD42024530770.

KEYWORDS

non-small cell lung cancer, tyrosine kinase inhibitors, hypertension, thrombotic events, network meta-analysis, NSCLC

Introduction

Lung cancer remains the leading cause of cancer-related mortality worldwide, with non-small cell lung cancer (NSCLC) comprising 80%–90% of primary lung malignancies. For patients with stage IV NSCLC, the standard treatment typically involves chemotherapy and palliative radiation therapy. Despite advancements in treatment options, including molecular targeted therapies and immunotherapy, the overall 5-year survival rate for stage IV NSCLC remains dismally low at 4%–6% (David et al., 2017).

Research has underscored the critical role of vascular endothelial growth factor (VEGF) in tumor growth, progression, and metastasis, primarily by promoting angiogenesis (Apte

et al., 2019). Targeting the VEGF signaling pathway has become a cornerstone in the development of anticancer therapies. Bevacizumab, a VEGF receptor tyrosine kinase inhibitor (VEGFR-TKI), effectively neutralizes VEGF, inhibiting the tumor's blood supply and thereby showing significant clinical efficacy across various cancers, including breast cancer, colorectal cancer, and NSCLC (Al Kawas et al., 2022; Ahluwalia et al., 2014; Cardones and Banez, 2006). Similarly, epidermal growth factor receptor (EGFR)-targeted therapies, such as cetuximab, have improved the prognosis for lung cancer patients (Le et al., 2021).

Despite the therapeutic benefits of antiangiogenic agents, these drugs are associated with increased risks of arterial thrombotic events and hemorrhagic complications. While hypertension represents another frequent adverse event, it can typically be managed with conventional antihypertensive medications (Krupitskaya and Wakelee, 2009). However, the precise magnitude of cardiovascular risks, particularly hypertension and thrombotic events, associated with antiangiogenic targeted therapies in NSCLC remains inadequately characterized (Castel et al., 2011).

Therefore, a comprehensive meta-analysis of contemporary randomized controlled trials could provide more robust evidence regarding the cardiovascular safety profile of antiangiogenic therapies in NSCLC, with particular emphasis on hypertensive and thrombotic complications.

Methods

Literature search

A comprehensive search was conducted using the following terms: ("EGFR-TKI" OR "VEGF-TKI" OR "Gefitinib" OR "Erlotinib" OR "Icotinib" OR "Afatinib" OR "Dacomitinib" OR "Osimertinib" OR "ALK inhibitors" OR "Brigatinib" OR "Lorlatinib" OR "Alectinib") AND ("NSCLC" OR "non-small-cell lung carcinoma" OR "non-small cell lung cancer"). Our search covered published articles from electronic databases, including PubMed, Embase, and the Cochrane Library, up to 1 June 2024. Additionally, we manually searched abstracts from the American Society of Clinical Oncology and the World Congress on Lung Cancer to identify unpublished studies and ongoing clinical trials. Only studies published in English were included, and we also hand-searched the references of the included studies.

Inclusion criteria

Studies were eligible if they compared tyrosine kinase inhibitors (TKIs) combined with chemotherapy or other treatments versus TKIs alone. The criteria for inclusion were (David et al., 2017): prospective randomized controlled trials (RCTs) comparing TKIs alone or in combination with chemotherapy in NSCLC patients (Apte et al., 2019); reported data on the number of patients with hypertension or thrombotic adverse reactions, as well as the total number of patients with adverse events; and (Al Kawas et al., 2022) original articles published in English. Exclusion criteria included (David et al., 2017): single-arm clinical trials (Apte et al., 2019); case reports or review articles; and (Al Kawas et al., 2022) clinical trials with fewer than 10 participants.

Data extraction

Data extracted from each study included the year of publication, first author, trial name, patient demographics (age, sex), ECOG score, disease status, smoking history, type of TKIs used, incidence of hypertension and thrombotic events, total number of subjects, and follow-up duration. Data extraction, study design, and results were reviewed by two independent reviewers. Disagreements were resolved through discussion, and if consensus was not reached, a third independent reviewer was consulted. Data were standardized according to pre-specified criteria to ensure consistency across studies. Data extraction was performed independently by two reviewers. In cases of discrepancies between reviewers, a third reviewer was consulted, and a consensus was reached through discussion. When necessary, we contacted the original authors for clarification or additional data. This process ensured the accuracy and completeness of the extracted data.

Risk of bias assessment

Two researchers independently assessed the risk of bias using the Cochrane Handbook tool, evaluating the following domains: (David et al., 2017): random sequence generation, (Apte et al., 2019), allocation concealment, (Al Kawas et al., 2022), blinding of participants and personnel, (Ahluwalia et al., 2014), completeness of outcome data (Cardones and Banez, 2006), selective reporting, and (Le et al., 2021) other potential sources of bias. Trials were categorized into three levels: high risk, low risk, and unclear risk (Higgins et al., 2011).

Data analysis

Randomized controlled trials (RCTs) conducted across various institutions frequently yield heterogeneous efficacy outcomes, challenging the establishment of definitive therapeutic hierarchies. Network meta-analysis emerges as a valuable methodological approach to facilitate comprehensive comparisons among diverse therapeutic agents evaluated in different RCTs. In this systematic review and network meta-analysis, we sought to evaluate and compare the cardiovascular safety profiles of various treatment strategies, specifically focusing on hypertensive and thrombotic risks in patients with non-small cell lung carcinoma. The surface under the cumulative ranking curve (SUCRA) probability was employed to establish a hierarchical ranking of therapeutic strategies based on their cardiovascular safety profiles (Sonbol et al., 2020). Statistical analysis was performed using R (version 4.2.1) with the gemtc and rjags packages. We used odds ratios (OR) with 95% confidence intervals (CI) for dichotomous adverse reaction data. Network meta-analysis (NMA) and Bayesian aggregation were conducted using Markov Chain Monte Carlo (MCMC) simulations (Moher et al., 2015). Funnel plots, generated with Stata (version 15.0), assessed potential bias in network comparisons (Salanti et al., 2011). Stata also produced network diagrams depicting hypertension occurrences as an adverse event. These diagrams visually represent evidence, with nodes indicating different interventions and connecting lines showing direct comparisons. The size of each node and line width are proportional

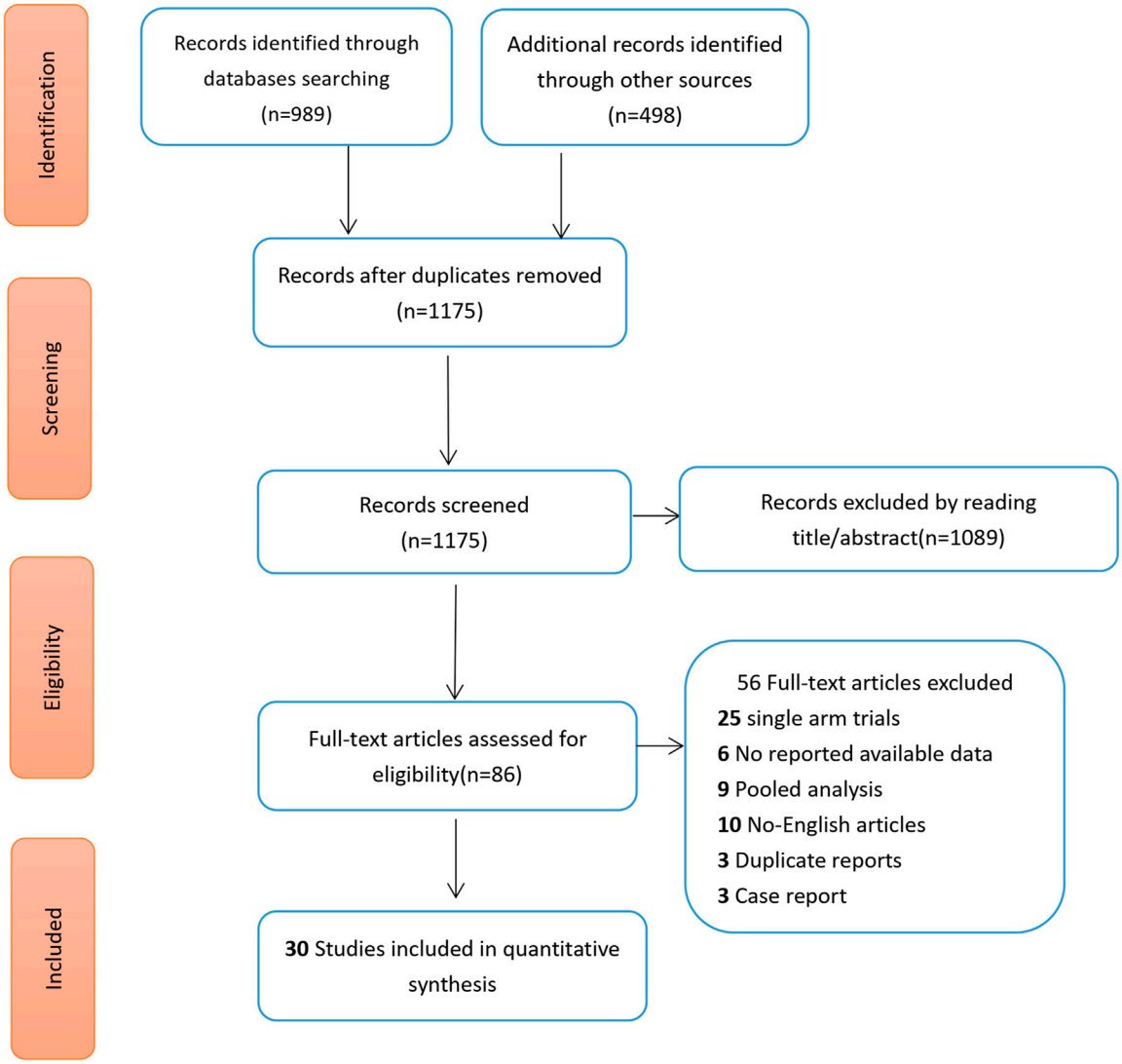

FIGURE 1
Literature screening flow chart.

to the number of cases (Chaimani et al., 2013). The treatment effect was summarized using the surface under the cumulative ranking curve (SUCRA), where a higher SUCRA value indicates a better treatment effect (Daly et al., 2019). To assess the robustness of our findings, we conducted sensitivity analyses by excluding studies with high risk of bias. Additionally, we performed subgroup analyses based on patient characteristics and treatment duration to explore potential sources of heterogeneity. These analyses helped to evaluate the consistency of our results across different study conditions and patient populations.

Results

Study selection

Following an extensive search, a total of 30 randomized controlled trials (RCTs) were included, involving 11,375 non-small cell lung cancer (NSCLC) patients treated with tyrosine kinase inhibitors (TKIs). Eleven vascular-targeted drugs were compared, focusing primarily on adverse events such as hypertension and thrombotic events (venous and arterial thrombosis). Figure 1 illustrates the search process: initially, 1,487 articles containing the search terms were identified. After removing duplicates, 86 articles were selected for full-text review based on their titles and abstracts. Ultimately, 30 RCTs were chosen based on their randomization methodology and the relevance of their outcome measures (Table 1) (Nakagawa et al., 2019; Han et al., 2018; Garon et al., 2014; Akamatsu et al., 2021; Ramlau et al., 2012; Ninomiya et al., 2023; Piccirillo et al., 2022; Liu et al., 2021; Kato et al., 2018; Besse et al., 2017; Zhao et al., 2021; Sun et al., 2018; Spigel et al., 2018; Cortot et al., 2020; Wakelee et al., 2017; Tiseo et al., 2017; Hanna et al., 2016; Karayama et al., 2016; Neal et al., 2016; Baggstrom et al., 2017; O'Brien et al., 2015; Pujol et al., 2015; Doebele et al., 2015; Twelves et al., 2014; Natale et al., 2011; Paz-Ares et al., 2012; Johnson et al., 2013; Herbst et al., 2011; Spigel et al., 2011; Heymach et al., 2008).

TABLE 1 Baseline characteristics of included studies.

First author	Year	Registration number	Control arm treatment	Patients in control arm (n)	Age	Male (%)	Disease stage	ECOG
Nakagawa et al. (2019)	2019	RELAY	Erlotinib	225	64 (56–70)	83 (37%)	Stage IV 189 (84%) Other 36 (16%)	= 0 119 (53%) = 1 106 (47%)
Han et al. (2018)	2018	ALTER 0303	Placebo	143	≤60 (62.9%) 61–69 (28.7%) ≥70 (8.4%)	97 (67.8%)	IIIB 7 (4.9%) IV 136 (95.1%)	= 0 22 (15.4%) = 1 120 (83.9%) = 2 1 (0.7%)
Garon et al. (2014)	2014	REVEL	Placebo plus docetaxel	625	61 (25–86)	415 (66%)	NA	= 0 199 (32%) = 1 425 (68%)
Akamatsu et al. (2021)	2021	UMIN000023761	Osimertinib	41	68 (43–82)	17 (41)	IIIB 2 (5) IV26 (63) Recurrence13 (32)	= 0 17 (42) = 1 24 (58)
Ramlau et al. (2012)	2012	NCT00532155	Placebo + Docetaxel	457	59.6 (27–80)	300 (65.6)	I II 43 (9.4) III 135 (29.6) IV 265 (58.0)	= 0 151 (33.0) = 1 283 (61.9) = 2 23 (5.0)
Ninomiya et al. (2023)	2023	jRCTs061180006	afatinib	50	71.0 (32–84)	22 (44.0)	III B 1 (2.0) IV 38 (76.0)	= 0 28 (56.0) = 1 22 (44.0)
Piccirillo et al. (2022)	2022	BEVERLY	Erlotinib	80	67.7 (60.7–73.6)	30 (37.5)	IIIB 5 (6.3) IV 75 (93.8)	= 0 47 (58.8) = 1 29 (36.3) = 2 4 (5.0)
Liu et al. (2021)	2021	NA/ALTER 1202?	Placebo	15	59 (43–75)	11 (73.3)	NA	= 1 13 (86.7) = 2 2 (13.3)
Kato et al. (2018)	2018	JO25567	erlotinib	77	67.0 (60–73)	26 (34%)	IV 62 (81%) Postoperative recurrence 15 (19%)	= 0 41 (53%) = 1 36 (47%)
Besse et al. (2017)	2017	IFCT-0703	Placebo	71	61 (44–71)	45 (63%)	IA 59 (83) IB 12 (17)	= 0 58 (82) = 1 13 (18)
Zhao et al. (2021)	2021	ACTIVE	Placebo Plus Gefitinib	156	60 (51–65)	62 (39.7)	IIIB 8 (5.1) IV 148 (94.9)	= 0 50 (32.1) = 1 105 (67.3)
Sun et al. (2018)	2018	KCSG-LU12-07	Placebo	47	67 (50–83)	43 (91.5%)	NA	= 0 3 (6.4%) = 1 44 (93.6%)
Spigel et al. (2018)	2018	NCT00892710	Pemetrexed	48	72 (51–84)	30 (63)	IIIB 5 (10) IV 43 (90)	NA
Cortot et al. (2020)	2020	IFCT-1103	Docetaxel	55	59.7 (35.8; 78.9)	42 (76.4%)	NA	= 0–1 51 (92.8%)
Wakelee et al. (2017)	2017	E1505	chemotherapy	749	61 (IQR 55,67)	375 (50%)	I (27) II (42) III (31)	NA

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TABLE 1 (*Continued*) Baseline characteristics of included studies.

First author	Year	Registration number	Control arm treatment	Patients in control arm (n)	Age	Male (%)	Disease stage	ECOG
Tiseo et al. (2017)	2017	FARM6PMFJM	cisplatin and etoposide chemotherapy regimen	103	63 (41–81)	70 (68)	NA	= 0 57 (55.3) = 1 35 (34) = 2 11 (10.7)
Hanna et al. (2016)	2016	LUME-Lung 2	Placebo + pemetrexed	360	59 (26–86)	208 (57.8)	Stage < IIIB 69 (19.2) Stage IIIB 52 (14.4) Stage IV 239 (66.4)	= 0 139 (38.6) = 1 221 (61.4)
Karayama et al. (2016)	2016	NA	Pemetrexed maintenance	55	66 (50–75)	39 (70.9)	IIIB 7 (12.7) IV 48 (87.3)	= 0 48 (87.3) = 1 7 (12.7)
Neal et al. (2016)	2016	ECOG-ACRIN 1512	Erlotinib/Cabozantinib	38/38	66.3 ± 9.8/65.9 ± 10.1	18 (47)/ 14 (37)	IV M1a 8 (21)/6 (16) IV M1b 21(55)/18 (47) Recurrent 9 (24)/14 (37)	= 0 9 (24)/9 (24) = 1 24 (63)/25 (66) = 2 5 (13)/4 (11)
Baggstrom et al. (2017)	2017	CALGB 30607	Placebo	104	66.3 ± 9.3	60 (57.7%)	IIIB 12 (11.5%) IV 92 (88.5%)	= 0 42 (40.4%) = 1 62 (59.6%)
O'Brien et al. (2015)	2015	EORTC 08092	Placebo	52	64.6 (25.9–80.7)	25 (48.1)	NA	= 0 11 (21.2) = 1 39 (75.0) = 2 2 (3.8)
Pujol et al. (2015)	2015	IFCT-0802	chemotherapy	37	60.1 (46–72)	26 (70.3%)	NA	= 0–1 35 (94.6%) = 2 2 (5.4%)
Doebele et al. (2015)	2015	NCT01160744	pemetrexed and carboplatin	71	18 to <65 years 37 (52.1) ≥65 years 34 (47.9)	45 (63.4)	NA	= 0–1 65 (91.5) = 2 4 (5.6)
Twelves et al. (2014)	2014	NCT00600821	Axitinib + paclitaxel/carboplatin	58	61.7	36 (62.1)	IIIB 6 (10.3) IV 52 (89.7)	= 0 16 (27.6) = 1 42 (72.4)
Natale et al. (2011)	2011	NCT00364351	vandetanib	623	61 (26–92)	381 (61)	IIIb 106 (17) IV 517 (83)	= 0 194 (31) = 1 363 (58) = 2 65 (10)
Paz-Ares et al. (2012)	2012	NA	placebo + gemcitabine + cisplatin	387	58 (22–77)	245 (63.3)	IIIB 47 (12.1) IV 340 (87.9)	= 0 143 (37.0) = 1 244 (63.0)
Johnson et al. (2013)	2013	ATLAS	Bevacizumab	373	64 (23–83)	196 (53)	IIIb 37 (10) IV 310 (83) Recurrent 25 (7)	= 0 173 (47) = 1 198 (53) = 2 1 (0.3)
Herbst et al. (2011)	2011	NCT00130728/BeTa	erlotinib	317	65	170 (54%)	NA	= 0 121 (38%) = 1 176 (56%) = 2 20 (6%)

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TABLE 1 (*Continued*) Baseline characteristics of included studies.

First author	Year	Registration number	Control arm treatment	Patients in control arm (n)	Age	Male (%)	Disease stage	ECOG
Spigel et al. (2011)	2011	SALUTE	Placebo	50	64 (47–82)	30 (60%)	NA	= 0 23 (46) = 1 21 (42) = 2 6 (12)
Heymach et al. (2008)	2008	NA	paclitaxel and carboplatin	52	59 (42–83)	37 (71%)	IIIB 5 (10) IV 47 (90)	= 0 16 (31) = 1 36 (69)

Smoking status	Experimental arm treatment	Patients in experimental arm (n)	Age	Male (%)	Disease stage	ECOG	Smoking status	Median follow-up (month)
Ever 73 (32%) Never 139 (62%) Unknown 13 (6%)	Ramucirumab +erlotinib	224	65 (57–71)	83 (37%)	Stage IV 195 (87%) Other 29 (13%)	= 0 116 (52%) = 1 108 (48%)	Ever 64 (29%) Never 134 (60%) Unknown 26 (12%)	20·7 months (IQR 15·8–27·2)
Once or now smoking 77 (53.8%) Non-smoker 66 (46.2%)	Anlotinib	294	≤60 (52.0%) 61–69 (42.5%) ≥70 (5.4%)	188 (64.0%)	IIIB 15 (5.1%) IV 277 (94.2%) Other 2 (0.7%)	= 0 59 (20.1%) = 1 233 (79.3%) = 2 2 (0.7%)	Once or now smoking 143 (48.6%) Non-smoker 151 (51.4%)	NA
Ever 483 (77%) Never 141 (23%) Unknown 1 (<1%)	Ramucirumab plus docetaxel	628	62 (21–85)	419 (67%)	NA	= 0 207 (33%) = 1 420 (67%)	Ever 518 (82%) Never 109 (17%) Unknown 1 (<1%)	9.5 months [IQR 4·4–14·9]
Never 20 (49) Smoker or former smoker 21 (51)	Osimertinib + bevacizumab	40	70 (41–82)	16 (40)	IIIB 2 (5) IV33(83) Recurrence 5 (12)	= 0 20 (50) = 1 20 (50)	Never 21 (53) Smoker or former smoker 19 (48)	16.0 (2.4–22.6)
NA	Aflibercept + Docetaxel	456	59.6 (27–84)	305 (66.9)	I-II 36 (7.9) III 125 (27.4) IV 284 (62.3)	= 0 149 (32.7) = 1 286 (62.7) = 2 21 (4.6)	NA	23.0 months
NA	afatinib plus bevacizumab	49	69.0 (48–83)	22 (44.9)	III B 2 (4.1) IV 37 (75.5)	= 0 32 (65.3) = 1 17 (34.7)	NA	24 months
Never 37 (46.3) Former/current 34 (42.5)	Erlotinib + bevacizumab	80	65.9 (57.9–71.8)	28 (35.0)	IIIB 3 (3.8) IV 77 (96.3)	= 0 52 (65.0) = 1 26 (32.5) = 2 2 (2.5)	Never 46 (57.5) Former/current 34 (42.5)	36.3 months (95% CI: 30.7–40.9)

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TABLE 1 (*Continued*) Baseline characteristics of included studies.

Smoking status	Experimental arm treatment	Patients in experimental arm (n)	Age	Male (%)	Disease stage	ECOG	Smoking status	Median follow-up (month)
Never 4 (26.7) Former 11 (73.3)	Anlotinib	27	60 (31–70)	19 (70.4)	NA	= 0 1 (3.7) = 1 24 (88.9) = 2 2 (7.4)	Never 11 (40.7) Former 15 (55.6) Current 1 (3.7)	11 months
Never smoker 45 (58%) Former light smoker 6 (8%) Other 26 (34%)	erlotinib plus bevacizumab	75	67.0 (59–73)	30 (40%)	IIIB 1 (1%) IV 60 (80%) Postoperative recurrence 14 (19%)	= 0 43 (57%) = 1 32 (43%)	Never smoker 42 (56%) Former light smoker 9 (12%) Other 24 (32%)	20.4 months (IQR 17.4–24.1)
Never 6 (8) Current/former 64 (92)	Pazopanib	71	57 (33–70)	41 (58)	IA 54 (76) IB 16 (24)	= 0 47 (66) = 1 24 (34)	Never 6 (8) Current/former 65 (92)	47 months (range 0.3–66 months)
Nonsmoker 121 (77.6) Smoker 35 (22.4)	Apatinib Plus Gefitinib	157	57 (51–65)	66 (42.0)	IIIB 5 (3.2) IV 152 (96.8)	= 0 48 (30.6) = 1 107 (68.2)	Nonsmoker 115 (73.2) Smoker 42 (26.8)	15.8 months (interquartile range 12.6–20.4 months)
Current or ex-smoker 41 (87.2%) Never smoker 6 (12.8%)	Pazopanib	48	66.5 (57–79)	40 (83.3%)	NA	= 0 1 (2.1%) = 1 47 (97.9%)	Current or ex-smoker 43 (89.6%) Never smoker 5 (10.4%)	30.1 months
Former smoker 26 (54) Current smoker 20 (42) Lifetime nonsmoker 2 (4)	Pemetrexed and Bevacizumab/ Pemetrexed, Bevacizumab, and Carboplatin	63/61	72 (50–90)/73 (48–90)	36 (57%)/ 34 (56%)	IIIB 4 (6)/2 (3) IV 58 (92)/59 (97)	NA	Former smoker 44 (70)/42 (70) Current smoker 16 (25)/13 (21) Lifetime nonsmoker 3 (5)/ 6 (10)	NA
Never smokers 9 (16.4%)	Paclitaxel plus bevacizumab	111	59.6 (18.6; 81.8)	78 (70.3%)	NA	= 0–1 103 (92.8%)	Never smokers9 (8.1%)	36.2 months (range: 28.6; 43.0),
NA	chemotherapy plus bevacizumab	752	61(IQR 54,67)	371 (49%)	I (25) II (45) III (29)	NA	NA	50·3 months (IQR 32.9–68.0)
NA	cisplatin + etoposide + bevacizumab	101	64 (45–79)	69 (68.3)	NA	= 0 53 (52.5) = 1 42 (41.6) = 2 6 (5.9)	NA	34.9 months (interquartile range, 22.5–41.5 months)
Current smoker 44 (12.2) Ex-smoker 194 (53.9) Never smoker 122 (33.9)	Nintedanib + pemetrexed	353	60 (21–84)	195 (55.2)	Stage < IIIB 57 (16.1) Stage IIIB 77 (21.8) Stage IV 219 (62.0)	= 0 135 (38.2) = 1 218 (61.8)	Current smoker 51 (14.4) Ex-smoker 193 (54.7) Never smoker 109 (30.9)	19.4 months (interquartile range [IQR] = 13.6–26.9)

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TABLE 1 (*Continued*) Baseline characteristics of included studies.

Smoking status	Experimental arm treatment	Patients in experimental arm (n)	Age	Male (%)	Disease stage	ECOG	Smoking status	Median follow-up (month)
Never smoker 13 (23.6) Former smoker 27 (49.1) Current smoker 15 (27.3)	Pemetrexed and bevacizumab maintenance	55	65 (39–75)	35 (63.6)	IIIB 6 (10.9) IV 47 (85.5)	= 0 50 (90.9) = 1 5 (9.1)	Never smoker 19 (34.5) Former smoker 20 (36.4) Current smoker 16 (29.1)	24.1 months (range; 12.7–47.1)
Current 8 (21)/9 (24) Former 25 (66)/23 (61) Never 5 (13)/6 (16)	Erlotinib + Cabozantinib	35	63.5 ± 9.0	18 (51)	IV M1a 5 (14) IV M1b 20 (57) Recurrent 10 (29)	= 0 8 (23) = 1 23 (66) = 2 4 (11)	Current 8 (23) Former 21 (60) Never 6 (17)	17.0 months
Nonsmoker 10 (9.6%) Past smoker 67 (64.4%) Current smoker 27 (26.0%)	Sunitinib	106	63.6 ± 10.0	57 (53.8%)	IIIB 14 (13.2%) IV 92 (86.8%)	= 0 40 (37.7%) = 1 66 (62.3%)	Nonsmoker 5 (4.7%) Past smoker 76 (71.7%) Current smoker 25 (23.6%)	20.6 months, with a range of 6.3–60.9 months
Never 10 (19.2) Past 35 (67.3) Current 4 (7.7)	Pazopanib	50	64.2 (28.4–81.1)	21 (42.0)	NA	= 0 18 (36.0) = 1 32 (64.0)	Never 11 (22.0) Past 26 (52.0) Current 11 (22.0)	13.4 months
NA	Chemotherapy + bevacizumab	37	61.2 (43–75)	25 (67.6%)	NA	= 0–1 33 (89.2%) = 2 3 (8.1%)	NA	37.7 months (25–50 months)
Never smoked or smoked <100 cigarettes16 (22.5)	pemetrexed and carboplatin + ramucirumab	69	18 to <65 years 37 (53.6) ≥65 years 32 (46.4)	36 (52.2)	NA	= 0–1 64 (92.8) = 2 3 (4.3)	Never smoked or smoked <100 cigarettes11 (15.9)	NA
Never smoked 6 (10.3) Ex-smoker 34 (58.6) Current smoker 18 (31.0)	Bevacizumab + paclitaxel/carboplatin	60	59.9	37 (61.7)	IIIB 5 (8.3) IV 55 (91.7)	= 0 16 (26.7) = 1 43 (71.7)	Never smoked 8 (13.3) Ex-smoker 34 (56.7) Current smoker 18 (30.0)	11 months
Smoke 493 (79)	erlotinib	617	61 (26–85)	393 (64)	IIIb 98 (16) IV 519 (84)	= 0 179 (29) = 1 358 (58) = 2 77 (13)	Smoke 472 (77)	15 months
Past or present smoker 287 (74.2) Nonsmoker 98 (25.3) Passive smoker 2 (0.5)	Sorafenib + gemcitabine + cisplatin	385	60 (28–81)	228 (59.2)	IIIB 47 (12.2) IV 338 (87.8)	= 0 146 (37.9) = 1 239 (62.1)	Past or present smoker 277 (72.1) Nonsmoker 105 (27.3) Passive smoker 2 (0.5)	NA
Never 66 (18) Former 178 (48) Current 129 (35)	Bevacizumab + Erlotinib	370	64 (31–88)	193 (52)	IIIb 32 (9) IV 317 (86) Recurrent 21 (6)	= 0 180 (49) = 1 190 (51)	Never 61 (17) Former 180 (49) Current 129 (35)	14.6 months

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TABLE 1 (*Continued*) Baseline characteristics of included studies.

Smoking status	Experimental arm treatment	Patients in experimental arm (n)	Age	Male (%)	Disease stage	ECOG	Smoking status	Median follow-up (month)
Never 33 (10%) Previous212 (67%) Current 72 (23%)	erlotinib plus bevacizumab	319	64.8	171 (54%)	NA	= 0 129 (41%) = 1 166 (52%) = 2 23 (7%)	Never 34 (11%) Previous 237 (74%) Current 48 (15%)	19 (0.2–34 months)
NA	bevacizumab	52	60 (38–77)	26 (50%)	NA	= 0 15 (29) = 1 30 (58) = 2 7 (14)	NA	8.1 month
Current/previous smoker 41 (79) Nonsmoker 11 (21)	Vandetanib	73	63 (27–83)	49 (67%)	IIIB 10 (14) IV 63 (86)	= 0 22 (30) = 1 51 (70)	Current/previous smoker 55 (75) Nonsmoker 17 (23)	NA

IQR, interquartile range; NA, Not Applicable. ECOG, status: Eastern Cooperative Oncology Group performance status.

The drugs analyzed in this meta-analysis include Aflibercept, Anlotinib, Axitinib, Bevacizumab, Cabozantinib, Erlotinib, Pazopanib, Ramucirumab, Sorafenib, Sunitinib, and Vandetanib. Most patients had a history of smoking, and the control groups were predominantly placebo.

Bias risk assessment

Bias risk was evaluated using the Cochrane risk of bias tool. Most studies clearly described random sequence generation, had no incomplete data, and showed no selective reporting, thus being assessed as having a low risk of bias. Two studies exhibited incomplete outcome data and were categorized as having a high risk of bias; one also displayed selective reporting. Overall, the quality of the included RCTs was deemed high (Supplementary Figure 1).

Network meta-analysis

Seventeen treatment regimens were analyzed for the risk of hypertension during vascular-targeted drug therapy (Figure 2). Erlotinib exhibited the lowest risk of hypertension, with a surface under the cumulative ranking curve (SUCRA) of 91.1%. Anlotinib had the highest risk of hypertension (SUCRA = 11.5%), significantly greater than that associated with Erlotinib (HR: 53.79, 95% CI: 1.62–1600.19). Chemotherapy was the next highest in risk after Erlotinib (HR: 1.24, 95% CI: 0.07–17.59, SUCRA = 88.8%). Sorafenib combined with chemotherapy ranked third, with a risk ratio of 0.31 compared to Erlotinib (95% CI: 0.01–8.62, SUCRA = 67.5%). Axitinib combined with chemotherapy had a higher risk of hypertension compared to chemotherapy alone (HR: 1.24, 95% CI: 1.28–60.97). Cabozantinib had a significantly higher risk of hypertension compared to Erlotinib (HR: 8.02, 95% CI: 1.19–61.83) (Figure 3). The cumulative ranking probability graph in Figure 4 shows that treatments with higher SUCRA values have a lower probability of inducing hypertension, with Erlotinib, chemotherapy, and Sorafenib combined with chemotherapy being the top three treatments with the lowest hypertension risk.

In terms of adverse thrombotic outcomes, four RCTs were analyzed, covering five treatment regimens. Erlotinib showed the lowest risk of thrombosis, with a SUCRA of 66.0%. Ramucirumab combined with Erlotinib had the second lowest risk (HR: 0.99, 95% CI: 0.26–3.74, SUCRA = 62.1%). Erlotinib combined with Cabozantinib ranked third (SUCRA = 61.3%). Cabozantinib had the highest risk of thrombosis, with a ratio of 2.27 compared to Erlotinib (95% CI: 0.31–22.89, SUCRA = 26.9%) (Figure 5).

Heterogeneity and sensitivity analyses

We observed moderate heterogeneity in the hypertension network (I^2 = 45%, p = 0.03) and low heterogeneity in the thrombosis network (I^2 = 20%, p = 0.25). Sensitivity analyses excluding high-risk-of-bias studies did not significantly alter our

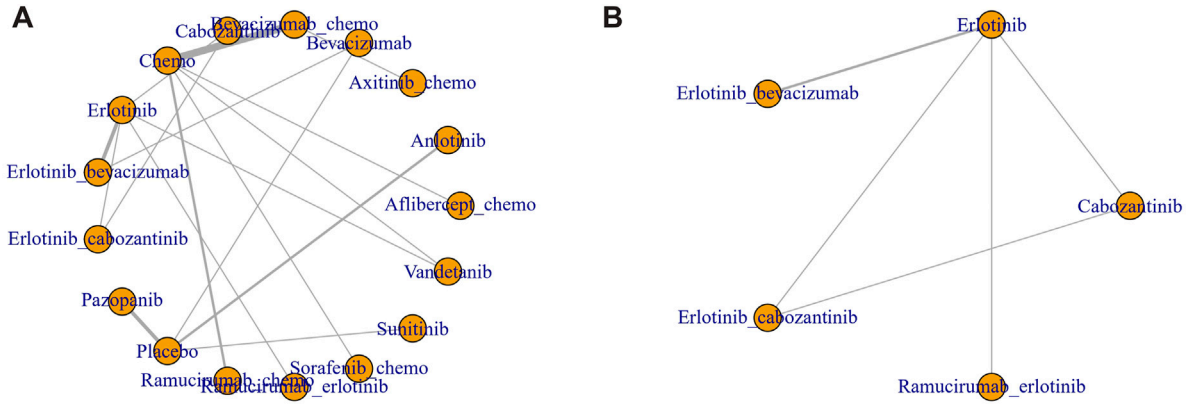

FIGURE 2
Network diagram of RCT. **(A)** Hypertension **(B)** Thrombosis. Each node represents one treatment. The size of the node is proportional to the number of participants randomized to that treatment. The edges represent direct comparisons. The width of the edge is proportional to the number of trials.

main findings, confirming the robustness of our results. Subgroup analyses revealed that EGFR mutation status and treatment duration did not significantly impact the relative safety rankings of the TKIs.

Publication bias

Funnel plots for both hypertension and thrombotic outcomes appeared roughly symmetrical (Figure 6), indicating no significant publication bias. This suggests that the results are reliable and not significantly influenced by the selective reporting of outcomes.

Discussion

Key findings

This study provides a comprehensive comparison of the cardiovascular safety profiles of various Tyrosine Kinase Inhibitors (TKIs) used in the treatment of Non-Small Cell Lung Cancer (NSCLC). Our network meta-analysis revealed that Erlotinib is associated with the lowest risks of both hypertension and thrombotic events among the evaluated treatments. In contrast, Anlotinib and Cabozantinib were associated with significantly higher risks of these adverse events.

To sustain their high proliferation rate, cancer cells require tumors to rapidly develop new vascular networks. However, the vasculature within tumors is often underdeveloped, which impairs its functionality (Carmeliet and Jain, 2011a). Abnormalities in tumor vascular development are partially due to irregular levels of growth factors secreted by tumor and stromal cells, with vascular endothelial growth factor (VEGF) playing a pivotal role (Carmeliet and Jain, 2011b). The poor functionality of tumor vasculature profoundly affects the tumor microenvironment, leading to hypoxia, reduced immune cell infiltration and activity, and an increased risk of metastatic dissemination. It has been proposed that antiangiogenic therapies could potentially correct these structural and functional defects in tumor vasculature (Carmeliet and Jain, 2011b; Viallard and Larrivée, 2017).

VEGF primarily interacts with two main receptors: vascular endothelial growth factor receptor-1 (VEGFR-1), also known as fms-like tyrosine kinase-1 (Flt-1), and VEGF receptor-2 (VEGFR-2). VEGFR-1 is the exclusive receptor for other VEGF family members (Papetti and Herman, 2002; Ceci et al., 2020) and is essential for hematopoiesis, matrix metalloproteinase (MMP) activation, and the migration of monocytes and other immune cells into the tumor microenvironment (TME) (Ferrara et al., 2003). In contrast, VEGFR-2 is critical for angiogenesis and vasculogenesis. VEGF binding to VEGFR-2 activates endothelial nitric oxide synthase (eNOS) and inducible nitric oxide synthase (iNOS) via the nitric oxide synthase (NOS) pathway (Zachary, 2003). This signaling pathway results in the release of vasodilators such as nitric oxide (NO), which increases vascular permeability (Lal et al., 2001). Upregulation of VEGF has been documented in various benign and malignant tumors, including melanoma, breast cancer, lung cancer, head and neck cancer, and ovarian cancer. In the tumor environment, the activation of the VEGF/VEGFR signaling axis ultimately leads to increased vascular density, invasiveness, immune evasion, and, in some cases, enhanced metastatic capacity (Jinnin et al., 2008).

The epidermal growth factor receptor (EGFR), a member of the ERBB family of cell surface receptor tyrosine kinases, is implicated in cancer progression. The binding of epidermal growth factor (EGF) to EGFR triggers phosphorylation of the receptor and other ERBB family members, leading to cell proliferation. EGFR signal transduction also contributes to tumor cell proliferation, resistance to apoptosis, angiogenesis, and metastasis (Chong and Jänne, 2013).

Recent molecular and clinical investigations have revealed intricate interactions between hypertension and VEGF signaling pathways. Specifically, hypertension-induced microvascular disruption may trigger elevated plasma VEGF expression, as evidenced by increased VEGF levels observed in patients with essential hypertension (EH) (Yang et al., 2017). This relationship appears bidirectional, with epidemiological data demonstrating significant associations between blood pressure dynamics and cancer risk (Radišauskas et al., 2016; Schairer et al., 2017).

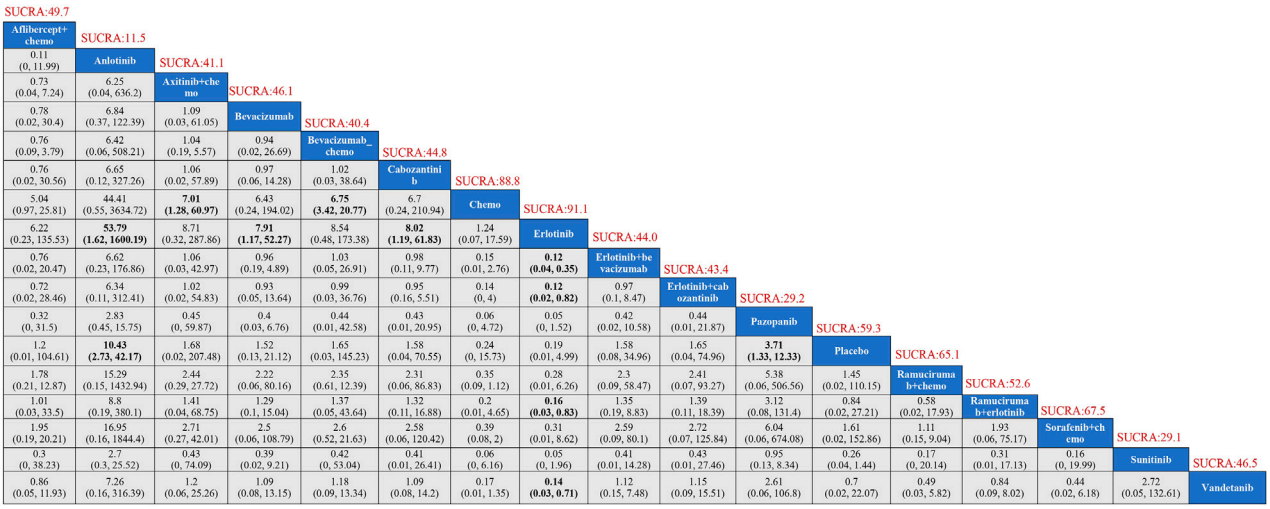

FIGURE 3
Results of TKIs compared with adverse reactions of hypertension. SUCRA, Surface Under the Cumulative Ranking Curve.

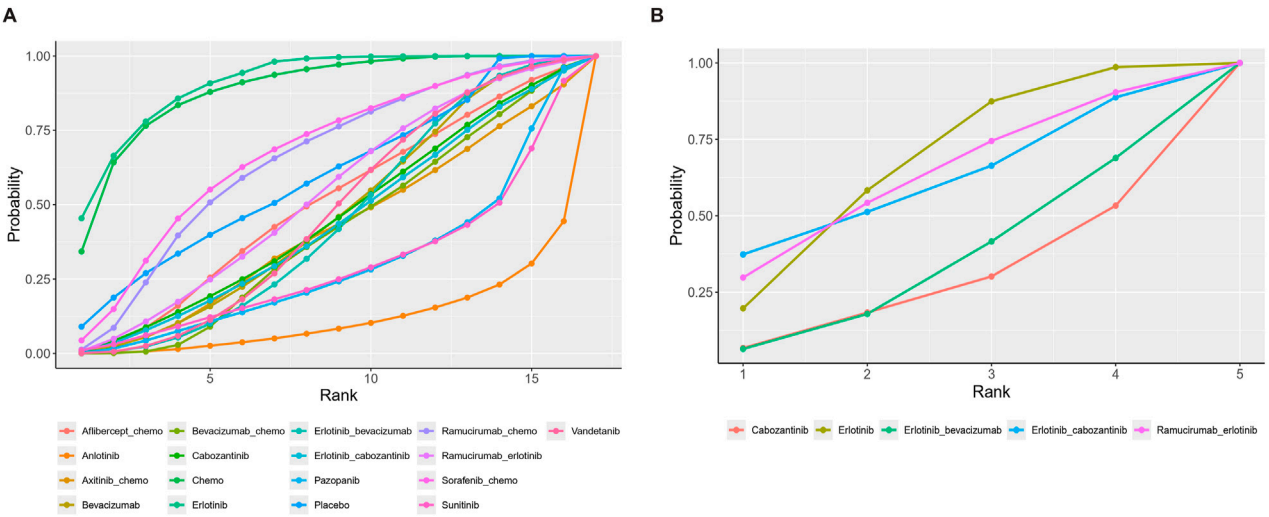

FIGURE 4
Cumulative ranking probability diagram. **(A)** Hypertension **(B)** Thrombosis. Each curve represents a treatment. The larger the area under the curve, the greater the probability of being the best treatment.

In the context of cancer-associated complications, venous thromboembolism (VTE) emerges as a principal cause of mortality. The administration of anti-VEGF therapies has been correlated with increased VTE incidence (Posch et al., 2016), though the precise molecular mechanisms underlying this association remain to be fully elucidated. Mechanistic studies have revealed that bevacizumab administration significantly enhances plasminogen activator inhibitor (PAI-1) expression across multiple compartments, including tumor tissue, plasma, and thrombi. This observation has been further validated in mouse human lung cancer xenograft models, where bevacizumab-induced PAI-1 upregulation promotes VTE formation. Clinical validation through randomized controlled trials has consistently identified a characteristic adverse event profile associated with bevacizumab, predominantly comprising hypertension, proteinuria, hemorrhagic complications, and thrombotic events (Sandler et al., 2004).

Notably, geriatric populations demonstrate heightened susceptibility to thromboembolic and hypertensive complications during anti-angiogenic therapy (Boehm et al., 2010). This vulnerability becomes particularly relevant in the context of long-term adjuvant or maintenance treatment regimens, where the therapeutic benefits of anti-angiogenic agents must be carefully balanced against their cardiovascular risk profile.

Our analysis supports the implementation of a cardiovascular risk-stratified approach to therapeutic selection. For patients with

SUCRA:26.9	SUCRA:66.1	SUCRA:33.7	SUCRA:61.3	SUCRA:62.1
Cabozantinib				
2.27 (0.31, 22.89)	**Erlotinib**			
1.3 (0.13, 16.65)	0.57 (0.17, 1.84)	**Erlotinib_bevacizumab**		
2.22 (0.31, 22.93)	0.98 (0.08, 11.56)	1.74 (0.12, 25.94)	**Erlotinib_cabozantinib**	
2.26 (0.21, 31.92)	0.99 (0.26, 3.74)	1.75 (0.29, 10.59)	1.01 (0.06, 16.18)	**Ramucirumab_erlotinib**

FIGURE 5
Results of TKIs compared with adverse reactions of thrombosis. SUCRA, Surface Under the Cumulative Ranking Curve.

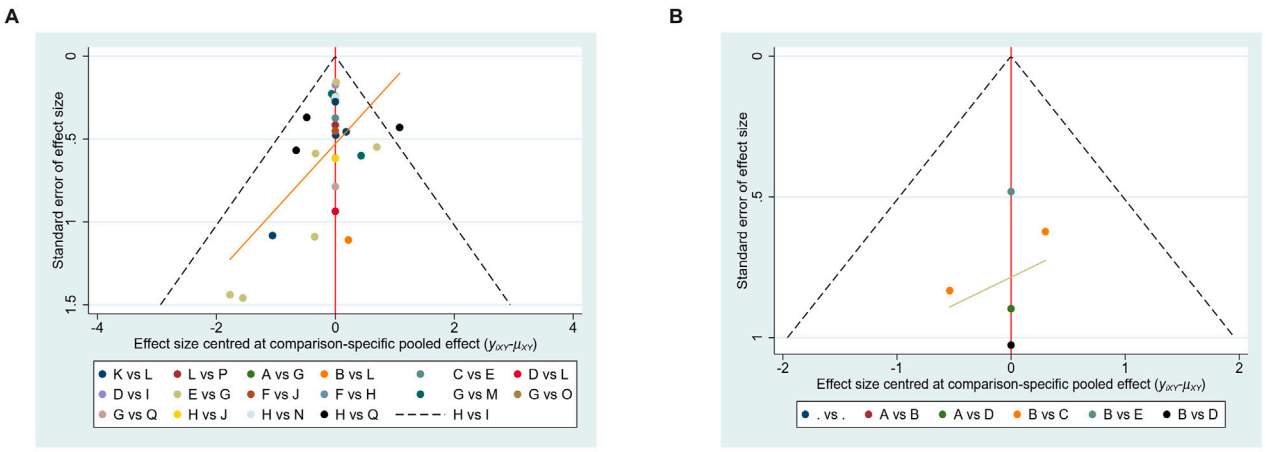

FIGURE 6
Funnel plot of network meta-analysis. **(A)** Hypertension **(B)** Thrombosis.

elevated cardiovascular risk profiles, we advocate for preferential utilization of agents demonstrating superior cardiovascular safety characteristics. This strategy holds the potential to significantly reduce the incidence of thrombotic and hypertensive complications while minimizing mortality risk. Furthermore, our findings provide an evidence-based framework to guide clinical decision-making and inform the development of cardiovascular risk-adapted guidelines for targeted therapy optimization.

In this study, we evaluated these anti-angiogenic drugs to compare their risks of hypertension and thrombosis and identified the drug with the fewest side effects. Clinicians can use this information to select drugs with fewer adverse effects based on the patient's underlying conditions, thereby improving the management of targeted therapy toxicity.

Our analysis indicates that Erlotinib has the lowest risk of both hypertension and thrombosis among the drugs studied. This conclusion was reached through constructing an indirect drug comparison network, providing highly credible evidence. Chemotherapy ranks second in terms of lowest hypertension risk. Anlotinib is associated with the highest risk of hypertension, suggesting that clinicians should carefully assess patients' baseline blood pressure and cardiovascular health before prescribing this drug. Additionally, Cabozantinib presents the highest risk of thrombosis, indicating that clinicians need to evaluate the risk of thrombosis in multiple organs and consider the prudent use of anticoagulants when administering this drug.

Clinical implications

The clinical implications of this study are significant. In treating NSCLC, especially in patients with pre-existing cardiovascular conditions, Erlotinib should be considered as a first-line option due to its lower risk of hypertension and thrombotic events.

Clinicians should exercise caution when prescribing Anlotinib and Cabozantinib, particularly in patients at high risk for cardiovascular complications. These findings underscore the importance of individualized treatment plans that weigh the benefits of tumor control against the risks of serious side effects.

Additionally, the results of this study suggest that more rigorous cardiovascular monitoring may be warranted for patients receiving high-risk TKIs, such as Anlotinib and Cabozantinib. This could involve regular blood pressure checks, thrombosis risk assessments, and the use of prophylactic measures to mitigate these risks.

Strengths and limitations

This study has several strengths, including the use of a Bayesian network meta-analysis to integrate data from multiple studies, providing a robust comparative analysis of TKI safety profiles. The large sample size and inclusion of diverse treatment regimens enhance the generalizability of our findings.

However, several limitations of this study and their potential impacts on our findings warrant careful consideration. First, significant heterogeneity was observed across included studies, mainly due to variations in study design, patient characteristics, and outcome definitions. While our random-effects model and subgroup analyses partially addressed this issue, the heterogeneity might have led to either over- or underestimation of treatment effects, particularly in smaller subgroups.

The language restriction to English publications might have resulted in missing valuable data, particularly from Asian countries where TKIs are extensively used. This potential language bias could be especially relevant for newer TKIs that are more commonly studied in non-English speaking regions, possibly affecting our effect estimates.

The varying quality of included studies and limited long-term cardiovascular outcome data represent additional limitations. Although we conducted quality assessment and sensitivity analyses, lower-quality studies might have influenced our estimates, particularly in comparisons with fewer studies. This impact could affect our ability to fully capture the cardiovascular safety profiles of different TKIs, especially for rare adverse events.

Further prospective investigations are warranted to elucidate the cardiovascular safety profiles of combination regimens incorporating targeted therapies and immune checkpoint inhibitors, with particular emphasis on risk stratification and predictive biomarker identification.

Conclusion

In this study, we conducted a network meta-analysis to compare the cardiovascular safety profiles of various Tyrosine Kinase Inhibitors (TKIs) used in the treatment of Non-Small Cell Lung Cancer (NSCLC). Our findings indicate that Erlotinib is associated with the lowest risk of both hypertension and thrombotic events, making it a preferred treatment option, especially for patients with pre-existing cardiovascular risk factors. Conversely, Anlotinib and Cabozantinib were found to carry significantly higher risks of these adverse events, necessitating cautious use and careful monitoring in clinical practice.

The results of this study provide valuable insights for clinicians in selecting appropriate TKIs, balancing the efficacy of cancer treatment with the potential for serious cardiovascular complications. These findings also underscore the importance of individualized treatment strategies, particularly in patients with a higher risk of hypertension or thrombotic disorders.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Author contributions

MT: Data curation, Formal Analysis, Methodology, Writing–original draft, Conceptualization, Validation. CP: Formal Analysis, Investigation, Software, Visualization, Writing–original draft. ZW: Formal Analysis, Software, Writing–original draft, Data curation, Project administration, Resources. CJ: Conceptualization, Resources, Supervision, Validation, Writing–review and editing.

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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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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2025.1491990/full#supplementary-material

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Almonertinib-induced interstitial lung disease in an NSCLC patient co-harboring EGFR Ex19del mutation and MET *de novo* amplification: a case report and literature review

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Lung cancer patients co-harboring EGFR Ex19del mutation and MET *de novo* amplification is extremely uncommon. Thus, the optimal therapeutic strategies, treatment-related complications, and prognosis for such patients remain unclear. Herein, we describe a case of patient co-harboring EGFR Ex19del mutation and MET *de novo* amplification who presented targeted (almonertinib)-induced interstitial lung disease (ILD). We propose that patients with EGFR Ex19del mutation and MET *de novo* amplification may benefit more from dual-targeted therapy than pemetrexed and carboplatin chemotherapy along with bevacizumab. However, dual-targeted therapy may increase the risk of ILD, so it is important to be alert to targeted-induced ILD, and unexplained fever may be an early warning signal for targeted-induced ILD, especially almonertinib-induced ILD. Timely intervention is needed to avoid greater harm when ILD occurs and, when ILD is effectively controlled, seize the opportunity to rechallenge the dual-targeted therapy may contribute to a better prognosis. In addition, the patients with targeted-induced ILD in the past need more rigorous monitoring and follow-up in the process of rechallenging the targeted drug therapy.

KEYWORDS

non-small cell lung cancer (NSCLC), Ex19del mutation and MET *de novo* amplification, almonertinib, interstitial lung disease (ILD), case report

1 Introduction

The incidence and mortality of lung cancer have increased globally in recent years. Moreover, non-small cell lung cancer (NSCLC) is the most common histological type, which accounts for 80%–85% of all lung carcinomas (1, 2). In the past decade, targeted therapies have revolutionized the treatment and improved the outcome for oncogene-driven NSCLC (3). Moreover, the epidermal growth factor receptor (EGFR) is one of the most common driver genes in NSCLC, which occur in 10% to 15% of the western population and 40% to 60% of the Asian population. What is more, in women and non-smoking Chinese people, the EGFR-sensitive mutation rate is even higher (4–6).

MET amplification as a *de novo* driver alteration occurring in NSCLC patients is not high (1%–5% of untreated NSCLC) (7, 8), which is always strongly associated with smoking. However, MET amplification has emerged as a significant mechanism of acquired resistance in various targeted therapies (5%–22%), such as EGFR mutation, KRAS G12C mutation, ALK fusion, ROS1 fusion and RET fusion, and particularly in EGFR-mutant NSCLC (7–17).

To our knowledge, the report about lung cancer patient co-harboring EGFR Ex19del mutation and MET *de novo* amplifications is extremely uncommon (18), and a unified standard treatment plan has not been formed yet. However, the certain thing is that the first-line dual-targeted regimens are not routinely recommended for this group of patients. For this reason, the experience related to dual-targeted therapy is not rich, and the experience about diagnosis and management of the toxic side effects, such as ILD, which is induced by targeted therapy for this group of patients, is relatively lacking. In addition, ILD induced by the combination of almonertinib (targeted to EGFR Ex19del mutation) and glumetinib (targeted to MET *de novo* amplifications) has not been reported. Thus, accumulating relevant experience in this field is necessary.

Herein, we report a case of lung adenocarcinoma co-harboring Ex19del mutation and MET *de novo* amplification. The patient got successful remission of ILD, which was induced by almonertinib. Up to now, the rechallenge of dual-targeted therapy (furmonertinib and glumetinib) is more than 2 months without recurrence of ILD.

2 Case presentation

The patient, a 60-year-old woman with no history of smoking, had no prior medical conditions, with a chief complaint of the pain in the right lumbosacral region, and in the right sacroiliac joint, bone destruction with soft tissue mass (malignant)? was found by lumbar computed tomography (CT) scan on 11 May 2023 (Figures 1A, B). Then, further workup was completed showing a 37 mm × 36 mm lesion (lung cancer)? in the upper left lung by chest CT on 20 May 2023 (Figure 2A). 12 days after the first visit, a sacroiliac bone (right side) biopsy was performed. The pathological results, in conjunction with immunohistochemistry findings, indicated TTF-1(+), CK7(+), Naspsin A(+), ALK(Ventana)(−), CK20(−), and PDL1(SP263) (TPS:0). Unfortunately, the first diagnosis was left lung adenocarcinoma with bone metastasis. PET-computed tomography (PET-CT) indicated multiple pulmonary, liver, bone, and lymph node (lung hilum, mediastinum) metastases, staging IV (cT2aN2M1). Meanwhile, molecular screening of sacroiliac bone-biopsy-tumor-tissue by a large gene new-generation sequencing (NGS) panel analysis identified EGFR 19 exon p.L747-P753 delinsS (33.9%), EGFR 19 exon p.L747S mutation (0.90%), TP53 exon8 p.V272L mutation (34.17%), MET (CN=9), CCNE1 (CN=11), RICTOR (CN=9), ATK3 (CN=9), CDK6 (CN=9), HGF (CN=9) amplification, microsatellite stable, and a level of 1.67Mut/Mb in tumor mutation burden.

The patient received six cycles of front-line pemetrexed and carboplatin chemotherapy along with bevacizumab-targeted therapy and bisphosphonate bone protection treatment on 15 June 2023 (Figure 2B) at a hospital. During the period of receiving the above therapy, the patient was repeatedly reexamined for neck, chest, and abdomen CT (Figures 2C, D), which all indicated that she had stable disease (SD). In order to control the right sacroiliac metastasis, radiation therapy was administered followed the chemotherapy and targeted therapy (5Gy×5f).

Given the first-line treatment response (SD), the adverse reactions of bone marrow suppression of chemotherapy (grade 3), and the results of genetic testing, targeted treatment of almonertinib (110 mg per day), combined with glumetinib (150 mg per day), was administered as a second line of treatment on 14 November 2023.

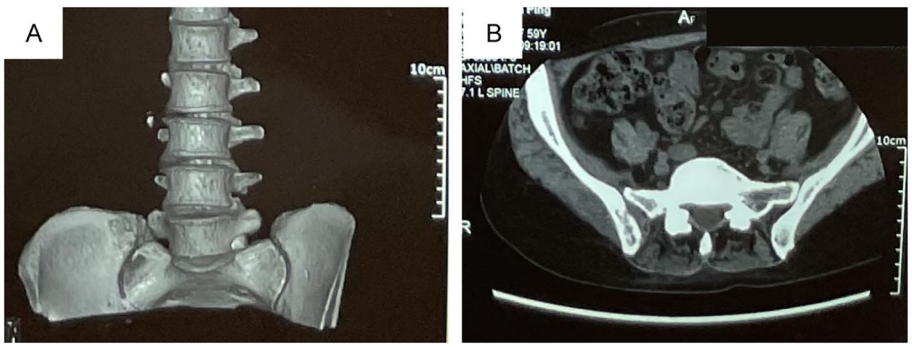

FIGURE 1
The right sacroiliac joint bone destruction with soft tissue mass (malignant?) was found by lumbar computed tomography (CT) scan on May, 11, 2023. **(A)** Three-dimensional reconstruction of the right sacroiliac joint. **(B)** Coronal CT scan of the right sacroiliac joint. The patient, a 60-year-old female with no history of smoking, had no prior medical conditions, with a chief complaint of the pain in the right lumbosacral region and was found the right sacroiliac joint bone destruction with soft tissue mass (malignant?) by lumbar computed tomography (CT) scan on May, 11, 2023 **(A, B)**.

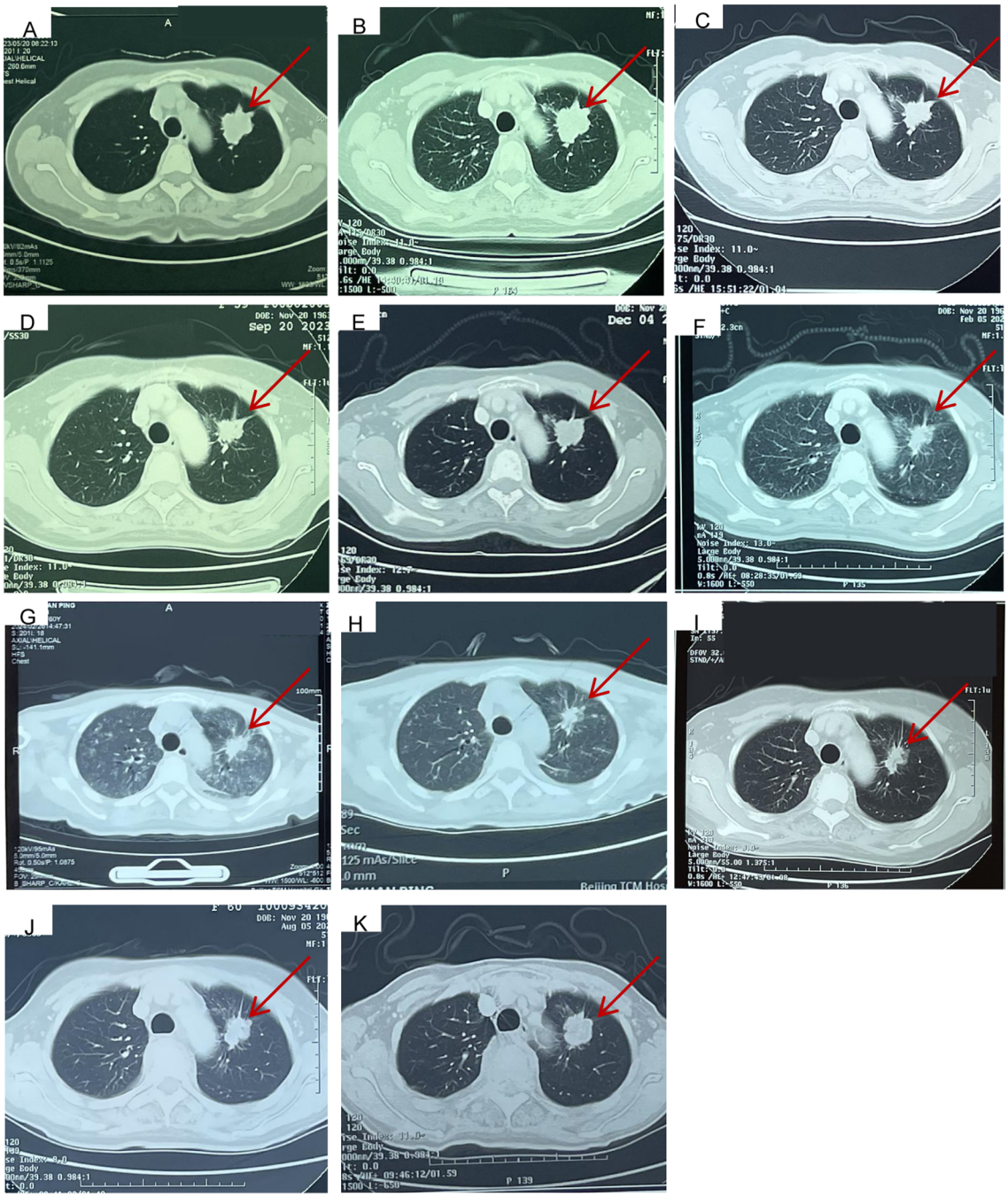

FIGURE 2
Computed tomography findings. **(A)** Primary lesion (26*37mm) in upper left lung at the time of first visit to Cancer Hospital, Chinese Academy of Medical Sciences on May, 20, 2023. **(B)** Baseline image (Primary lesion 29*36mm) before taken front-line pemetrexed and carboplatin chemotherapy along with bevacizumab targeted therapy at Jun, 15, 2023. **(C)** Response evaluation (Primary lesion 29*22mm, SD) after taken 2 cycles of pemetrexed and carboplatin chemotherapy along with bevacizumab targeted therapy at Jul, 24, 2023. **(D)** Response evaluation (Primary lesion 29*22mm, SD) after taken 4 cycles of pemetrexed and carboplatin chemotherapy along with bevacizumab targeted therapy at Sept, 20, 2023. **(E)** Twenty-one days after taken almonertinib combined with glumetinib targeted therapy (Primary lesion 30*28mm, SD) at Dec, 5, 2023. **(F)** eighty-four days after taken almonertinib combined with glumetinib targeted therapy (Primary lesion 26*18mm, PR) at Feb, 5, 2024. **(G)** The emergency chest CT indicated diffuse interstitial lung disease (ILD) at Feb, 26, 2024, (Primary lesion 28*20mm, SD). **(H)** The ILD has been well controlled at Mar, 4, 2024, (Primary lesion 28*20mm, SD). **(I)** twenty-two days after the rechallenge of the dual-targeted therapy at May, 7, 2024, (Primary lesion 28*19mm, SD). **(J)** Response evaluation (Primary lesion 28*19mm, SD) at Aug, 5, 2024. **(K)** Response evaluation (Primary lesion 28*25mm, SD, but showing a slow progress trend) at Nov, 11, 2024.

20 days later, the examination for neck, chest, and abdomen CT (Figure 2E) indicated SD. Due to the prevalence of novel coronavirus pneumonia, the patient did not receive regular reexamination. However, 77 days later after taking almonertinib and glumetinib (29 January 2024), she developed a fever as high as 39.4°C, accompanied by cough, expectoration, and shortness of breath after exercise. Intermittent hormone and anti-infection treatments were given at a hospital, but there was no significant

improvement in the above symptoms. To our satisfaction, the reexamination for neck, chest, and abdomen CT (Figure 2F) on 5 February 2024 indicated partial response (PR). Based on the above information, the attending doctor considered that her fever was related to glumetinib and suggested stopping treatment with glumetinib. However, after stopping glumetinib on 20 February 2024, the patient still had an intermittent fever as high as 39.5°C.

Thus, she was admitted to our hospital for further treatment on 23 February 2024. A series of relevant laboratory examinations were requested (Table 1). However, the patient was unexpectedly found to have severe shortness of breath and difficulty in breathing on 26 February 2024 (Figures 3A–C). Moreover, inspiratory crackles were

TABLE 1 Demographic characteristics and laboratory and imaging findings of the patient.

Demographic characteristics	
Age-yr	60
Gender	Female
Smoking history	No
Initial findings on admission to our hospital	
Past medical history	Almonertinib, glumetinib
Primary symptoms	fever, cough, expectoration, shortness of breath after exercise.
Laboratory findings on admission to our hospital	
White blood cell count (10^9 /liter)	4.05
Neutrophils (%)	54.1
Eosinophils (%)	1.8
Lymphocytes (%)	27.8
Hemoglobin (g/liter)	92
Platelet count (10^9 /liter)	107
C-reactive protein (mg/liter)	47.5
Erythrocyte sedimentation rate (mm/hour)	62
Procalcitonin	0.34
Alanine aminotransferase (U/liter)	103.3
Aspartate aminotransferase (U/liter)	63.7
Total protein	44.1
Albumin (g/liter)	22
Creatine kinase (U/liter)	263.4
Myoglobin (ug/liter)	125.1
Creatinine (umol/liter)	55.2
Uric acid (umol/liter)	206.6
Activated partial-thromboplastin (sec)	0.88
Thrombin time	16.9
Fibrinogen (g/liter)	3.23
D-dimer (mg/liter)	0.31
(1,3)- β- D-glucan concentration (pg/ml)	26.6
Antinuclear antibody series	Antinuclear antibody, Cytoplasmic antibody, centromere antibody, anti-dsDNA antibody, anti-nRNP antibody, anti-Sm antibody, anti-SS-A antibody, anti-SS-B antibody, anti-Scl-70 antibody, anti-Jo-1 antibody, anti-rRNA antibody, anti-mitochondrial-M2 antibody, anti- histone antibody, anti-centromere antibody, anti-proliferating cell nuclear antigen antibody,anti-nucleosome antibody, anti-Ro52 antibody, anti-PM-Scl antibody, anti-dsDNA antibody were negative.
Culture of bacteria (urine, sputum, stool)	Negtive
Culture of fungi (urine, sputum, stool)	Negtive
2019 Novel Coronavirus nucleic acid	Negtive
Multiple virus testing	Human respiratory syncytial virus antibody, Adenovirus antibody, influenza virus A antibody, influenza virus B antibody, Parainfluenza virus 1-4 antibody were negative.
C. pneumoniae antibody	Negtive
M. pneumoniae antibody	Negtive
L. pneumophila1-12 antibody	Negtive
Multiple Respiratory pathogen (nucleic acid)	Streptococcus pneumoniae, Staphylococcus aureus, methicillin-resistant Staphylococcus aureus, Klebsiella pneumoniae, Pseudomonas aeruginosa, Acinetobacter baumannii, Stenotrophomonas maltophilus, Haemophilus influenzae, Pneumocystis pneumoniae, Mycoplasma pneumoniae, Chlamydia pneumoniae, Mycobacterium tuberculosis complex, Legionella pneumophila, Cartamola pneumoniae, Nocardia, Chlamydia trachomatis, Chlamydia psittaci were negative.
Pathogen identification using bronchoalveolar lavage fluid (metagenomics next-generation sequencing)	Coving more than 25000 Pathogenic microorganisms: Bacteria (11836), viruses (11021), fungi (1872), parasites (421), rickettsia (105), mycoplasma/chlamydia (118), mycobacteria (153), and only found Human Herpesvirus 4 positive.
Image findings on admission to our hospital	
chest CT on Feb, 26, 2024	diffuse interstitial lung disease (ILD) along with lung infection.
chest CT on Mar, 4, 2024	improvement in the interstitial lung disease and lung infection compared to Feb, 26, 2024.

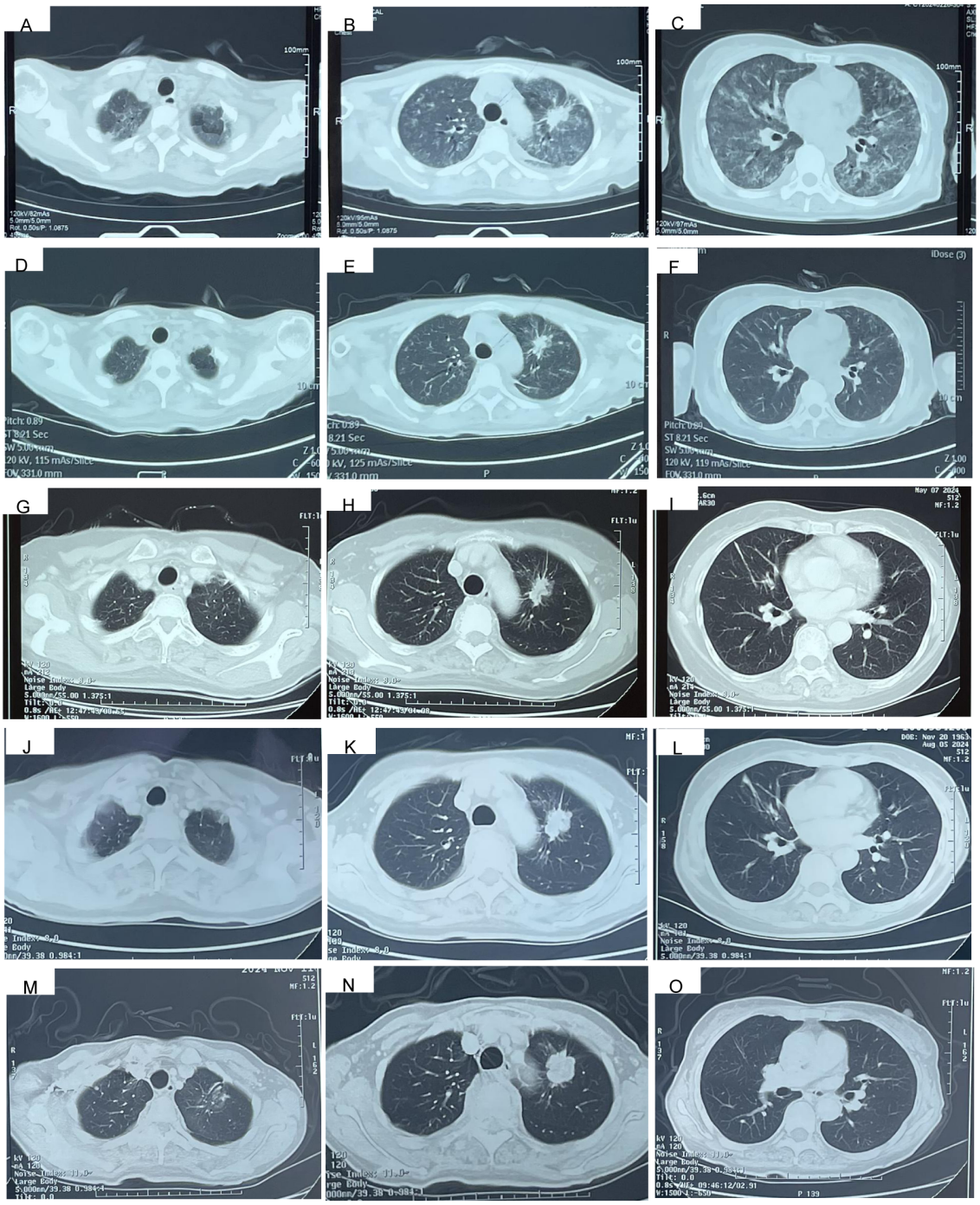

FIGURE 3
The ILD changes of the patient. **(A–C)** 105 days after the treatment of almonertinib, 99 days after the treatment of glumetinib, and stopped taking glumetinib for 6 days. **(D–F)** The ILD has been well controlled after he anti-infection and methylprednisolone (40 mg/day) for 8 days. **(G–I)** 50 days after the treatment of furmonertinib, 22 days after the treatment of furmonertinib and glumetinib without recurrence of ILD. **(J–L)** The ILD has been well controlled at Aug, 5, 2024. **(M–O)** The ILD has been well controlled at Nov, 11, 2024.

heard over the lower zones of the lung. The emergency chest CT indicated diffuse ILD along with lung infection (Figure 2G). We organized related discussions, and almonertinib-induced ILD was considered in the absence of other potential causes, so she stopped taking almonertinib by our proposal. After methylprednisolone (40 mg/day, 8 days) along with oxygen uptake, she was supplemented with calcium tablet and gastric mucosal protection. The respiratory condition gradually improved, and chest CT also showed a noticeable improvement in the interstitial lung disease and lung infection on 4 March 2024 (Figures 2H, 3D–F), so the methylprednisolone was decreased gradually, and completely discontinued on 6 May 2024. Based on the ILD which has been well controlled, the attending doctor suggested to choose furmonertinib (80 mg per day, targeted to the EGFR Ex19del mutation) on 19 March

2024, and follow-up for 1 month showed that the patient did not feel any discomfort. Thus, glumetinib was rechallenged on 16 April 2024. To our satisfaction again, although this patient has not received sufficient antitumor treatment for a considerable period of time (57 days), the reexamination for neck, chest, and abdomen CT (Figures 2I, 3G–I) on 7 May 2024 still indicated SD.

The reexamination for neck, chest, and abdomen CT (Figures 2J, 3J–L) on 5 August 2024 indicated SD. The rebiopsy of the sacroiliac bone (right side) performed on 30 August 2024 indicated TTF-1(3+), PDL1(22C3) (TPS:3%), and PDL1(22C3Neg) (−), and the molecular screening of sacroiliac bone biopsy tumor tissue by a large gene new-generation sequencing (NGS) panel analysis identified EGFR 19 exon p.L747-P753 mutation (38.6%), TP53 exon8 p.V272L mutation (40.7%), CD8 exon2 p.A50D (13.5%), WPN exon33 p.A1297G (2.3%), IL7R exon3 p.N106I mutation (14.6%), and CCNE1 (CN=3.9) amplification. Then, targeted treatment of sunvozertinib (150 mg per day) combined with glumetinib (150 mg per day) was administered as a third line of treatment om 14 September 2024. The reexamination for neck, chest, and abdomen CT (Figures 2K, 3M–O) on 12 November 2024 indicated SD but showed a slow progress trend, so it was adjusted to sunvozertinib (150 mg per day) combined with vinorelbine (30 mg biw).

At the time of this writing (2 January 2025), the patient was still without recurrence of ILD (Table 1).

3 Discussion

We reported a case of initially diagnosed advanced lung adenocarcinoma co-harboring EGFR Ex19del mutation and MET *de novo* amplifications (Table 2). The effectiveness of the front-line pemetrexed and carboplatin chemotherapy along with bevacizumab (six cycles) was limited. However, the patient responded positively to the second-line dual-targeted therapy of almonertinib (110 mg per day), combined with glumetinib (150 mg per day), but ILD was found 3 months later. After anti-infection and methylprednisolone (40 mg/day, 8 days) along with oxygen uptake, calcium tablet and gastric mucosal protection was supplemented. The respiratory condition gradually improved, and chest CT also showed a noticeable improvement. Up to now (2 January 2025), the patient is still without recurrence of ILD.

Although EGFR-sensitive mutation is very common in the Asian population, and MET amplification as a *de novo* driver alteration occurring in untreated NSCLC patients is approximately 1%–5% (7, 8), the co-harboring EGFR Ex19del mutation and MET *de novo* amplification is really rare (18, 19). Thus, a unified standard treatment plan has not been formed. Although the first-line dual-targeted regimens are not routinely recommended for this group of patients, the treatment of dual-targeted (second-line) was more effective than carboplatin chemotherapy along with bevacizumab (first-line) for the patient we reported. Furthermore, the patient we reported felt that the overall tolerance process of dual-targeted therapy was better than carboplatin chemotherapy along with bevacizumab. Unfortunately, the dual-targeted treatment was stopped due to ILD.

Antineoplastic agent-induced ILD, which was primarily associated with chemotherapy, targeted therapy, and immunotherapy, is as the primary cause (23%–51%) of drug-induced ILD (20). Although risk factors vary among different antineoplastic agents, physicians also should carefully evaluate the risk for ILD before the start of any anticancer therapy, which is available at https://doi.org/10.1016/j.esmoop (20). Usually, men, who smoke, who are 55 years old and above, and with pneumopathy (chronic obstructive pulmonary disease, history of interstitial pneumonia, pulmonary infectious diseases), presence of contralateral pulmonary metastasis, normal lung area less than 50%, and combined heart disease, were more likely to confront with ILD (21–24). However, the risk of drug-induced ILD increases when causative drugs are used in combination, and for some drugs, can be dose-dependent (20). The risk factors for the patient we reported were the combination of targeted drugs (almonertinib and glumetinib) and advanced age. At present, the mechanisms of EGFR-TKI-induced ILD are not yet completely understood. The reported mechanisms including preventing the regeneration and proliferation of damaged epithelium, inhibiting protein kinase B and extracellular signal-regulated kinase (ERK) 1/2, and activating p38 mitogen-activated protein kinase (MAPK) disrupt the balance of cell survival, producing the cytokine interleukin-6 (IL-6) and so on (22, 25). Usually, the above risk factors are unavoidable, but the progression

TABLE 2 The treatment for the patient.

The case timeline	The treatment for the patient
From mid-Jun, 2023 to mid-Nov, 2023	Six cycles of front-line pemetrexed and carboplatin chemotherapy along with bevacizumab-targeted therapy, bisphosphonate bone protection treatment and radiation therapy.
From Nov, 14, 2023 to late-Jan, 2024	Targeted treatment of almonertinib (110mg per day, targeted to the EGFR Ex19del mutation) combined with glumetinib (150mg per day, targeted to the MET de-novo amplifications) as a second line of treatment.
In late-Feb, 2024	Stopping treatment with glumetinib due to intermittent fever as high as 39.5°C fever and received methylprednisolone (40 mg/day, 8 days) along with oxygen uptake, supplemented by calcium tablet and gastric mucosal protection.
From Mar, 4, 2024 to May, 6, 2024	Methylprednisolone was gradually reduced and completely discontinued.
From mid-Apr, 2024 to mid-Sep, 2024	Gemetinib treatment again after 1 month observation of taking furmonertinib (80mg per day, targeted to the EGFR Ex19del mutation) without any discomfort.
From mid-Sep, 2024 to mid-Nov, 2024	Sunvozertinib (150mg per day) combined with glumetinib (150mg per day) was administered as a third line of treatment.
From mid-Nov, 2024 to present	Sunvozertinib (150mg per day) combined with vinorelbine (30mg biw)

of ILD can be well controlled in time through early judgment and intervention.

As antineoplastic agent-induced ILD can be difficult to identify and manage, and in most cases only sporadically (26), the relevant experience of most doctors is insufficient, and currently there are no specific guidelines on the diagnosis and treatment of it. It is recommended that physicians should use the Pneumotox online platform (https://doi.org/10.1016/j.esmoop.2022.100404) to know the risk of ILD before antineoplastic agent therapy. Once ILD is suspected, multidisciplinary interaction is very important in the diagnosis and management of targeted drug-induced ILD. The symptoms of ILD are generally non-specific, with the most frequent being non-productive cough, asthenia, and chest pain. Dyspnea, low-grade fever, cough, fatigue, and chest pain and tightness should be carefully evaluated, and dyspnea on exertion is the most important symptom to be alert to with the occurrence of ILD (27). Physical examination and careful patient history-taking (in order to obtain detailed information on the drugs taken by the patient, comorbidities, and any potential risk factors, as well as to rule out any other cause of ILD and to define the temporal relationship between the onset of symptoms and exposure to the potentially causative drug) (28), measurement of vital signs (especially respiratory rate, arterial oxygen saturation, and abnormal pulmonary auscultation may detect alterations in the normal vesicular murmur and typical pulmonary crackles), relevant laboratory tests, respiratory function tests (a baseline assessment with these tests should be carried out as soon as drug-induced ILD is suspected, which shows a restrictive spirometric pattern with a decline in total lung capacity and should be repeated over time to monitor respiratory function), and lung diffusion capacity for carbon monoxide and computed tomography are the important components of an accurate diagnosis, at the same time, although microbial and serological testing are not specific, but could help to exclude or confirm infectious causes (viruses, bacteria, fungi, and so on). High-resolution CT (HRCT) is currently the most sensitive diagnostic modality for detecting ILD since its early stages, and a follow-up CT scan should be repeated along with assessment of therapeutic response (26); the CT features are areas of ground-glass opacity (GGO), consolidation and lung volume reduction (29–31), and the corresponding pathological features which are thickening of the alveolar walls, deposition of hyaline membranes, and infiltration of inflammatory cells. Up to one-third of patients with drug-induced ILD can be asymptomatic, so incidental diagnosis in patients with radiological evidence of interstitial pneumonia may occur (32). For the patient we reported, the HRCT taken on 5 February 2024 has shown signs of ILD, and the clinical symptoms at that time were fever, cough, expectoration and shortness of breath after exercise. The attending doctor considered that her fever was glumetinib-induced ILD, so stopping of treatment with glumetinib was suggested. However, the progression of ILD was not alleviated by discontinuing glumetinib. When she came to our hospital, the patient did not tell us that her chest CT suggested ILD, and she did not know she had ILD; her main complaint was a fever of unknown cause, so a series of relevant laboratory examinations have been taken (Table 1), excluding lung inflammation, virus infection, rheumatism, tuberculosis, cardiac failure, and so on. Moreover, until the patient was unexpectedly found to have severe shortness of breath and difficulty in breathing on 26 February 2024 and the emergency chest CT indicated significant progression of ILD, a diagnosis of almonertinib-induced ILD was determined, so almonertinib was urgently stopped. Then, the family sent the chest CT results taken on 26 February 2024, and we found that ILD had already existed at that time. The judgment and intervention of ILD in this patient was not timely, which emphasized careful patient history-taking and vigilance for targeted-induced ILD contributed to the judgment of targeted-induced ILD timely. Otherwise, it will cause serious consequences.

Almonertinib, a new third-generation EGFR-TKI, was approved by the National Medical Products Administration as first-line treatment of locally advanced or metastatic NSCLC with 19Del and 21L858R mutation on 16 December 2021. Moreover, the main advantage is almonertinib and its metabolites have weak inhibition on wild-type EGFR, so there are fewer side effects (33). A higher proportion of adverse events with almonertinib are rash and elevation of creatine phosphokinase, aspartate aminotransferase, and alanine aminotransferase; ILD was extremely rare. ILD was only observed in the cohort receiving 260 mg in the phase I study (34), no ILD was reported in the phase II study (APOLLO) (35), and only two cases of ILD were observed in the phase III study (AENEAS) (36). Up to now, there are only two case reports of almonertinib-induced ILD: one was reported in 2020 by Ting Jiang (a 70-year-old woman, 110 mg per day, 3 months later ILD was found) (37); another was reported in 2023 by Xiaokui Tang (a 71-year-old man, 110 mg per day, 3 months later ILD was found) (38). In addition, Longqiu Wu reported a case of osimertinib-induced ILD and then switched to almonertinib for further treatment with success (39). Probably based on the above report and experience, the attending doctor considered the ILD of the patient we reported to be glumetinib induced, so pausing of treatment with glumetinib was first suggested, but almonertinib was continued. Furthermore, for the patient we reported, 77 days after taking almonertinib and glumetinib, she developed a fever as high as 39.4° C, accompanied by cough, expectoration, and shortness of breath after exercise. The time of occurrence almonertinib-induced ILD was shorter than previously reported, which may be due to the aggravation of toxic and side effects of dual-targeted therapy (almonertinib combined with glumetinib). However, from the perspective of the whole diagnosis and treatment process, we are more inclined to almonertinib-induced ILD. Although the risk of drug-induced ILD increases when causative drugs are used in combination (26), the presence of glumetinib-induced ILD cannot be completely ruled out.

As recommended in the review of "Drug-induced interstitial lung disease during cancer therapies: expert opinion on diagnosis and treatment" (26), the treatment approach in case of drug-induced ILD mainly consists in the discontinuation of the offending drug and start of immunosuppressive therapy and is always driven by the grade of severity of the clinical manifestations. In grade 3 ILD, hypoxic patients should receive oxygen therapy according to the degree of hypoxemia, and the timely and definitive discontinuation of the anticancer drug and the initiation of corticosteroid therapy at 1 mg/kg/day–2 mg/kg/day of methylprednisolone or equivalent are essential. If the patients respond well and revert to grade 1 (complete resolution of the symptoms with possible persistence of the radiological features),

steroid therapy can be progressively tapered after 8–12 weeks; however, rapid steroid de-scalation may increase the risk of ILD reactivation (26). For the patient, we reported methylprednisolone (40 mg/day) along with oxygen uptake for 3 days; the patient felt her respiratory condition gradually improved, and chest CT also showed a noticeable improvement in the ILD on 4 March 2024, so the methylprednisolone was decreased gradually and completely discontinued on 6 May 2024.

After the remission of almonertinib-induced ILD, it is necessary to choose appropriate drugs to control tumor progression. Although we did not obtain the rechallenge recommendations of EGFR-TKI drug after almonertinib-induced ILD, most literatures confirm that when an EGFR-TKI is discontinued due to ILD, replacing other EGFR-TKI drugs can usually successfully control tumor progression (40–42). For the patient we reported, based on the ILD which has been well controlled, the attending doctor suggested to choose furmonertinib, which, as a novel, third-generation EGFR-TKI, is safe and well tolerated in NSCLC patients with EGFR-sensitive mutations and EGFR T790M-resistant mutations to control tumor progression. Moreover, follow-up for 1 month showed that the patient did not feel any discomfort. Thus, glumetinib was rechallenged. According to the changes of her condition, medication was adjusted to sunvozertinib (150 mg per day) combined with glumetinib (150 mg per day) on 14 September 2024. Then, it was adjusted to sunvozertinib (150 mg per day) combined with vinorelbine (30 mg biw) on 11 November 2024. However, there were no adverse drug reactions such as ILD, and the patient did not feel any discomfort either.

As a whole, for this patient, the effectiveness of dual-targeted therapy was the highest. Besides ILD, the patient did not feel any other discomfort. As targeted therapy may induce new mutations or cause the disappearance of existing targets, re-biopsy was thus necessary and the occurrence of ILD should always be looked out for.

4 Conclusion

This study reports that patients with EGFR Ex19del mutation and MET *de novo* amplification may benefit more from dual-targeted therapy than pemetrexed and carboplatin chemotherapy along with bevacizumab. However, dual-targeted therapy may increase the risk of ILD, so it is important to be alert to targeted-induced ILD, and unexplained fever may be an early warning signal for targeted-induced ILD, especially almonertinib-induced ILD. Timely intervention is needed to avoid greater harm when ILD occurs and, when ILD is effectively controlled, seize the opportunity to rechallenge the dual-targeted therapy, which may contribute to a better prognosis. In addition, the patients with targeted-induced ILD in the past need more rigorous monitoring and follow-up in the process of rechallenging the targeted drug therapy.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding authors.

Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

WY: Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Writing – original draft. LS: Methodology, Writing – original draft. HW: Methodology, Writing – original draft. YL: Formal analysis, Writing – original draft. XJ: Data curation, Writing – original draft. HL: Data curation, Writing – original draft. GY: Supervision, Writing – review & editing. WX: Supervision, Writing – review & editing.

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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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Case report: A patient with EGFR L861Q positive adenosquamous lung carcinoma transforming into large cell neuroendocrine cancer after treatment with Almonertinib

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Almonertinib, a third-generation epidermal growth factor receptor tyrosine kinase inhibitor, is selective for both epidermal growth factor receptor tyrosine kinase inhibitor–sensitizing and T790M resistance mutations. However, resistance to the third-generation EGFR-TKIs is still inevitable. Econdary EGFR mutations, and bypass pathway activation have been reported with Almonertinib therapy. This article presents a rare case report of a patient with EGFR L861Q positive adenosquamous lung carcinoma who transformed into large cell neuroendocrine carcinoma following treatment with Almonertinib. The patient exhibited disease progression 8 months after initiating Almonertinib treatment, and a blood genetic test revealed mutations in EGFR L861Q and EGFR L858R. A subsequent lung biopsy after progression confirmed the diagnosis of large cell neuroendocrine carcinoma, and subsequently treatment with cisplatin and etoposide was effective. Transformation into neuroendocrine carcinoma is one of the mechanisms behind resistance to Almonertinib in adenosquamous lung carcinoma. EGFR mutations may persist even after transformation into neuroendocrine carcinoma. For non-small cell lung cancer patients undergoing Almonertinib therapy, this case report emphasizes the importance of performing a timely pathological biopsy upon the emergence of resistance.

KEYWORDS

Almonertinib, EGFR, mutation, neuroendocrine, large cell neuroendocrine carcinoma, LCNEC, adenosquamous carcinoma

1 Introduction

Adenosquamous carcinoma (ASC) of the lung is a relatively rare subtype of non-small cell lung cancer (NSCLC), accounting for only 2%-3% of all lung cancers (1, 2). Studies have shown that ASC is more commonly found in male patients, and a history of smoking has been confirmed as a high-risk factor for ASC (1, 3–6). Known mutations in ASC include those in EGFR, ERBB2, KRAS, BRAF, PIK3CA, RET, ALK, and others (7). This article reports a rare case of a patient diagnosed with EGFR positive adenosquamous lung carcinoma, who experienced disease progression following treatment with Almonertinib. Repeat biopsies revealed that the resistance mechanism was transformation into large cell neuroendocrine carcinoma (LCNEC). Chemotherapy treatment was administered in response to this finding, leading to successful disease control in the patient.

2 Case reports

The patient is a 43-year-old Han Chinese male with no history of smoking. The timeline of the clinical course of the patient was presented in Figure 1. In November 2021, he presented with symptoms of cough, hemoptysis, and chest tightness. A CT scan revealed a cancer of the right upper lobe, with mediastinal right hilar and right pleural metastases. In December 2021, biopsies of the lung mass and pleura were conducted, with the pathology indicating adenosquamous carcinoma. Immunohistochemistry revealed nests of carcinoma cells with focal solid areas, CK(+), CK7(+), CK5/6(+), P63(+), P40(+), weakly positive for TTF-1, and S100 (-) (Figure 2A). The clinical stage was cT4N1M1a, IVa. Tissue genetic testing results showed an EGFR L861Q mutation (AF-70.50%) and a PTEN mutation (AF-67.20%). The patient subsequently started oral Almonertinib 110mg qd and regular monitoring showed a stable disease (SD) response. In August 2022, a follow-up CT indicated right pleural metastases and pericardial effusion, with the treatment response evaluated as progressive disease (PD). As the patient refused repeat biopsy, blood genetic testing was performed, revealing EGFR L861Q mutation (AF-11.00%), EGFR L858M mutation (AF-11.94%), and other mutations including RB1 (AF-9.20%), TP53 (AF-12.97%), PTEN (AF-12.51%), and SMARCA4 (AF-0.96%). The patient then received three cycles of pemetrexed, cisplatin, bevacizumab, and sintilimab treatments. In December 2022, a CT scan showed occlusion of the right main bronchus, atelectasis of the right lung, and metastases to the right hilar and mediastinal lymph nodes. There was invasion into the right pleura and pericardium, with increased right pleural and pericardial effusions. In February 2023, a CT scan showed a further increase in pleural and pericardial effusion, along with liver, brain, and bone metastases. From August 2022 to February 2023, the patient's chest tightness and dyspnea symptoms progressively worsened. Due to a significant rise in neuron-specific enolase (NSE), the patient underwent another lung biopsy in February 2023, which revealed large cell neuroendocrine carcinoma. Immunohistochemistry showed P40 (-) and P63 (-), TTF-1(+), CK7(-), CD56(+), Syn(+), and CgA(+), negative for ALK (D5F3) and PD-L1 (TPS: 0%), with Ki-67(95%+) (Figures 2B–E). The findings suggested a transformation from ASC to LCNEC following targeted therapy. Following this, the patient received two cycles of an "EP" regimen (cisplatin + etoposide) chemotherapy in March and April 2023. After chemotherapy, the follow-up CT scan showed a partial response (PR), and the patient's symptoms significantly improved.

3 Discussion

To our knowledge, this is the first reported case of an ASC patient transforming into LCNEC following treatment with Almonertinib. ASC is an infrequent subtype of NSCLC, defined by the presence of admixed glandular and squamous cell components, each comprising more than 10% of the tumor. ASC generally exhibits more aggressive behavior and is associated with a poorer prognosis compared to cancers of solely adenocarcinoma or squamous cell histology (6, 8). Recent studies suggest that both glandular and squamous components in ASC likely originate from a single clonal event, followed by transdifferentiation from adenocarcinoma to squamous cell carcinoma (9). The frequency of EGFR mutations in ASC is comparable to that in pulmonary

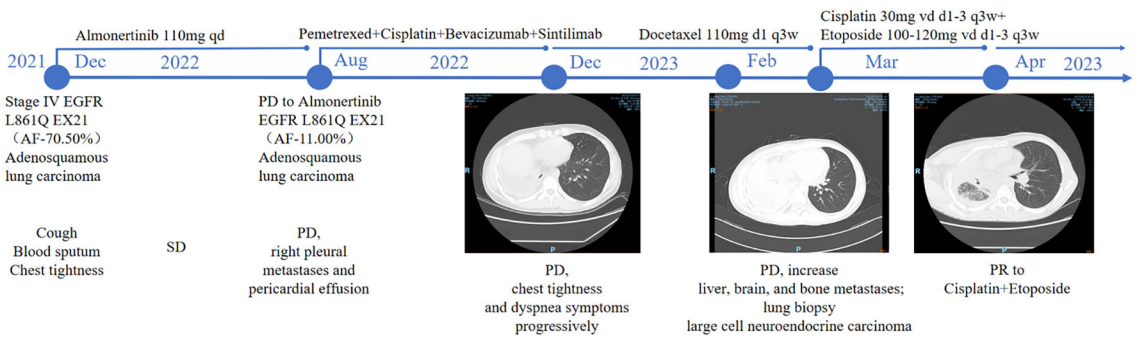

FIGURE 1
Timeline of the clinical course of the patient. Arrows indicate the link between the clinical event and the date of biopsy time point.

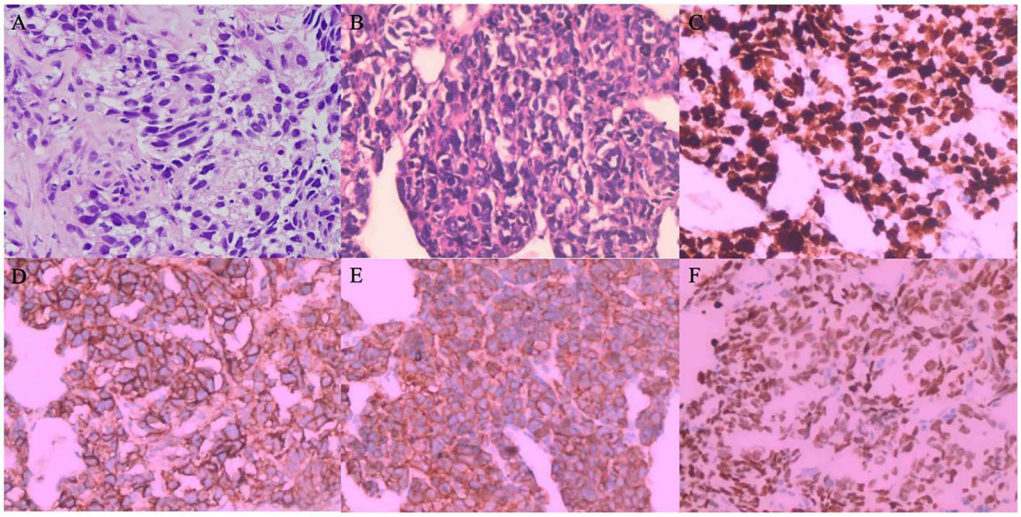

FIGURE 2
(A–E) Hematoxylin & Eosin Staining and Immunohistochemical Staining - **(A)** Hematoxylin and eosin-stained section (200x, December 2021) depicting focal solid nests of tumor cells diagnostic of adenosquamous carcinoma. **(B)** Hematoxylin and eosin staining reveals cellular architecture (200x, February 2023); **(C)** High Ki-67 index (>95%) suggests aggressive proliferation; **(D)** CD56 positivity indicates neuroendocrine differentiation; **(E)** Synaptophysin positivity and **(F)** TTF-1 expression confirm neuroendocrine phenotype and lung origin, consistent with a transition to large cell neuroendocrine carcinoma. **(B)** Hematoxylin and eosin staining reveals cellular architecture depicting focal solid nests with the infiltrative growth. Tumor cells had large dark irregular nuclei with atypical and numerous mitotic figures diagnosing of large cell neuroendocrine carcinoma (200x, February 2023); **(D)** CD56 positivity suggests neuroendocrine differentiation; **(E)** Synaptophysin immunoreactivity further supports neuroendocrine features; **(F)** TTF-1 expression, consistent with lung origin, all indicative of a transition to large cell neuroendocrine carcinoma. **(D)** CD56 immunostaining and **(E)** highlighting positive expression (200x, February 2023) characteristic of large cell neuroendocrine carcinoma.

adenocarcinoma (10, 11), and patients with EGFR-mutant ASC respond favorably to EGFR-TKI therapies (12).

Almonertinib is the first third-generation EGFR-TKI drug developed independently in China, designed to overcome the common T790M resistance mutation. The AIM study, reported at the ESMO Asia 2022, enrolled advanced non-squamous NSCLC patients with uncommon EGFR mutations and indicated that Almonertinib was effective for first-line treatment of NSCLC patients with uncommon EGFR mutations other than EGFR ex20ins (13). Almonertinib demonstrated better efficacy in patients with G719X, L861Q, and S768I mutations compared to other genotypes. The results of the AENEAS study highlighted that in first-line treatment of locally advanced or metastatic NSCLC patients with EGFR mutations, Almonertinib significantly prolonged median progression-free survival (PFS) (19.3 months versus 9.9 months) and duration of response (DOR) (18.1 months versus 8.3 months), with a more favorable safety profile compared to gefitinib (14).

In this present case, the patient was diagnosed with EGFR L861Q positive ASC and treated with Almonertinib. However, after 8 months, disease progression was noted. Despite the extended survival benefits that third-generation EGFR-TKIs have brought to NSCLC patients with EGFR mutations, the problem of resistance remains unavoidable. In phase II clinical trials, resistance mechanisms to second-line Almonertinib predominantly involved secondary EGFR mutations (such as cis C797S and L718Q mutations) as well as bypass activation (including mutations in PIK3CA, JAK2, BRAF, KRAS, HER2 amplification, and FGFR3-TACC3 fusion) (15). After disease progression, our patient underwent repeat blood genetic testing, which identified mutations in EGFR L861Q, EGFR L858M, RB1, TP53, PTEN, and SMARCA4. With the repeat biopsy suggesting LCNEC, we can ascertain that the resistance mechanism was transformation into a neuroendocrine tumor rather than secondary EGFR mutations or bypass activation.

LCNEC and SCLC both belong to high-grade neuroendocrine carcinomas, sharing similar clinical and genomic features, suggesting a common pathway for transformation. In studies by Ferre (16) and Marcoux (17), median times from initiation of treatment to phenotypic transformation for EGFR-mutant adenocarcinomas were 16 and 17.8 months, respectively. Possible reasons for transformation from adenocarcinoma to SCLC include: 1. coexistence of adenocarcinoma and SCLC at tumor onset, with SCLC eventually superseding other histological types following TKI treatment; 2. besides originating from pulmonary neuroendocrine cells (18), SCLC may arise from other lung epithelial cells (19), with type II pneumocytes having the potential to differentiate into both histologies, possibly giving rise to both EGFR-mutant adenocarcinoma and SCLC (20); 3. inactivation of TP53 and RB1 genes (20–22), which are commonly lost in SCLC, plays an inducing role in the occurrence of SCLC (23). Additionally, loss of RB family members P107 or P130, amplification of the MYC family,

alterations in the PTEN pathway, and high expression of BCL-2 are associated with SCLC cell growth, proliferation, and survival (24). Changes in the lung stroma and immune microenvironment might also contribute to occurrence of SCLC (25). Other genetic pathways that are probably involved in the histopathological transformation are NOTCH and ASCL1 (26). ASCL1 is targeted by NOTCH signaling (27) and research suggested that one inactivating NOTCH mutation was sufficient to induce neuroendocrine differentiation from nonneuroendocrine tumor cells or tumor precursors (28). While research on the transformation mechanism of LCNEC is scarce, given the clinical and genomic similarities between LCNEC and SCLC (29, 30), we speculate that the pathways of transformation to LCNEC are similar to those of SCLC, warranting further studies. Moreover, while the mechanism of adenocarcinoma transformation is relatively well understood, the mechanism by which ASC transforms into a neuroendocrine carcinoma following EGFR-TKI treatment remains to be further explored.

Studies have indicated that NSCLC patients with concurrent EGFR/RB1/TP53 mutations are more prone to transform into SCLC (31), especially those with a high frequency of AID/APOBEC mutations and genomic amplifications. Our patient's secondary genetic testing revealed an EGFR/RB1/TP53 triplet mutation set. Regrettably, after developing resistance to EGFR-TKI therapy, he refused repeat biopsy and instead received three cycles of combined therapy with pemetrexed, cisplatin, bevacizumab, and sintilimab. Owing to ongoing tumor progression and significantly elevated NSE levels, we performed a lung biopsy 6 months post resistance to EGFR-TKI therapy, which confirmed a diagnosis of LCNEC. Treatment for LCNEC currently centers around chemotherapy, with the optimal regimen still debated; often, SCLC chemotherapy protocols are referenced. Thus, we opted for the EP regimen, and after two cycles, a follow-up CT scan indicated overall tumor shrinkage with a PR evaluation, and the patient's symptoms substantially relieved, confirming the efficacy of the treatment.

4 Conclusion

Our case demonstrates that transformation into a neuroendocrine tumor is one of the mechanisms of acquired resistance to Almonertinib, and that the retention of EGFR mutations may also occur in LCNEC. Identifying the histological diagnosis and driver mutations is important in deciding treatment options. Therefore, we recommend timely repeat biopsies for patients who develop resistance to EGFR-TKI therapy, particularly those with concurrent EGFR/RB1/TP53 mutations in NSCLC, in order to obtain the best treatment strategies to further extend patient survival and improve quality of life. Chemotherapy can be considered for the EGFR/RB1/TP53 mutation triad. Chemotherapy remains effective for neuroendocrine carcinoma post-tumor transformation. We look forward to the new development of molecular detection methods for early identification of transformation risks in the future.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by Ethics Committee of Guangzhou University of Chinese Medicine (approval ID: K-2025-009). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

KC: Writing – original draft, Conceptualization, Formal analysis. YZ: Conceptualization, Validation, Investigation, Visualization, Writing – review & editing. RS: Data curation, Formal analysis, Writing – original draft. ZK: Data curation, Writing – review & editing. YC: Supervision, Resources, Funding acquisition, Writing – review & editing.

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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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Targeted treatment and survival in advanced non-squamous non-small cell lung cancer patients – a nationwide and longitudinal study

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Objectives: We aimed to describe treatment patterns, time on treatment (ToT) and overall survival (OS) for patients with advanced non-squamous, EGFR+, ALK+ and ROS1+ NSCLC in Norway.

Materials and methods: We extracted data on patients ≥ 18 years diagnosed with advanced non-squamous NSCLC between 2015 and 2022 from the Cancer Registry of Norway and data on cancer drug therapy from the Norwegian Patient Registry and the Norwegian Prescribed Drug Registry. ToT was measured from the date treatment was collected or administered until the last dispensing was depleted or last hospital drug administration. OS was measured from date of diagnosis until death.

Results: In total, 5,279 patients were included, of whom 449 EGFR+, 131 ALK+ and 38 ROS1+. 75% of EGFR+ patients, 88% of ALK+ patients, and 58% of ROS1+ patients received at least one systemic treatment within the first three months after diagnosis. Median follow-up was 13, 19, and 4 months for EGFR+, ALK+, and ROS1+, respectively. The median ToT in first line (1L) for EGFR+ patients was 11 months for osimertinib (CI: 10.1-NA) and 9 months (CI: 8.2-11.2) for afatinib, dacomitinib, erlotinib and gefitinib. For ALK+ patients, median ToT in 1L was 20 months (CI: 14.7-23.7for alectinib, 11 months (CI: 4.7-NA) for brigatinib, and 7 months (CI: 2.9-21.6) for crizotinib. For the five ROS1+ patients treated with crizotinib in 1L, median ToT was 5 months (CI: 2.4-NA). For all patients with a targetable genomic alteration, unadjusted median OS was higher (p-value = 0.025) for patients diagnosed in 2020-2022 (median OS: 23 months, CI: 19.5-NA) compared to patients diagnosed in 2015-2019 (median: 19 months, CI: 16.5-21.2).

Conclusions: ToT for targeted therapies was shorter than progression-free survival in clinical trials. However, patients eligible for targeted therapy still had a survival improvement during the study period.

KEYWORDS

ROS, ALK, EGFR, real world data, lung cancer, time on treatment

Introduction

Lung cancer accounts for about 13% of all new cancer diagnoses and is the leading cause of cancer-related deaths worldwide (1, 2). Approximately 80-85% of patients have non-small cell lung cancer (NSCLC) (3). About half of NSCLC patients are diagnosed with advanced, metastatic disease and have a poor prognosis (4). In Norway, 5-year relative survival for patients diagnosed with stage IV lung cancer was estimated to be 8.3% for patients diagnosed in the period 2018 through 2022 (3).

Over the past decades, several effective systemic therapies for NSCLC have been introduced (5, 6), largely because drugs designed to target oncogenic driver alterations have been developed (7). These protein kinase inhibitors (TKI's) have proven to be more effective than chemotherapy regimens that used to be standard first line treatment for all advanced NSCLC. Since 2010, drugs targeting Epidermal Growth Factor Receptor (EGFR) mutations, Anaplastic Lymphoma Kinase (ALK) translocations and ROS1 fusions have become available through the Norwegian public health care system (EGFR-inhibitors since 2010, ALK-inhibitors since 2013 and ROS1-inhibitors since 2019). According to national guidelines, all non-squamous NSCLC tumors should be tested for EGFR-, ALK-, and ROS1-alterations since the corresponding inhibitors became available at public hospitals in our country (8). These three mutations are usually mutually exclusive and represents 11.5%, 2.4%, and 1-2% of adenocarcinomas, respectively (3, 9, 10).

The effectiveness of targeted therapies has also been seen in studies using real-world data (5, 11–14), but there is limited data on implementation rates of molecular testing, implementation of first-, second- and third-generation TKI's, treatment across lines of therapy, ToT, and impact on overall survival (OS). Utilizing data from public Norwegian registries, we aimed to report such data for patients diagnosed with advanced non-squamous NSCLC in Norway between 2015 and 2022.

Materials and methods

Data sources

The study population was identified from the Cancer Registry of Norway (CRN). Data on drug treatment for each patient were collected from the CRN, the Norwegian Patient Registry (NPR) and the Norwegian Prescribed Drug Registry (NorPD).

Health institutions in Norway are required by law to notify CRN of any new cancer case, and CRN encompassed 99.2% of all lung cancer patients between 2018 and 2022 (15). Clinical stage (cTNM according to TNM v7 from 01.01.2015-31.12.2016, and v8 from 01.01.2017-31.12.2022) has been recorded for more than 80% of cases since 2017 (disease stage was classified as "local", "regional" and "advanced" until 2017) (16). Data on EGFR and ALK status have been included in the CRN since 2013 and ROS1 status from 2022 onwards.

From the CRN, we extracted date of diagnosis, disease stage at diagnosis, histological subtype, biomarker (EGFR, ALK and ROS1) status, patient characteristics (sex, year of birth, and date of death if applicable), and whether patients underwent surgery or radiation therapy.

Data on medical treatment were collected from multiple sources. The NorPD include data on all subcutaneous and oral cancer drugs dispensed at Norwegian pharmacies from 2004, the NPR holds information on all hospital encounters (in- and outpatient visits) and hospital administered drugs from 2008, and the CRN holds information on hospital administered drugs from 2008 and all cancer drugs administered subcutaneously and oral from 2019. The CRN does not cover drug treatments in hospitals in the Northern region (approx. 10% of the population), but all Norwegian hospitals are covered by the NPR. Combined, these data hold information on all medical systemic treatment administered at public hospitals during the study period except oral study drugs dispensed through clinical trials.

Study population

We extracted data on all patients aged 18 or above diagnosed with advanced non-squamous NSCLC (stages IIIB, IIIC or IV) between January 1, 2015, and December 31, 2022 according to the CRN. Patients who were diagnosed with lower stage disease and later developed advanced disease were not included, and we excluded patients treated with curative intent in the primary setting.

We then defined three biomarker-defined subgroups (EGFR+, ALK+ and ROS1+) and one with the remaining non-squamous NSCLC patients. Patients were assigned to subgroups if they a) were registered as being biomarker positive in the CRN or b) received a

specific targeted treatment within the first three months of diagnosis. The time period for inclusion of patients to biomarker subgroups were based on when targeted therapies were approved for use in the public health care sector and when biomarker results were reported to CRN.

EGFR+

Patients registered as being EGFR+ in the CRN (n = 431) and patients with unknown EGFR-status who received an EGFR inhibitor (afatinib, dacomitinib, gefitinib or osimertinib) within the first three months since diagnosis (n = 18). Erlotinib-treatment was not used to assign patients to this group since it is sometimes used to treat patients who are not EGFR+ (30 patients without known EGFR+ received erlotinib within the first three months of diagnosis). One patient was recorded as being both EGFR+ and ALK+, while eight patients were both EGFR+ and ROS1+. These patients were assigned to the EGFR+ subgroup since they received EGFR-inhibitor therapy.

ALK+

Patients recorded as being ALK+ in the CRN (n = 119) and patients with unknown ALK-status who received an ALK inhibitor (alectinib, brigatinib or ceritinib) within the first three months of diagnosis (n = 12). Lorlatinib-treatment was not used to assign patients to the ALK+ subgroup as lorlatinib was not recommended for first line treatment during the study period. Patients treated with crizotinib were included if they received alectinib or brigatinib as subsequent treatment, since these are likely to have been considered to have ALK+ and not ROS1+ disease.

ROS1+

Patients recorded as being ROS1+ in the CRN (n = 36) and patients with unknown ROS1-status who received entrectinib after crizotinib treatment (n = 2), since these are likely to have been considered having ROS1+ and not ALK+ disease.

Other non-squamous NSCLC

All other non-squamous NSCLC patients in the study population.

Variables and outcomes

Treatment classification

Systemic drug treatment was identified based on the Anatomical Therapeutic Chemical (ATC) code and classified as protein kinase inhibitors (targeted therapy), chemotherapy (ChT), or immunotherapy (IO), according to CRNs classification (17, 18).

Erlotinib (L01EB02), afatinib (L01EB03), and gefitinib (L01EB01) were all as first line treatment options for EGFR+ patients before 2013, while dacomitinib (L01EB07) and osimertinib (L01EB04) were introduced as first line treatments with public reimbursement in 2020 and 2021, respectively.

For ALK+ patients, crizotinib (ATC-code L01XE16) was approved for use in the public health care sector in Norway as second line treatment in 2012, and as first line treatment in 2017. Alectinib (L01ED03) and ceritinib (L01ED02) were approved as first line treatment in 2018. Brigatinib (L01ED04) was approved as second line treatment following crizotinib in 2019, and as a first line treatment in 2021. Lorlatinib (L01ED05) was approved as second line treatment for ALK+ patients in 2019 and as a first line treatment in 2022.

For ROS1+ patients, crizotinib (L01XE16) was approved as first line treatment in 2018 and entrectinib (L01EX14) in 2021.

Quadruple treatment was defined as combination treatment with atezolizumab (L01FF05), bevacizumab (L01FG01), paclitaxel (L01CD01) and carboplatin (L01XA02). Platinum doublet treatment was defined as treatment with cisplatin (L01XA01) or carboplatin (L01XA02) in combination with vinorelbine (L01CA04), etoposide (L01CB01), paclitaxel (L01CD01), pemetrexed (L01BA04) or gemcitabine (L01BC05).

Treatment patterns

As clinicians may prescribe IO and/or ChT while they wait for biomarker test results, first line treatment was defined as the first targeted therapy received within three months since diagnosis. If no targeted therapy was given during the first three months, the first non-targeted therapy (received within three months) was considered first line treatment. Three months is deemed as a reasonable threshold after which biomarker test results should have been received and acted upon by clinicians.

Treatment patterns were presented using Sankey flow diagrams, a data visualization technique that allows for describing change of treatment across treatment lines (19). Line not reached (LNR) indicates that patients were still on treatment at the end of the study period (last 12 weeks of the data collection period).

Time on treatment

ToT was estimated using the Kaplan-Meier estimator (20) and presented as drug survival curves and median ToT (mToT). ToT was estimated based on the defined daily dose (DDD) for each drug dispensing (targeted therapies) or assumed to be four weeks on average per treatment course for IO and ChT. ToT was estimated for first line treatments and for all treatment lines combined (i.e., total ToT for all treatment lines (mTToT), allowing for drug switch). Drug treatment was considered discontinued when a) patients did not receive a new drug after the previous one would have been depleted, b) a treatment gap of 12 weeks or more, c) death, or if another drug treatment was administered.

Overall survival

OS was estimated from date of diagnosis to death or end of follow-up using the Kaplan-Meier estimator (20). To investigate changes in OS over time, results were stratified based on year of diagnosis (2016-2019 vs 2020-2022 for ALK+ and 2015-2019 vs 2020-2022 for all other subgroups).

Reporting guidelines and ethics

This study follows Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for observational studies. The study was approved by the Regional Ethics Committee of Norway South-East D (Reference number 485084) and registered at http://ClinicalTrials.gov (Reference number NCT05834348). All analyses were conducted using R version 4.1.2 (2021).

Results

Patient characteristics

The overall population comprised 5,279 patients (Figure 1). Baseline characteristics are listed in Table 1. Median age was 71 (25^{th} and 75^{th} percentile: 64, 77) years, and 48% were female. Median follow-up was 5.5 (25^{th} and 75^{th} percentile: 1.9, 14.1) months.

618 patients were assigned to one of the three biomarker subgroups (EGFR+, ALK+, or ROS1+). In general, ALK+ patients (median age 64, 25^{th} and 75^{th} percentile: 52.5, 73) were younger than EGFR+ (median 70 years,25^{th} and 75^{th} percentile: 59, 78) and ROS1+patients (median 74.5 years,25^{th} and 75^{th} percentile: 62.5, 78), and the proportion of females was lower (ALK+ 52%, EGFR+ 66%, ROS1 + 68%). There were no differences in stage distribution or proportions with adenocarcinomas across these subgroups.

Median follow-up was 12.7 months (25^{th} and 75^{th} percentile: 5.3, 24) for EGFR+ patients, 18.7 months (25^{th} and 75^{th} percentile: 5.8, 8.9) for ALK+ patients, and 4.0 months (25^{th} and 75^{th} percentile: 1.6, 8.9) for ROS1+ patients. During follow-up, 88% of EGFR+, 94% of ALK+, and 46% of ROS1+ patients received at least one targeted therapy.

For other non-squamous NSCLC patients, median age at diagnosis was 71 years (25^{th} and 75^{th} percentile: 65, 77), proportion females was 46%, median follow-up time was 4.9 months (25^{th} and 75^{th} percentile: 1.6, 12.5), and 2% received a targeted therapy during the study period.

Treatment patterns and time on treatment

EGFR+

449 patients were categorized as EGFR+ patients, of which 75% (n=335) received systemic treatment outside of clinical studies within the three first months after diagnosis (Figure 2). Overall, osimertinib was the most common first line treatment (31% of those who received first line treatment, n=104), followed by gefitinib (26%, n=86) and erlotinib (15%, n=50). The choice of first line EGFR-inhibitor therapy changed during the study period according to changes in national guidelines and time of reimbursement (8). Afatinib, erlotinib and gefitinib were most commonly used prior to 2020, while osimertinib was most commonly used after reimbursement for first line therapy was approved in 2021.

Of the 335 EGFR+ patients who received first line treatment, 41% (n=139) received second-line treatment, most commonly IO and/or ChT (38% of those who received second line treatment, n=53), osimertinib (18%, n=25), afatinib (16%, n=22), and erlotinib (14%, n=19). Of the 196 patients who did not receive second-line treatment, 41% (n=80) were still on first line treatment at the end of follow-up (LNR), 54% (n=106) died while on first line treatment, and 5% (n=10) stopped treatment after first line but were alive at the end of the study period (follow-up of 14 to 88 weeks without treatment).

Among the 139 patients who received second-line treatment, 32% patients (n=44) continued to third line, most commonly IO

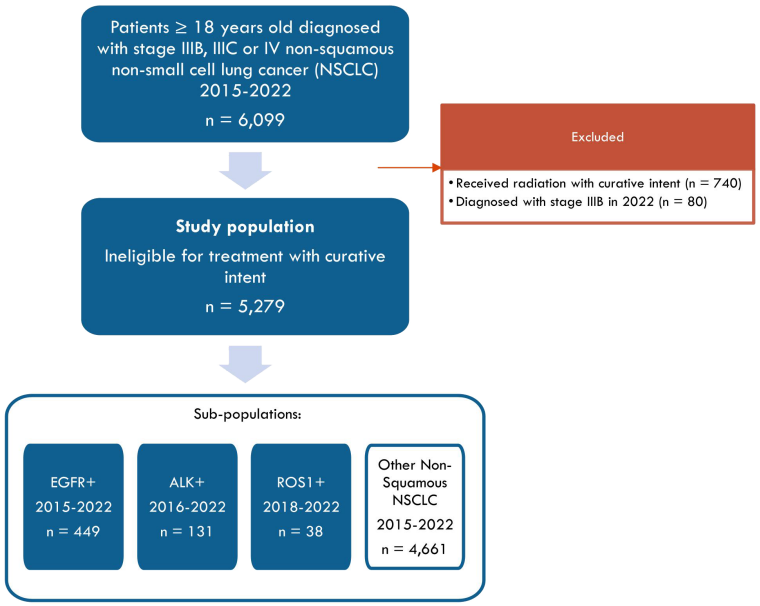

FIGURE 1
Study flow chart.

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TABLE 1 Patient characteristics for patients diagnosed with advanced NSCLC in Norway between 2015 and 2022.

	All	All biomarker subgroups	EGFR+	ALK+	ROS1+	Other non-squamous NSCLC
Number of patients	5279	618	449	131	38	4661
Year of diagnosis	2015-2022	2015-2022	2015-2022	2016-2022	2018-2022	2015-2022
Median age at diagnosis (25^{th} percentile, 75^{th} percentile)	71 (64, 77)	69 (59, 77)	70 (59, 78)	64 (52.5, 73)	74.5 (62.5, 78)	71 (65, 77)
Mean age at diagnosis (SD)	70.2 (10.2)	67.1 (13)	68.3 (12.6)	62.6 (13.3)	69.5 (13.3)	70.7 (9.7)
Proportion female	48.3%	62.9%	65.7%	51.9%	68.4%	46.3%
Percent received targeted therapy	10.3%	87.4%	88.3%	94.1%	46.4%	1.8%
Median follow-up (from diagnosis until death/end of data) (months) (25^{th} percentile, 75^{th} percentile)	5.5 (1.9, 14.1)	13.4 (4.6, 24.5)	12.7 (5.3, 24)	18.7 (5.8, 32.7)	4.0 (1.6, 8.9)	4.9 (1.6, 12.5)
Percent dead during study period	78.5%	58.9%	63.7%	47.3%	42.1%	81.1%
Stage at time of diagnosis						
IIIB	5.4%	3.5%	3.6%	4.6%	0%	5.6%
IIIC	2.9%	1.6%	1.1%	1.5%	7.9%	3.1%
IVA	36.2%	36.2%	36.1%	35.1%	42.1%	36.2%
IVB	55.5%	58.6%	59.2%	58.8%	50.0%	55.1%
Morphology						
Adenocarcinoma	82.4%	94.7%	95.3%	92.4%	94.7%	80.8%
Non-small cell carcinoma UNS**	15.3%	5.0%	4.6%	6.1%	5.3%	16.7%
Large cell neuroendocrine carcinoma	2.2%	0.3%	0%	1.5%	0%	2.4%

SD, Standard deviation.

and/or ChT (39% of those who received third line treatment, n=17) or osimertinib (30%, n=13).

Swimmer plots showing the length of treatment duration for each EGFR+ patient is presented in Supplementary Figures 4A1, A2.

Patients who received osimertinib in first line had a mToT of 11 months on osimertinib (CI: 10.1-NA), and a mTToT of 14 months (CI: 11.1-NA) for all lines. The mToT for the first line treatment with the other EGFR-inhibitors (afatinib, dacomitinib, erlotinib and gefitinib) was 9.4 months (CI: 8.2-11.2), and total mTToT was 15.8 months (CI: 13.7-18.1). Results for each individual treatment are presented in Supplementary Figure 3.

In total, 29 EGFR+ patients were treated with platinum doublet while 19 patients received quadruple treatment after targeted therapy. The mToT on these treatments were 3.0 and 2.6 months, respectively (Supplementary Figure 2).

ALK+

There were 131 patients defined as having ALK+ disease. Among these, 88% patients (n=115) received systemic treatment within the first three months since diagnosis (Figure 3). The most common first line treatments were alectinib (48% of those who received first line treatment, n=55), crizotinib (25%, n=29), and brigatinib (18%, n=21).

Of the 115 patients who received first line treatment, 44% patients (n=51) received second line treatment, most commonly alectinib (26%, n=14) or lorlatinib (22%, n=12). Among the remaining 64 patients who did not receive second line treatment, 61% patients (n=39) were still on first line treatment at the end of follow-up (LNR). Furthermore, 38% (n=24) died before reaching a subsequent treatment line. One patient stopped treatment after 27 months of first line treatment, but was still alive at the end of follow-up after 11 months without treatment.

Of the 51 patients who received a second line treatment, 39% (n=20) reached a third line, most commonly lorlatinib (30% of those who received a third line treatment, n=6). Among the remaining 31 patients who did not receive third line treatment, 52% patients (n=16) were still on second line treatment with alectinib, lorlatinib, ceritinib or crizotinib at the end of follow-up (LNR), whereas 42% (n=13) died while on second line treatment. Two patients stopped treatment but were still alive at the end of follow-up.

Swimmer plots showing the length of treatment duration for each ALK+ patient is presented in Supplementary Figure 4B.

Patients treated with alectinib in first line had a mToT on alectinib of 20 months (CI: 14.7-23.7). When combining all lines of treatment, the mTToT was 28 months (CI: 18-NA) (i.e., median time on subsequent treatment was 8 months). Those who received lorlatinib had the longest time on second-line treatment (median of 13 months, CI: 5.3-NA) (Supplementary Figure 1).

Patients treated with brigatinib in first line had a mToT of 11 months (CI: 4.7-NA), while their mTToT for all lines of treatment was 16 months (CI: 11.1-NA). For first line crizotinib, corresponding numbers were 7 (CI: 2.9-21.6) and 19 months (CI: 10.5-37.0).

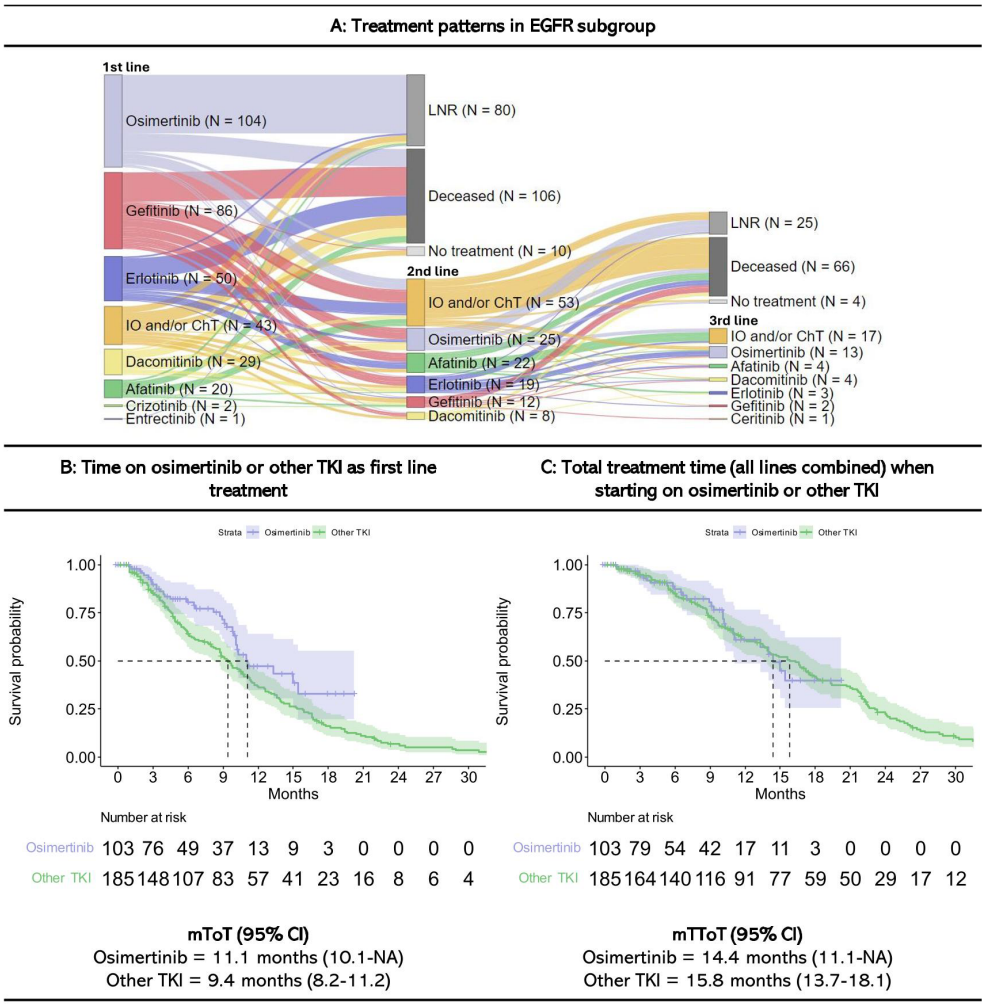

FIGURE 2
Treatment patterns and time on treatment for EGFR+ patients starting treatment within three months since diagnosis. Figures are restricted to EGFR patients who received treatment within the first three months since diagnosis. 114 patients neverreceived systematic treatment within the first three months since diagnosis. A detailed description of treatment patterns by patient is provided in Supplementary Figure 4. IO, Immunotherapy; ChT, Chemotherapy; LNR, Line not reached; Deceased, Dead prior to reaching line; mToT, median time on treatment; mTToT, median total time on treatment; TKI, Tyrosine Kinase Inhibitors (other TKI includes afatinib, dacomitinib, erlotinib and gefitinib); CI, confidence interval. **(A)** Treatment patterns, **(B)** Time on osimertinib or other TKI in first line, and **(C)** Total treatment time (all lines combined) when starting on osimertinib or other TKI in EGFR+ patients.

ROS1+

38 patients were assigned to the ROS1+ subgroup, of whom 58% (n=22) received systemic treatment within three months since diagnosis (Figure 4). Even though targeted therapy was available, the most common first line treatment was IO and/or ChT (59% of those who received first line treatment, n=13). Of the patients receiving first line treatment, 31% (n=7) never received second line treatment, while 41% (n=9) were still on first line treatment at the end of follow-up on.

Swimmer plots showing the length of treatment duration for each ROS1+ patient is presented in Supplementary Figure 4C.

The five patients treated with crizotinib as first line therapy had a mToT of 5 months (CI: 2.4-NA), and a mTToT of 18 months (CI: 4.9-NA) (i.e., the treatment given post crizotinib resulted in 13 more months on treatment).

Overall survival

For all patients assigned to biomarker subgroups, median OS was 19 months (CI: 16.5-21.2) for those diagnosed between 2015 and 2019, and 23 months (CI: 19.5-NA) for those diagnosed between 2020 and 2022 (Figure 5). Median OS among EGFR+ patients was 18 months (CI: 15.3-19.3) and 23 months (CI: 15.6-NA) for those diagnosed between 2015-2019 and 2020-2022, respectively. Median OS among ALK+ patients diagnosed in the earlier years was 24 months (CI: 17.4-54.7), and not reached for those diagnosed between 2020 and 2022 (CI: 23.3-NA). OS for ROS1+ patients was not estimated due to small sample size. Other patients (no biomarker) with non-squamous NSCLC had a median OS of 5 months (CI: 4.9-5.8) (2015-2019) and 7 months (CI: 5.8-7.0) (2020-2022). 1-year and 2-year overall survival rates are presented in Supplementary Table 3.

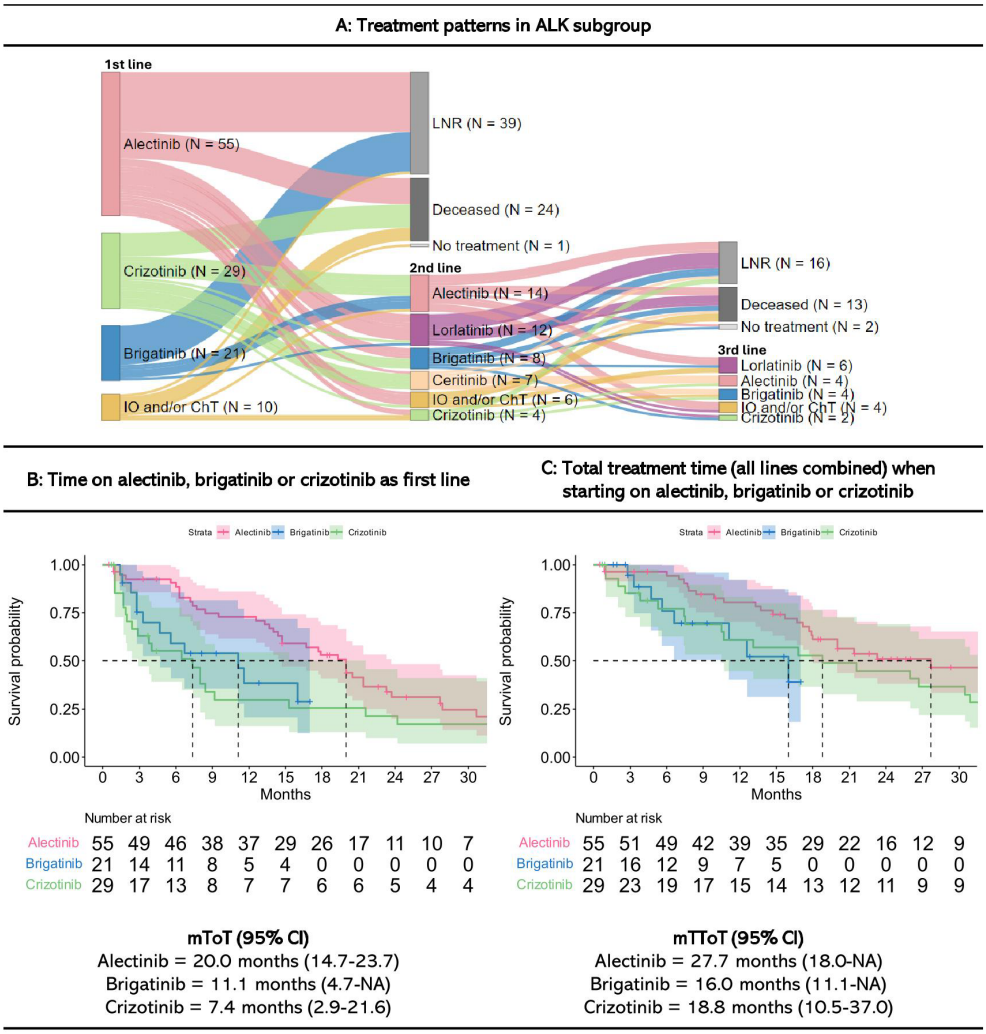

FIGURE 3
Treatment patterns and time on treatment for ALK+ patients starting treatment within three months since diagnosis. Figures are restricted to patients who received treatment within the first three months since diagnosis. 16 patients never received systematic treatment within the first three months since diagnosis. A detailed description of treatment patterns by patient is provided in Supplementary Figure 4. IO, Immunotherapy; ChT, Chemotherapy; LNR, Line not reached; Deceased, Dead prior to reaching line; NA, Not annotated; mToT, median time on treatment; mTToT, median total time on treatment; CI, confidence interval. **(A)** Treatment patterns, **(B)** Time on alectinib, brigatinib, and crizotinib as first line, and **(C)** Total treatment time (all lines combined) when starting on alectinib, brigatinib or crizotinib in the ALK+ subgroup.

Discussion

Most patients diagnosed with advanced non-squamous NSCLC with a confirmed biomarker for EGFR, ALK or ROS1 in Norway from 2015 to 2022 received systemic treatment within the first three months since diagnosis (75%, 88%, and 58%, respectively). For EGFR+ patients, the mToT was 11.1 months osimertinib in first line, compared to 9.4 months for the other EGFR-inhibitors. ToT on platinum doublet or quadruple treatment following targeted therapy was limited and similar for both regimens. Among those who received an ALK-inhibitor in the first line, mToT in first line were longer for alectinib (20.0 months) compared to brigatinib (11.1 months) and crizotinib (7.4 months). For all patient subgroups, the mOS was higher for patients diagnosed in 2020-2022 compared to patients diagnosed in 2015-2019, but the survival improvement was larger for patients receiving targeted therapies than for other patients.

Our CRN data does not contain information on progression dates, and response evaluations are not always done as stringent in clinical practice as in trials. However, the ToT we observed may serve as an indirect measure of progression-free survival (PFS) (21). In ARCHER1050, the authors report a mPFS of 14.7 months for dacomitinib and 9.2 months for gefitinib for EGFR+ patients (22). The results are somewhat higher than our estimated mToT (8.2 months for dacomitinib and 8.9 months for gefitinib). In the FLAURA trial, the authors found a mPFS of 18.9 months for osimertinib and 10.2 months for patients treated with erlotinib or gefitinib (23). In our data, mToT on osimertinib was 11.1 months while the other EGFR inhibitors had 2-3 months shorter mToT. The ALEX study (24) reported a mPFS of 34.8 months for alectinib and

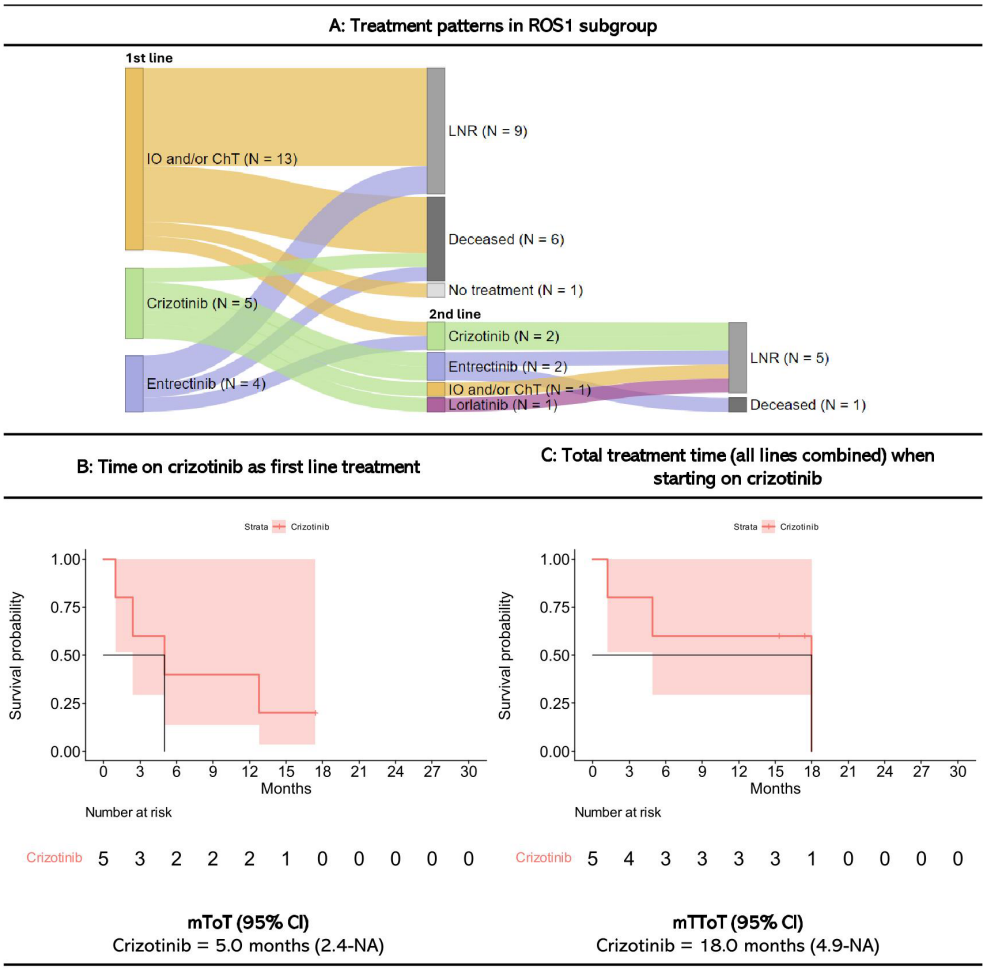

FIGURE 4
Treatment patterns and time on treatment for ROS1+ patients starting treatment within three months since diagnosis. Figures are restricted to ROS1 patients who received treatment within the first three months since diagnosis. 16 patients never received systematic treatment within the first three months since diagnosis. A detailed description of treatment patterns by patient is provided in Supplementary Figure 4. IO, Immunotherapy; ChT, Chemotherapy; LNR, Line not reached; Deceased, Dead prior to reaching line; mToT, median time on treatment; mTToT, median total time on treatment; CI, confidence interval. **(A)** Treatment patterns, **(B)** Time on crizotinib as first line treatment, and **(C)** Total treatment time (all lines combined) when starting on crizotinib for ROS1+ patients.

10.9 months for crizotinib, while it was 24.7 months for brigatinib and 9.4 months for crizotinib (results from the non-Asian population) in the ALTA 1L study (25). Similar results have also been reported by researchers using real-world data (26, 27). In comparison, we found a mToT of 20.0 months (alectinib), 11.1 months (brigatinib), and 7.4 months (crizotinib), which corresponds to findings from a population-based study from Denmark (12). A North American study investigating time on lorlatinib as second line treatment for ALK+ patients (28) found comparable results to our study, with mToT of 15.3 months for lorlatinib in second line. In the PROFILE 1001 (29), the reported mPFS for crizotinib in ROS1+ patients was 19.3 months, compared to a mToT of 5 months in our study. Our estimated mToT is also lower than findings from previous real world evidence studies. A sytematic litterature review and meta-analysis found a mPFS 14.5 months for crizotinib in ROS1+ patients which is more in line with the results from PROFILE 1001 (30). The patients in our data are older (median age is 74) than in PROFILE 1001 (median age 55) and in the sytematic litterature review where the median age ranged from 48-68. The follow-up time and sample size for ROS1+ patients in our study were limited due to the relative recent introduction of ROS1+testing in Norway.

Shorter ToT observed in clinical practice than in randomized controlled trials may have several explanations. Participants in clinical trials are in general younger, have better performance status, less comorbidity, and are usually followed more closely than most patients seen in the clinic. In addition, we excluded patients who develop metastases after receiving potentially curative treatment. These patients may have a better prognosis than those diagnosed with *de novo* advanced disease (31).

In our study, the median OS for EGFR+ patients increased from 18 months for those diagnosed in 2015-2019 to 23 months for those diagnosed in 2020-2022. The ARCHER1050 study reported a mOS of 34.1 months in the dacomitinib arm, and 27.0 months in the gefitinib arm (30), while the FLAURA study reported a mOS of 38.6 months for patients on osimertinib and 31.8 months among those

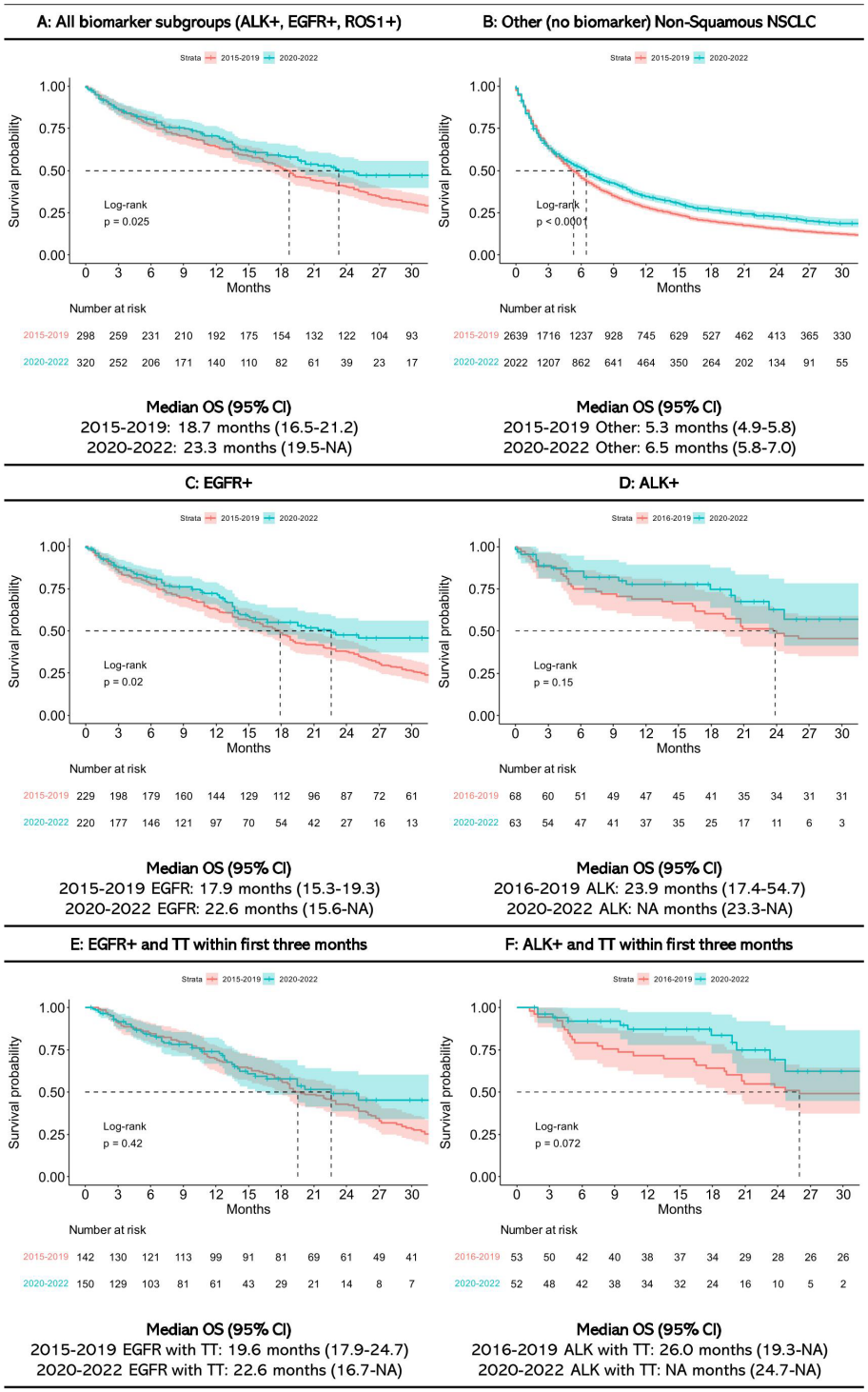

FIGURE 5
Overall survival in **(A)** All biomarker subgroups, **(B)** Other Non-Squamous NSCLC, **(C)** EGFR+, **(D)** ALK+, **(E)** EGFR+ and targeted treatment (TT) within first three months, and **(F)** ALK+ and TT within first three months.

receiving erlotinib or gefitinib (32). The median 1-year OS increased from 69% (95% CI: 59-81%) for ALK+ patients diagnosed in 2016-2019 to 78% (95% CI: 68-89%) for those diagnosed in 2020-2022. In the ALEX study, the 1-year OS for patients in the alectinib arm was 84%, while it was 83% for those in the crizotinib arm (24). Treatment switches, a more heterogenous population (as discussed above regarding ToT) may explain the survival differences between these trials and our study cohort. For example, a study concluded that patients treated with osimertinib in first line who were ineligible for the FLAURA-trial had 18 months shorter median OS than those who were eligible for that trial (33). Although our study does not enable us to assess a potential causal relationship between the introduction of targeted therapies in advanced NSCLC and increased OS, we did, in line with a

previous study (5), observe an OS improvement after the introduction of targeted therapies in general, and with the introduction of later generation agents.

The main strength of this study lies in the completeness of our CRN which covers 99.2% of all lung cancer patients in Norway. Furthermore, our health care services are public, and access to services is regarded independent of income, societal status, age, etc., although some differences are unveiled (34). Thus, the national registries cover virtually all Norwegian NSCLC cancer patients and much information about the treatment they receive. National treatment guidelines are well recognized by the clinical communities and are believed to ensure quite uniform treatment across hospitals and regions. However, the study has several limitations. First, we did not have information on oral drug treatment received by participants in clinical trials (e.g., the TREM-study (35) which offered second-line osimertinib (enrolment period 2015-2017) or the ongoing FIOL-study which offered first-line osimertinib therapy to EGFR+ patients (enrolment period 2018-2022) (36)), which probably explains why a lower proportion of EGFR patients (88.3%) in our cohort were recorded to have received targeted therapy than ALK+ patients (94.1%). Second, methods for molecular testing vary between hospitals, but our Cancer Registry do not include information on the methods used. Third, although ROS1 testing was implemented in 2019, the results were not reported to CRN prior to 2022. Fourth, EGFR/ALK status was missing in the CRN for 30-36% of the patients between 2017 and 2022. Test rates for EGFR and ALK increased during the study period from 75% to 85% for EGFR, and from 70% to 89% for ALK patients (37, 38). Thus, the assignment to subgroups was made based on the treatment received for 4.0% of the EGFR+ patients (we exclude erlotinib-treatment for allocation to this group, but this accounted for only 30 patients and is not likely to have influenced our results), 9.2% of the ALK+ patients, and 5.3% for ROS + patients. Although having a confirmed test result is preferable, we consider it unlikely that patients have received these specific targeted therapies without having the relevant oncogenic alteration. Fifth, we only had data on drugs dispensed to patients and DDD, not prescribed doses. Some patients may have used a higher or lower dose than the DDD, which may influence the estimated ToT. Several factors may determine the choice of drug treatment (e.g., clinician or patient preferences) and whether the patient discontinue treatment. Most importantly, our CRN does not contain information on whether treatments were discontinued due to toxicity, whether treatment was continued beyond progression, and we did not assess whether e.g. chemotherapy was added to targeted therapy. This hampers interpretation of the data on treatment beyond the first line. Most notably, the quadruple combination does not appear to provide any clinical benefit over chemotherapy alone, but the numbers are small. Finally, since the different drugs became available at different timepoints, the observation period varies, which might explain why the total ToT did not increase with the introduction of osimertinib as first-line treatment of EGFR+ patients, whereas the survival time did improve.

The treatment landscape for advanced NSCLC has changed rapidly over the last years, and studies like ours can serve as important evaluations of to what extent changes in diagnostic workup, especially molecular testing, and treatment have been implemented. During the study period, only targeted therapies for EGFR+, ALK+, and ROS1+ NSCLC were available at public hospitals in Norway, and these were the subgroups with sufficient follow-up data to include in this study. Currently, more targeted therapies are available and NSCLC tumors are now being tested for a broader range of oncogenic drivers. Furthermore, reports like ours serve as valuable supplements to results from randomized controlled trials on selected patients which inform both clinicians, patients, relatives and decision makers in health care about the clinical impact of new therapies. Considering that high costs of new cancer drugs have become a challenge for most health services, such data might also be used to support both primary and *post-hoc* evaluations of cost-effectiveness of drugs. Economic evaluations are commonly based on data from trials, including participants that do not necessarily represent the typical patients seen in the clinic. Registry data as presented in this report may provide valuable information to decision makers when seen in combination with the results from trials.

Conclusion

The vast majority of Norwegian advanced non-squamous NSCLC patients with targetable oncogenic alterations receive appropriate targeted therapy, and these patients have a much longer survival time than patients without such alterations, confirming the effectiveness of these therapies in patients seen in everyday clinical practice. There was an encouraging survival improvement during the study period which may be attributed to the introduction of later generation agents, though the observed mToT for the targeted therapies was shorter than reported mPFS in clinical trials.

Data availability statement

According to Norwegian legislation, the Norwegian Data Protection Authority and the Norwegian Directorate of eHealth, we are not allowed to share original study data publicly. Requests to access these datasets should be directed to helsedata.no, service@helsedata.no.

Ethics statement

Written informed consent was not obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article because the Regional Ethics Commitee (REK) waived the requirement for written conset. This project was evaluated by REK South-East D (reference number 485084).

Author contributions

JN: Data curation, Formal analysis, Visualization, Writing – original draft. AB: Conceptualization, Funding acquisition, Project administration, Writing – review & editing. ØH: Conceptualization,

Funding acquisition, Methodology, Project administration, Writing – review & editing. CB: Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Visualization, Writing – original draft. IE: Conceptualization, Data curation, Formal analysis, Methodology, Writing – original draft. FO: Formal analysis, Methodology, Visualization, Writing – original draft. ÅH: Methodology, Supervision, Validation, Visualization, Writing – review & editing. LF: Conceptualization, Methodology, Supervision, Validation, Visualization, Writing – review & editing. OB: Conceptualization, Supervision, Validation, Visualization, Writing – review & editing. BG: Conceptualization, Investigation, Methodology, Supervision, Validation, Visualization, Writing – original draft.

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Conflict of interest

JN, IE, FO, and CB are affiliated with Oslo Economics and have performed consultancy assignments for several private and public companies in recent years. ØH is employed by Pfizer Norway AS and owns shares in Pfizer. AB is a former employee of Pfizer Norway and was at the time of manuscript submission employed by Astra Zeneca Norway. ÅH, OB, and BG have all received payments from multiple pharmaceutical companies in recent years, including from Pfizer Norway related to work with this study.

The remaining author declares 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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Generative AI statement

The author(s) declare that no Generative AI was used in the creation of this manuscript.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2025.1506041/full#supplementary-material

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Adverse event profiles of EGFR-TKI: network meta-analysis and disproportionality analysis of the FAERS database

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Background: Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors (EGFR-TKIs) in clinical use show promise but can cause AEs, impacting patients' wellbeing and increasing costs.

Methods: This study utilized two methods: network meta-analysis (NMA) and disproportionality analysis (DA). For NMA, we searched PubMed, Embase, Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov up to 10 September 2024, for phase II/III RCTs comparing EGFR-TKI monotherapy with chemotherapy or other EGFR-TKIs. Using STATA 18.0, we calculated odds ratios (ORs) with 95% confidence intervals (CIs) and assessed heterogeneity via Chi-squared and I^2 tests. Adverse events (AEs) were ranked using the surface under the cumulative ranking curve (SUCRA). For DA, we analyzed FAERS data (January 2004-June 2024), evaluating AE signals with reporting odds ratios (RORs) and 95% CIs; signals were considered significant if the ROR and its 95% CI lower bound exceeded 1. Primary outcomes for NMA included all-grade AEs, grade ≥3 AEs, specific AEs, and AE-related mortality. For DA, outcomes included EGFR-TKI as the primary AE cause, time from treatment to AE, and AE-related mortality.

Results: NMA: 48% of EGFR-TKI patients experienced AEs, with 32.7% being severe. Afatinib showed highest toxicity; Icotinib was safest. Osimertinib was associated with highest risks of leukopenia (8%) and thrombocytopenia (9%). DA: Osimertinib had strongest links to cardiac diseases and blood/lymphatic disorders. Gefitinib had the strongest signal for interstitial lung diseases; Erlotinib for anorexia. Most AEs occurred within 30 days, but cardiac disorders had a median onset of 41 days. Osimertinib had the highest AE-related mortality, with cardiac disorders leading in fatalities.

Conclusion: This study used NMA and DA to explore EGFR-TKI-related AEs. Drugs varied in AE profiles, mostly mild, but Osimertinib and Dacomitinib were associated with more severe events. Osimertinib carried a high cardiac risk, delayed onset, and high mortality. Thus, comprehensive patient assessment and close monitoring are crucial with EGFR-TKI use.

KEYWORDS

epidermal growth factor receptor, EGFR, network meta-analysis, disproportionality analysis, FAERS database, real-world study, pharmacovigilance analysis

1 Introduction

EGFR is a tyrosine kinase receptor critical for tumor cell proliferation and survival. Upon ligand binding, EGFR becomes activated, forming dimers that stimulate downstream signaling pathways, promoting cell differentiation, proliferation, and potentially carcinogenesis. EGFR overexpression is closely linked to tumor angiogenesis and local metastasis (Sabbah et al., 2020; Sigismund et al., 2018). Approved EGFR Tyrosine Kinase Inhibitors (TKIs), such as Gefitinib, Erlotinib, Lapatinib, and Icotinib, constitute the first-generation EGFR inhibitors. They reversibly bind to the EGFR's PTK domain, effectively blocking ATP binding and inhibiting EGFR activation and cellular proliferation (Dutta and Maity, 2007; Sabbah et al., 2020; Sigismund et al., 2018). In contrast, second-generation EGFR-TKIs, including Afatinib, Neratinib, and Dacomitinib, covalently bind to EGFR, achieving irreversible kinase inhibition and demonstrating superior efficacy compared to first-generation TKIs (Stasi and Cappuzzo, 2014). The third-generation EGFR inhibitor Osimertinib stands out by forming stable covalent bonds with EGFR harboring the T790M mutation, addressing resistance issues associated with first- and second-generation TKIs (Nagasaka et al., 2021; Li et al., 2022; Dong et al., 2021).

Additionally, Vandetanib, which inhibits kinases beyond EGFR, is classified as a multi-kinase inhibitor. These drugs have been approved for treating various solid tumors, including non-small cell lung cancer (NSCLC), head and neck cancer, pancreatic cancer, and esophageal cancer (Kelly et al., 2015; Dutton et al., 2014; Propper et al., 2014; Harrington et al., 2015). However, they are associated with a range of toxicities, such as diarrhea, rash, mucositis, and fatigue (Zhang et al., 2017; Sheng et al., 2016), significantly impacting patients' physiological functions and quality of life, leading to reduced adherence and increased treatment costs. Notably, EGFR-TKI toxicity profiles vary across trials, prompting further investigation into this area.

We investigated the characteristics of AEs associated with EGFR-TKIs using NMA and DA based on the FAERS database. NMA, which integrates evidence from multiple studies, provides a comprehensive and indirect assessment of different intervention measures, thereby resolving issues of missing or conflicting evidence and enhancing the reliability of the results (Florez et al., 2024; Zhang et al., 2017; Sheng et al., 2016). DA leverages extensive spontaneous reporting data from the global FAERS database to capture the diversity and complexity of EGFR-TKI-related AEs, promptly identify potential safety issues, and explore the distribution

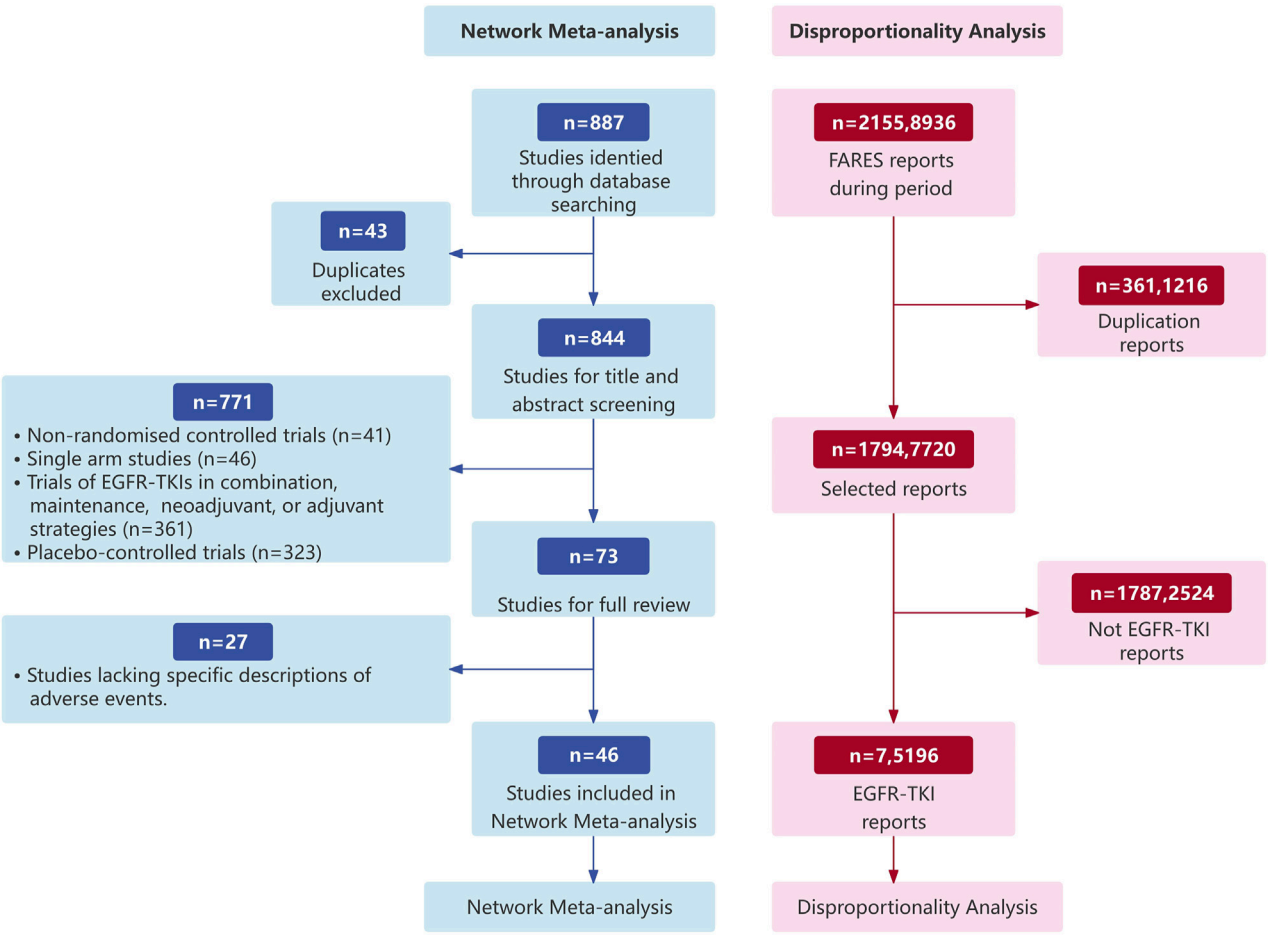

FIGURE 1
Flow diagram of the study design.

TABLE 1 PubMed retrieval strategy.

No	Query
#1	"Receptors, Vascular Endothelial Growth Factor" [Mesh]
#2	((((((((((((((((((((Epidermal Growth Factor Receptor Tyrosine Kinase inhibitor [Title/Abstract]) OR (EGFR-TKI [Title/Abstract])) OR (Epidermal Growth Factor Receptor Kinase [Title/Abstract])) OR (Epidermal Growth Factor Receptor Tyrosine Kinase [Title/Abstract])) OR (EGF Receptors [Title/Abstract])) OR (Receptor, Epidermal Growth Factor [Title/Abstract])) OR (VEGF [Title/Abstract])) OR (Vascular Endothelial Growth Factor [Title/Abstract])) OR (VEGF Receptors [Title/Abstract])) OR (Receptors, VEGF [Title/Abstract])) OR (Vascular Endothelial Growth Factor Receptor [Title/Abstract])) OR (VEGF Receptor [Title/Abstract])) OR (Gefitinib [Title/Abstract])) OR (Erlotinib [Title/Abstract])) OR (Icotinib [Title/Abstract])) OR (Afatinib [Title/Abstract])) OR (Dacomitinib [Title/Abstract])) OR (Osimertinib [Title/Abstract])) OR (Vandetanib [Title/Abstract]))
#3	#1 OR #2

characteristics of these AEs across different populations (Fang et al., 2014; Fusaroli et al., 2024). The real-time updating capability of the FAERS database ensures the timeliness and accuracy of our analysis on EGFR-TKI-related AEs. Through these two approaches, we conducted an in-depth analysis of the characteristics of EGFR-TKI-related AEs.

2 Materials and methods

This study employed a hybrid approach, integrating two methodologies: NMA and DA. The latter was grounded in the FAERS database, with the objective of elucidating the characteristics of AEs associated with EGFR-TKI drugs (Figure 1).

2.1 Network meta-analysis

2.1.1 Search strategies

We searched the PubMed, Embase, Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov databases using 'NSCLC' and "EGFR" as primary search terms, limited to RCTs, to identify relevant literature in all languages up to 10 September 2024. Additionally, we examined the reference lists of related articles to find additional studies. The detailed search strategy is presented in Table 1.

2.1.2 Study selection

Inclusion criteria: (1) Phase II or III RCTs comparing the safety of EGFR-TKI monotherapy with chemotherapy or other EGFR-TKIs; (2) Studies must provide detailed data on systemic AEs (including all grades and/or ≥ Grade 3) and/or specific AEs (all grades).

Exclusion criteria: (1) Trials involving EGFR-TKIs in combination therapy, maintenance therapy, neoadjuvant therapy, or adjuvant therapy; (2) Trials comparing EGFR-TKIs with monoclonal antibodies, immunotherapy, certain pathway inhibitors, or other non-conventional chemotherapy methods; (3) Trials involving treatments not approved by any food and drug administration authority; (4) Exclusion of original trial data if safety results have been updated in subsequent data from mature or longer follow-up periods to avoid duplication and obsolescence.

2.1.3 Data extraction

The primary outcomes were all-grade and ≥Grade 3 systemic AEs. Two researchers (T.C. and J.Y.) independently extracted information from each study into a predefined electronic spreadsheet, including baseline characteristics and the number of patients experiencing AEs. AEs designated as treatment-related were preferred; however, if such data were unavailable in the trial, any reported AE data were used instead. Data from supplementary materials were also checked and extracted. When necessary, study authors and pharmaceutical companies were contacted to request complete and updated information.

2.1.4 Risk of bias assessment

The research team (X.Y.L., M.J.G., J.W.L.) independently assessed the risk of bias for each study using the Cochrane Risk of Bias Tool (Higgins et al., 2011; Fang et al., 2014; Fusaroli et al., 2024). The following potential sources of bias were considered: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases. Studies were categorized as having a low risk, unclear risk, or high risk of bias. A risk of bias graph was generated using Review Manager version 5.4.

2.1.5 Statistical analysis

All analyses were conducted using STATA 18.0 software. OR and their 95% confidence intervals (95% CI) were calculated to evaluate binary variables. Heterogeneity was assessed using the Chi-squared test and I^2 statistics. Significant statistical heterogeneity was indicated when $I^2 > 50\%$, necessitating the use of a fixed-effects model; otherwise, a random-effects model was employed (Peters et al., 2006; Zintzaras and Ioannidis, 2005). Statistical significance was set at $P < 0.05$. The NMA integrated both direct and indirect evidence. In each loop, IF were used to assess heterogeneity. If the 95% confidence interval of IF included zero, it indicated no significant statistical differences (Song et al., 2003; Peters et al., 2006; Zintzaras and Ioannidis, 2005). Sensitivity analyses were conducted to assess the robustness of the results. The SUCRA was employed to rank AEs associated with EGFR-TKI and chemotherapy, where a higher SUCRA value indicates greater toxicity of the intervention (Salanti et al., 2011; Peters et al., 2006; Zintzaras and Ioannidis, 2005).

TABLE 2 Algorithms we used for signal detection.

Algorithms	Equation	Criteria
ROR	$ROR = \frac{(a/c)}{(b/d)} = \frac{ad}{bc}$	Lower limit of 95% CI > 1, N ≥ 3
	$95\%CI = eln\ (ROR) \pm 1.96\ (1/a+1/b+1/c+1/d)^{0.5}$	
Equation		
a: number of reports containing both the target drug and target adverse drug reaction		
b: number of reports containing other adverse drug reaction of the target drug		
c: number of reports containing the target adverse drug reaction of other drugs		
d: number of reports containing other drugs and other adverse drug reactions		
95%CI: 95% confidence interval		
ROR: Reporting Odds Ratio		

2.2 Disproportionality analysis

2.2.1 Data collection

The data for this study were obtained from the FAERS database. We downloaded AE reports from the FDA website covering the period from the first quarter of 2004 to the second quarter of 2024. Due to the presence of duplicate reports in the FAERS database, we only utilized the most recent reports for each patient and those that included complete age information. In FAERS, the descriptions of AEs adhere to the Medical Dictionary for Regulatory Activities (MedDRA), established by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). For our study, the names of AEs were based on MedDRA version 27.0. EGFR-TKI drugs were defined as the following eight medications: Gefitinib, Erlotinib, Icotinib, Afatinib, Dacomitinib, Osimertinib and Vandetanib, Lapatinib and Neratinib were excluded from this analysis due to its frequent use in combination therapy, which complicates the accurate assessment of AEs for individual drugs. In the FAERS database, AEs are classified at different levels, including "System Organ Classes (SOC)" based on organ systems and "Preferred Terms (PT)" based on specific AEs. We extracted clinical characteristics of the a forementioned drugs, including gender, age, reporting region, and reporter. Additionally, we collected data on the number of AEs, the time elapsed since the initial medication use, and the number and proportion of deaths.

2.2.2 Data deduplication

Due to the self-reporting nature of data collection in the FAERS database, instances of duplicate or withdrawn/deleted reports are common. To address this issue, FDA official guidelines provide specific rules for data deduplication and lists of reports to be deleted. This study rigorously followed the guidelines provided on the FDA's official website for data cleaning. The deduplication process involved first using the method recommended by the FDA. Specifically, we selected the PRIMARYID, CASEID, and FDA_DT fields from the DEMO table and sorted them by CASEID, FDA_DT, and then PRIMARYID. For records with identical CASEIDs, the one with the most recent FDA_DT was retained; if both CASEID and FDA_DT were the same, the record with the highest PRIMARYID value was kept. Additionally, since the first quarter of 2019, each quarter's data package includes a list of reports to be deleted. After initial deduplication, these reports were further removed based on their CASEIDs as listed.

2.2.3 Statistical analysis

The DA is used to detect signals of AEs induced by EGFR-TKIs. This analysis compares the proportion of AE reports for EGFR-TKIs with those for all other drugs. The detection of AE signals is evaluated through the ROR and the 95% confidence interval (CI) (Table 2). Specifically, when both the ROR and the lower limit of the corresponding 95% CI are greater than 1, the risk signal is considered significant (Oshima et al., 2018; Hamano et al., 2021). All data analyses were independently conducted by two or more authors. All statistical analyses were performed using SAS 9.4.

3 Results

3.1 Network meta-analysis

3.1.1 Description of selected studies

Initially, we reviewed a total of 887 potential records from databases. After removing duplicates, 884 records were screened based on their titles and abstracts, and 73 full-text articles were retrieved and reviewed (Figure 1). Ultimately, 46 RCTs met the inclusion criteria, encompassing 15,773 patients who received one of eight different treatments, including Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors (EGFR TKIs) and chemotherapy. Among these participants, 6,954 (44.4%) were female. The median follow-up duration was 21.0 months. The main characteristics of all studies are reported in Table 3.

Figure 2 illustrates the evidence network. Figure 3 depicts the impact of each direct comparison on the overall effect estimate within the network. Figure 4 provides a comprehensive assessment of the risk of bias, with the primary sources of high risk being related to participant and personnel blinding, largely due to the considerable proportion of open-label studies.

TABLE 3 Baseline characteristics of studies included in the network meta-analysis.

No	Study (phase)	Tumor type	No. of patients (female%)	Median age (Year)	Treatment	Median follow-up (Months)
1	AURA3, 2020 (III) (Papadimitrakopoulou et al., 2020)	NSCLC	279 (62)	62	Osimertinib 80 mg, QD	23.5
			140 (69)	63	Pemetrexed 500 mg/m2 +Carboplatin AUC = 5/Cisplatin 75 mg/m2, Q3W	20.3
2	LUX-Lung 7, 2017 (IIb) (Paz-Ares et al., 2017)	NSCLC	160 (57)	63	Afatinib 40 mg, QD	42.6
			159 (67)	63	Gefitinib 250 mg, QD	42.6
3	ARCHER1050, 2021 (III) (Cheng et al., 2021)	NSCLC	225 (56)	61	Gefitinib 250 mg, QD	47.9
			227 (64)	62	Dacomitinib 45 mg, QD	47.9
4	WJOG5108L, 2016 (III) (Urata et al., 2016)	NSCLC	276 (54.3)	67	Erlotinib 150 mg, QD	26.5
			275 (54.5)	68	Gefitinib 250 mg, QD	25.1
5	CTONG0901, 2017 (III) (Yang et al., 2017)	NSCLC	128 (53.1)	NG	Erlotinib 150 mg, QD	22.1
			128 (53.9)	NG	Gefitinib 250 mg, QD	22.1
6	LUX-Head and Neck 3,2019 (III) (Guo et al., 2019)	HNSCC	228 (15)	55.5	Afatinib 40 mg, QD	6.4
			112 (12)	58	Methotrexate 40mg/m2, QW	6.4
7	ARCHER1009, 2014 (III) (Ramalingam et al., 2014)	NSCLC	439 (34)	64	Dacomitinib 45 mg, QD	7.1
			439 (37)	62	Erlotinib 150 mg, QD	7.1
8	Kim et al., 2012 (II) (Kim et al., 2012)	NSCLC	48 (85.4)	60	Erlotinib 150 mg, QD	NG
			48 (85.4)	56	Gefitinib 250 mg, QD	NG
9	ISTANA, 2010 (III) (Lee et al., 2010)	NSCLC	82 (32.9)	57	Gefitinib 250 mg, QD	NG
			79 (43)	58	Docetaxel 75mg/m2, Q3W	NG
10	LUX-Head and Neck 1,2015 (III) (Machiels et al., 2015)	HNSCC	322 (15)	60	Afatinib 40 mg, QD	6.7
			161 (15)	59	Methotrexate 40mg/m2, QW	6.7
11	LUX-Lung 8, 2015 (III) (Soria et al., 2015)	LUSC	398 (16)	65	Afatinib 40 mg, QD	6.7
			397 (17)	64	Erlotinib 150 mg, QD	6.7
12	Li et al., 2014 (II) (Li et al., 2014)	LUAD	61 (34.4)	54	Erlotinib 150 mg, QD	14.7
			62 (37.1)	55	Pemetrexed 500 mg/m2, Q3W	14.7
13	TAILOR, 2013 (III) (Garassino et al., 2013)	NSCLC	107 (29.4)	66	Erlotinib 150 mg, QD	33
			104 (33.6)	67	Docetaxel 75 mg/m2, Q3W or 35 mg/m2, Q4W	33
14	IFCT-0301, 2010 (II) (Morère et al., 2010)	NSCLC	43 (11.6)	70	Gefitinib 250 mg, QD	NG
			42 (21.4)	71	Docetaxel 75 mg/m2, Q3W	NG
15	ICOGEN, 2013 (III) (Shi et al., 2013)	NSCLC	200 (41.2)	57	Icotinib 125 mg, TID	NG
			199 (43.4)	57	Gefitinib 250 mg, QD	NG
16	Kim et al., 2016 (II) (Kim et al., 2016)	NSCLC	48 (27.1)	67	Gefitinib 250 mg, QD	60.6
			47 (29.8)	64	Pemetrexed 500 mg/m2, Q3W	60.6
17	Natale et al., 2009 (II) (Natale et al., 2009)	NSCLC	85 (61)	61	Gefitinib 250mg, QD	NG
			83 (58)	63	Vandetanib 300mg, QD	NG
18	PF-00299804, 2012 (II) (Ramalingam et al., 2012)	NSCLC	94 (41)	60	Dacomitinib 45 mg, QD	NG
			94 (40)	62	Erlotinib 150 mg, QD	NG

(Continued on following page)

TABLE 3 (*Continued*) Baseline characteristics of studies included in the network meta-analysis.

No	Study (phase)	Tumor type	No. of patients (female%)	Median age (Year)	Treatment	Median follow-up (Months)
19	V-15–32, 2008 (III) (Maruyama et al., 2008)	NSCLC	244 (38.4)	NG	Gefitinib 250 mg, QD	21
			239 (38.1)	NG	Docetaxel 60 mg/m2, Q3W	21
20	Stewart et al., 2009 (II) (Stewart et al., 2009)	HNSCC	158 (16)	NG	Gefitinib 250mg, QD	NG
			161 (16)	NG	Methotrexate 40mg/m2, QW	NG
21	SIGN, 2006 (II) (Cufer et al., 2006)	NSCLC	68 (30.8)	63	Gefitinib 250 mg, QD	9.2
			71 (30.1)	60	Docetaxel 75 mg/m2, Q3W	9.4
22	ENSURE, 2015 (III) (Wu et al., 2015)	NSCLC	110 (61.8)	58	Erlotinib 150 mg, QD	28.9
			104 (60.7)	56	Gemcitabine 1250 mg/m2 +Cisplatin 75 mg/m2, Q3W	27.1
23	HORG, 2013 (III) (Karampeazis et al., 2013)	NSCLC	166 (18.7)	65	Erlotinib 150 mg, QD	29
			166 (16.9)	66	Pemetrexed 500 mg/m2, Q3W	27.3
24	Lilenbaum et al., 2008 (II) (Lilenbaum et al., 2008)	NSCLC	52 (55.8)	NG	Erlotinib 150 mg, QD	NG
			51 (45.1)	NG	Carboplatin AUC = 6 +Paclitaxel 200 mg/m2, Q3W	NG
25	OPTIMAL, 2011 (III) (Zhou et al., 2011)	NSCLC	83 (58.5)	57	Erlotinib 150 mg, QD	15.6
			72 (59.7)	59	Gemcitabine 1000 mg/m2 +Cisplatin AUC = 5, Q3W	15.6
26	IPASS, 2009 (III) (Mok et al., 2009)	NSCLC	607 (79.5)	57	Gefitinib 250 mg, QD	5.6
			589 (79.1)	57	Carboplatin AUC = 5/6 +Paclitaxel 200 mg/m2, Q3W	5.6
27	KCSG-LU08-01, 2012 (III) (Sun et al., 2012)	NSCLC	68 (85.3)	58	Gefitinib 250 mg, QD	15.9
			67 (85.1)	64	Pemetrexed 500 mg/m2, Q3W	15.9
28	INTEREST, 2008 (III) (Kim et al., 2008)	NSCLC	729 (36.4)	61	Gefitinib 250 mg, QD	7.6
			715 (33.4)	60	Docetaxel 75 mg/m2, Q3W	7.6
29	DELTA, 2014 (III) (Kawaguchi et al., 2014)	NSCLC	150 (28.0)	68	Erlotinib 150 mg, QD	8.9
			150 (29.1)	67	Docetaxel 60 mg/m2, Q3W	8.9
30	TITAN, 2012 (III) (Ciuleanu et al., 2012)	NSCLC	196 (20.7)	59	Erlotinib 150 mg, QD	27.9
			213 (27.6)	59	standard docetaxel or pemetrexed dosing schedule	24.8
31	WJTOG3405, 2010 (III) (Mitsudomi et al., 2010)	NSCLC	87 (68.6)	64	Gefitinib 250 mg, QD	2.7
			88 (69.8)	64	Cisplatin 80 mg/m2 +Docetaxel 60 mg/m2, Q3W	2.7
32	EURTAC, 2012 (III) (Rosell et al., 2012)	NSCLC	84 (67.4)	65	Erlotinib 150 mg, QD	18.9
			82 (78.2)	65	Docetaxel 75 mg/m2 or gemcitabine 1250 mg/m2 +Cisplatin 75 mg/m2, Q3W	14.4
33	Heigener, 2014 (II) (Heigener et al., 2014)	NSCLC	144 (32.4)	76	Erlotinib 150 mg, QD	NG
			140 (32.4)	76	Carboplatin AUC = 5+Vinorelbine 25 mg/m2 on days 1 and 8, Q3W	NG
34	CONVINCE, 2017(III) Shi et al., 2017	NSCLC	148 (70.9)	56	Icotinib 125 mg, TID	NG
			137 (69.3)	56	Cisplatin 75 mg/m2 +Pemetrexed 500 mg/m2, Q3W	NG

(Continued on following page)

TABLE 3 (*Continued*) Baseline characteristics of studies included in the network meta-analysis.

No	Study (phase)	Tumor type	No. of patients (female%)	Median age (Year)	Treatment	Median follow-up (Months)
35	Han et al., 2017 (II) (Han et al., 2017)	NSCLC	41 (56.1)	NG	Gefitinib 250 mg, QD	NG
			40 (57.5)	NG	Pemetrexed 500 mg/m2 + Carboplatin AUC = 5, Q4W, 6 cycles	NG
36	IFCT-0504, 2015 (II) (Cadranel et al., 2015)	NSCLC	66 (38.8)	67	Erlotinib 150 mg, QD	69.4
			66 (39.4)	68	Paclitaxel 90 mg/m2 + Carboplatin AUC = 6, Q4W	69.4
37	LUX-Lung 6, 2014(III) (Wu et al., 2014)	NSCLC	242 (64)	58	Afatinib 40 mg, QD	16.6
			122 (68)	58	gemcitabine 1000 mg/m^2, on day 1 and day 8+ cisplatin 75 mg/m^2, on day 1	16.6
38	CTONG0806, 2014 (II) (Zhou et al., 2014)	NSCLC	81 (33.3)	58	Gefitinib 250 mg, QD	10.6
			76 (38.2)	56	Pemetrexed 500 mg/m2, Q3W	10.6
39	PROSE, 2014 (III) (Gregorc et al., 2014)	NSCLC	134 (26.1)	66	Erlotinib 150 mg, QD	32.4
			129 (29.5)	64	Pemetrexed 500 mg/m2 or Docetaxel 75mg/m2, Q3W	32.4
40	LUX-Lung3, 2013 (III) (Sequist et al., 2013)	NSCLC	229 (63.9)	62	Afatinib 40 mg, QD	16.4
			111 (67.0)	61	Pemetrexed 500 mg/m2 + Cisplatin 75 mg/m2, Q3W	16.4
41	First-SIGNAL, 2012 (III) (Han et al., 2012)	LUAD	159 (88.0)	57	Gefitinib 250 mg, QD	35
			150 (89.3)	57	Gemcitabine 1250 mg/m2 + Cisplatin 80 mg/m2, Q3W	35
42	Kelly et al., 2012 (IIb) (Kelly et al., 2012)	NSCLC	101 (32.6)	62	Erlotinib 150 mg, QD	NG
			97 (31.0)	63	Pralatrexate 190 mg/m2, Q4W	NG
43	Maemondo et al., 2010 (III) (Maemondo et al., 2010)	NSCLC	114 (63.2)	63.9	Gefitinib 250 mg, QD	17.6
			114 (64)	62.6	Paclitaxel 200 mg/m2 + Carboplatin AUC = 6, Q3W	17.6
44	INVITE, 2008 (II) (Crinò et al., 2008)	NSCLC	94 (22.7)	74	Gefitinib 250 mg, QD	6.4
			96 (26.3)	74	Vinorelbine 30 mg/m2, Q3W	6.2
45	ZEST,2011(III) (Natale et al., 2011)	NSCLC	623 (39)	61	Vandetanib 300mg, QD	7
			617 (36)	61	Erlotinib 150 mg, QD	7
46	BATTLE,2011(II) (Kim et al., 2011)	NSCLC	59(NG)	NG	Erlotinib 150 mg, QD	NG
			54(NG)	NG	Vandetanib 300mg, QD	NG

NSCLC, non-small cell lung cancer.
HNSCC, head and neck squamous cell carcinomas.
LUSC, lung squamous cell carcinoma.
LUAD, lung adenocarcinoma.
NG, not given.

3.1.2 Overview

Among the studies reviewed, 26 reported on the number of patients experiencing any grade of systemic AEs (AEs), while 32 documented those experiencing at least one grade 3 or higher AE. In the chemotherapy group, 2,221 patients (82.1%) experienced all-grade AEs, and 1,794 patients (46.1%) had grade 3 or higher AEs. Over 100 different types of specific AEs were reported based on their incidence and clinical relevance. Among them, 20 AEs of interest were identified, including Rash, Alopecia, Fatigue, Dry skin, Stomatitis, Anorexia, Nausea/Vomiting, Constipation, Myalgia/Arthralgia, Aspartate aminotransferase (AST) increased, Alanine aminotransferase (ALT) increased, Creatinine increased, Anemia, White blood cell decreased, Platelet count decreased, Dyspnea, Pneumonia, Insomnia, Chest pain, and Interstitial lung disease (ILD).

3.1.3 Systemic AEs

In a cohort of 5671 patients undergoing EGFR-TKI therapy, 48% reported experiencing at least one systemic AEs. Of these,

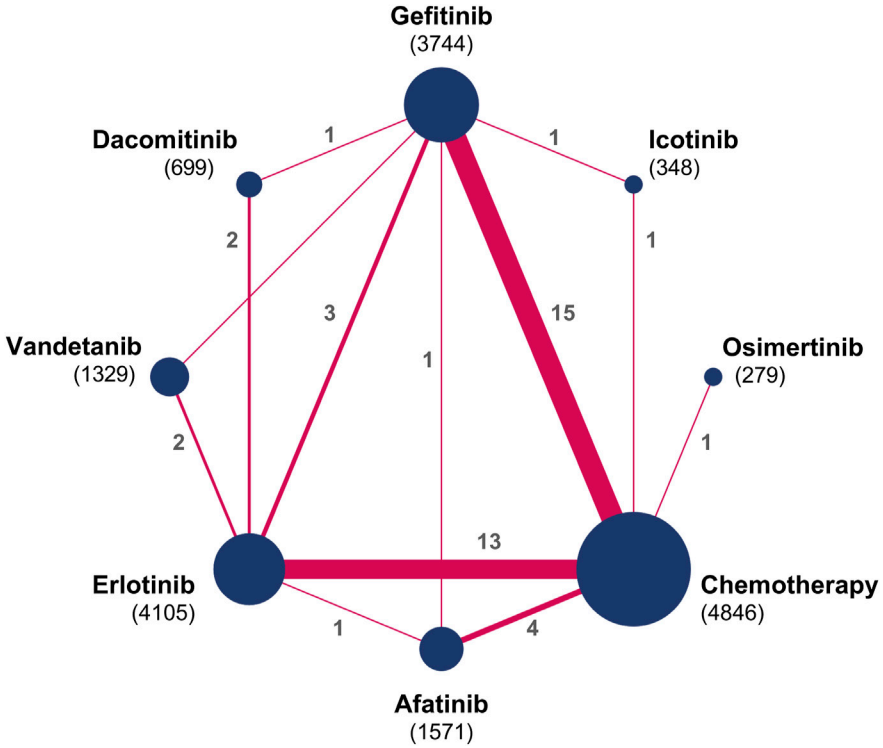

FIGURE 2
Network diagrams for comparisons on systemic AEs. Circular nodes denote treatments, with each node's size proportional to the total number of patients (in parentheses) assigned to that treatment. Lines signify direct comparisons; the width of each line corresponds to the number of trials (indicated beside the line) examining the respective comparison.

32.7% encountered AEs of grade three or higher severity. In contrast, within the chemotherapy group, the total incidence of any-grade AEs was 2221 individuals (82.1%), with 1794 (46.1%) suffering from AEs of grade three or above, as summarized in the Table 4. Notably, The study involving Vandetanib did not report data on the number of participants experiencing at least one systemic AE.

In terms of systemic all-grade AEs (Table 5, lower triangle), Afatinib induced the most frequent toxicity. Compared to Osimertinib, Afatinib showed significant differences in systemic all-grade AEs with other drugs, including chemotherapy. Dacomitinib was the second most toxic, significantly differing from Gefitinib and Icotinib. Among these, Icotinib was the safest EGFR-TKI, showing significant differences with all drugs except Osimertinib; Gefitinib was the second safest, significantly different from Erlotinib and Osimertinib.

In the context of AEs of grade≥3 (Table 5, upper triangle), chemotherapy exhibits the highest toxicity, significantly differing from Gefitinib, Erlotinib, and Icotinib. Among EGFR-TKIs, Afatinib is identified as the most toxic, also markedly different from Gefitinib, Erlotinib, and Icotinib, followed by Osimertinib. Notably, Icotinib stands out as the safest EGFR-TKI, with Gefitinib ranking second in terms of safety.

Comparative analysis demonstrated distinct safety profiles across EGFR-TKI generations. Among first-generation agents, icotinib exhibited a significantly lower risk of all-grade adverse events (AEs) compared to gefitinib and erlotinib ($p < 0.05$), whereas no statistically significant difference was observed between gefitinib and erlotinib. Although numerical variations existed in grade ≥3 AEs among the three agents, none achieved statistical significance. Within second-generation EGFR-TKIs, afatinib demonstrated a higher incidence of grade ≥3 AEs relative to dacomitinib ($p = 0.02$), while all-grade AE rates showed no inter-agent statistical disparity.

We ranked the drugs based on their Surface Under the Cumulative Ranking (SUCRA) values, as illustrated in Figure 5. For all-grade AEs, the ranking from highest to lowest toxicity is as follows: Afatinib (SUCRA = 95.4%), Dacomitinib (80.1%), Chemotherapy (56.2%), Erlotinib (53.5%), Osimertinib (33.4%), Gefitinib (27%), and Icotinib (4.5%). For grade 3 and higher AEs, the ranking is: Chemotherapy (92.9%), Afatinib (70.4%), Osimertinib (66.7%), Dacomitinib (61%), Erlotinib (37.4%), Gefitinib (15.5%), and Icotinib (6.1%).

3.1.4 Specific AEs

We conducted a statistical analysis of the incidence rates of AEs across all grades (Figure 6). Among all EGFR-TKI-induced AEs, rash had the highest incidence rate. Afatinib led to a 67% incidence rate of rash, followed by Gefitinib at 52%, and Vandetanib had the lowest incidence rate at 28%. Regarding Hepatic insufficiency, Gefitinib exhibited higher incidence rates than other EGFR-TKIs and chemotherapy, with an AST increased incidence rate of 24% and alanine ALT increased at 23%. Erlotinib had the next highest rates, with both AST and ALT increased at 19%. In terms of hematologic

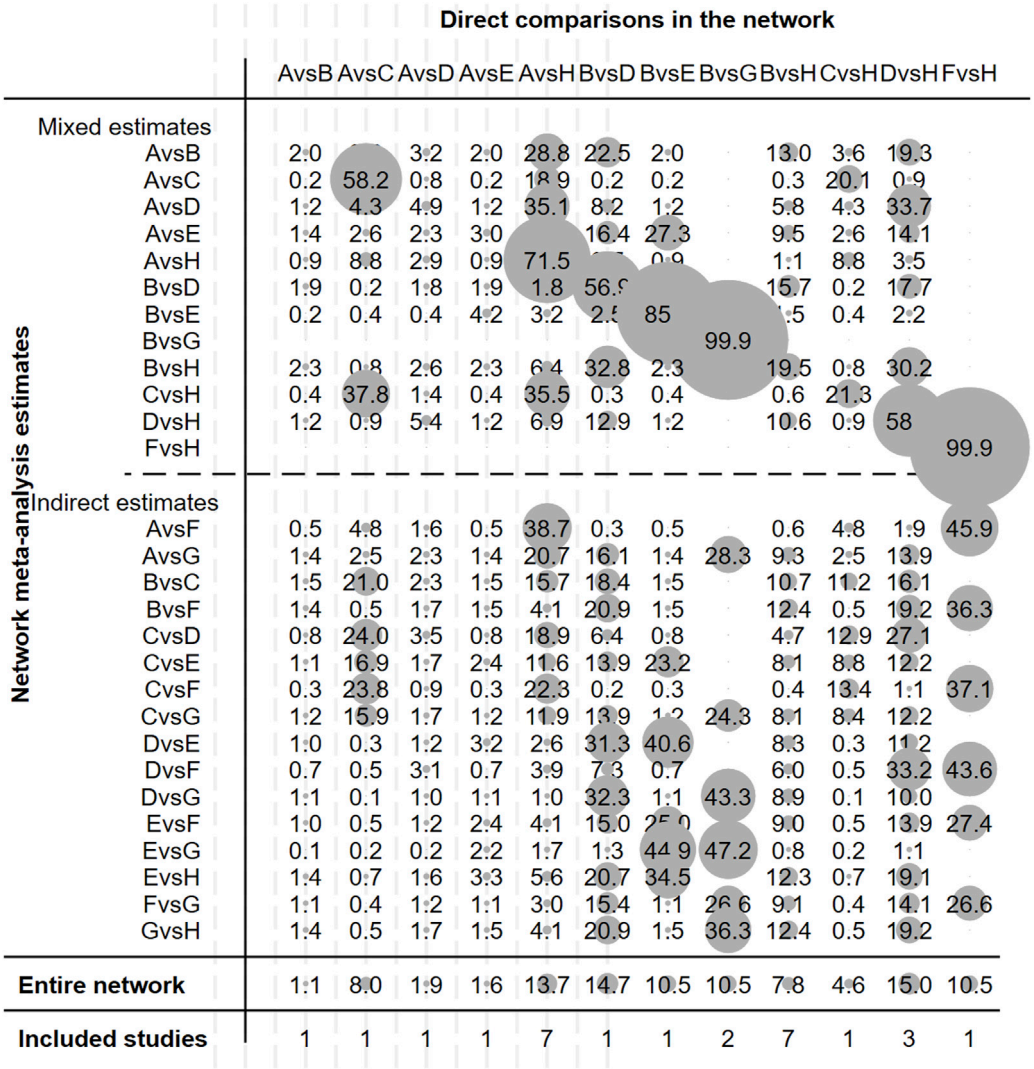

FIGURE 3
Contribution plot of studies included in this network meta-analysis. Note: A, Gefitinib; B, Erlotinib; C, Icotinib; D, Afatinib; E, Dacomitinib; F, Osimertinib; G, Vandetanib; H, Chemotherapy.

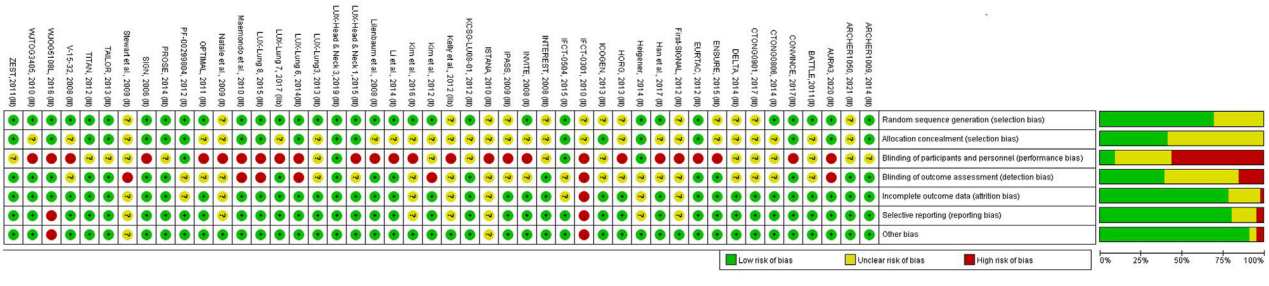

FIGURE 4
Summary of results from assessment of studies using the Cochrane risk of bias tool.

AEs, Erlotinib had a significantly higher anemia incidence rate at 27%, slightly above the chemotherapy group's 26%. For leukopenia and thrombocytopenia, Osimertinib showed the highest incidence rates among EGFR-TKIs at 8% and 9%, respectively, but these were still much lower than the chemotherapy group's 29% and 19%. Additionally, chest pain was only reported in patients treated with

TABLE 4 Number and incidence of AEs induced by different drugs.

	All grade AE			≥3grade AE		
	AEs Count	Total participants	Adverse event rate	AEs Count	Total participants	Adverse event rate
Gefitinib	1,797	2,233	80.5%	727	3,253	22.3%
Erlotinib	1,502	1,767	85.0%	459	5,655	8.1%
Afatinib	1,263	1,342	94.1%	515	1,571	32.8%
Icotinib	201	384	57.8%	21	384	5.5%
Dacomitinib	579	606	95.5%	252	606	41.6%
Osimertinib	275	279	98.6%	104	279	37.3%
Vandetanib	NA	NA	NA	NA	NA	NA
EGFR-TIK	5,617	6,611	85.0%	2,078	11,748	17.7%
Chemotherapy	2,221	2,705	82.1%	1,794	3,890	46.1%

TABLE 5 Pooled estimates of the network meta-analysis.

All-grade AEs	≥Grade 3 AEs					
Gefitinib	1.47 (0.90, 2.38)	0.67 (0.25, 1.78)	**2.79 (1.58, 4.95)**	2.27 (0.95, 5.45)	2.63 (0.76, 9.17)	**4.06 (2.87, 5.73)**
0.61 (0.33, 1.12)	**Erlotinib**	0.46 (0.16, 1.31)	**1.90 (1.05, 3.46)**	1.55 (0.65, 3.70)	1.80 (0.51, 6.38)	**2.77 (1.83, 4.19)**
2.53 (1.24, 5.15)	**4.15 (1.76, 9.78)**	**Icotinib**	**4.18 (1.40, 12.53)**	3.41 (0.93, 12.48)	3.95 (0.84, 18.63)	**6.08 (2.27,16.30)**
0.20 (0.11, 0.38)	**0.34 (0.18, 0.61)**	**0.08 (0.03, 0.19)**	**Afatinib**	0.81 (0.30, 2.20)	0.94 (0.26, 3.46)	1.45 (0.88, 2.41)
0.33 (0.12, 0.92)	0.54 (0.22, 1.32)	**0.13 (0.04,0.43)**	**1.61 (0.56, 4.61)**	**Dacomitinib**	1.16 (0.26, 5.15)	1.78 (0.73, 4.34)
1.16 (0.11, 12.53)	1.91 (0.17, 21.02)	0.46 (0.04,5.36)	5.69 (0.51, 62.99)	3.53 (0.28, 44.91)	**Osimertinib**	1.54 (0.46, 5.11)
0.59 (0.41, 0.86)	0.97 (0.59, 1.60)	**0.23 (0.11, 0.48)**	**2.90 (1.71, 4.90)**	1.80 (0.67, 4.80)	0.51 (0.05, 5.32)	**Chemotherapy**

The numbers in the cells are odds ratios, with 95% confidence intervals in parentheses. If the number is greater (less) than 1, it indicates that the treatment defined by the column is more (less) toxic. The bold numbers demonstrate a statistically significant difference in adverse event toxicity between the two drugs.

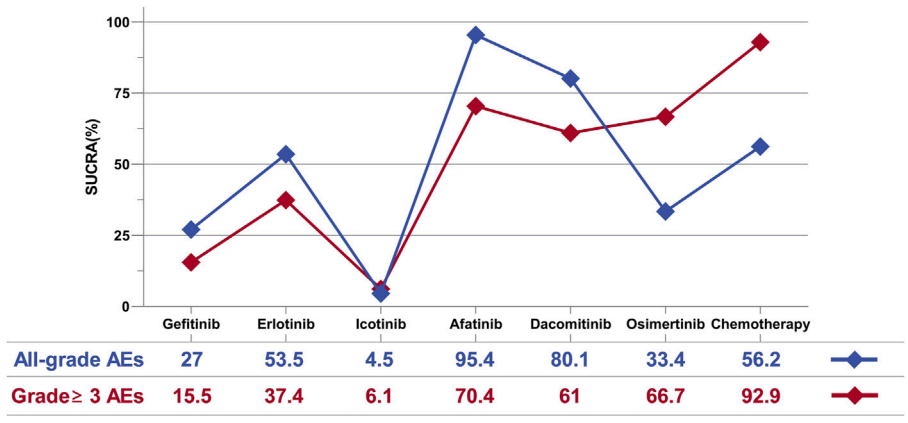

FIGURE 5
Surface under the cumulative ranking curve for AEs.

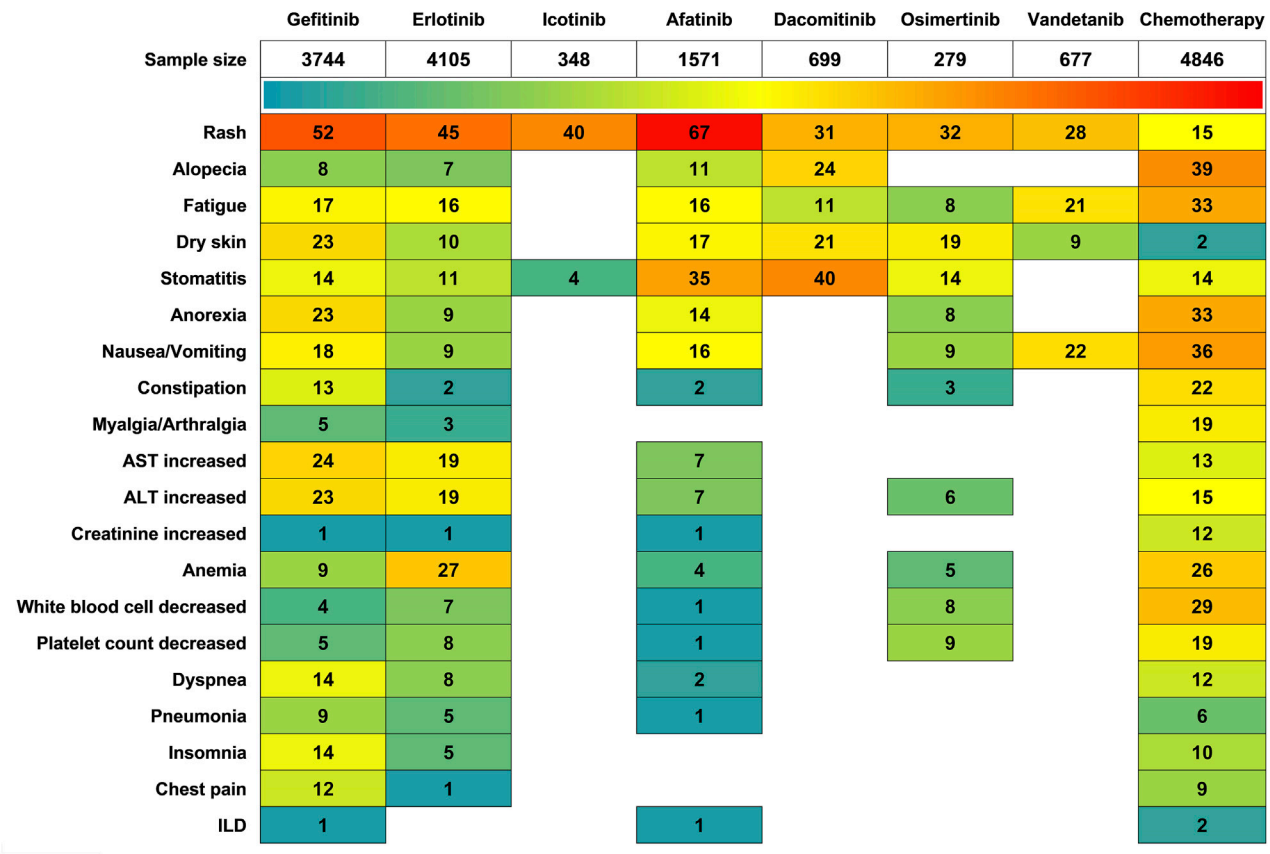

FIGURE 6
Heatmap of AEs Incidence Induced by different treatments.

Gefitinib and Erlotinib, with incidence rates of 12% and 1%, respectively, compared to 9% in the chemotherapy group. Notably, both Gefitinib and Afatinib had an interstitial lung disease (ILD) incidence rate of 1%, while no reports were made for the other EGFR-TKIs.

Comprehensive safety evaluations revealed distinct toxicity patterns across EGFR-TKI generations. Regarding first-generation agents, icotinib demonstrated superior tolerability with significantly lower incidence rates of most adverse events (AEs) compared to both gefitinib and erlotinib. Notably, erlotinib exhibited higher frequencies of hematological toxicities (e.g., anemia, leukopenia, thrombocytopenia) than gefitinib, while maintaining comparable or marginally lower rates in other non-hematological AEs. In the second-generation class, dacomitinib showed advantageous AE profiles over afatinib for common toxic effects including rash, fatigue, and nausea/vomiting, though it demonstrated elevated risks of alopecia, xerosis cutis, and stomatitis. These inter-agent contrasts emphasize the necessity for personalized selection of second-generation TKIs based on patients' susceptibility to specific toxicities and individual quality-of-life priorities.

We compared the specific AEs of interest across different EGFR-TKIs through OR (Table 6), Afatinib has a significantly higher risk of oral mucositis compared to Gefitinib (OR = 5.49), Erlotinib (OR = 4.97), and all other EGFR-TKIs, including Icotinib (OR = 8.01), Dacomitinib (OR = 1.61), and Osimertinib (OR = 4.17). Afatinib also exhibits higher risks of increased creatinine levels, pneumonia, and rash than those reported for other EGFR-TKIs. Osimertinib poses a significant risk of leukopenia, which is higher than that of Vandetanib (OR = 10.25) and Afatinib (OR = 11.41), as well as Gefitinib (OR = 6.23) and Icotinib (OR = 10.66). Similarly, Osimertinib's risk of thrombocytopenia is greater than that of Gefitinib (OR = 1.74), Erlotinib (OR = 3.13), and Afatinib (OR = 8.8). Gefitinib shows a higher risk of nausea/vomiting compared to other EGFR-TKIs: Erlotinib (OR = 1.85), Icotinib (OR = 1.72), Afatinib (OR = 1.52), Dacomitinib (OR = 1.44), Osimertinib (OR = 3.23), and Vandetanib (OR = 2.08). Additionally, Gefitinib has a higher risk of AST increased and ILD compared to Erlotinib and Afatinib, with no reports of this AE for other EGFR-TKIs. Erlotinib has a higher risk of ALT increased compared to Gefitinib (OR = 1.09), Afatinib (OR = 4.35), Dacomitinib (OR = 2.94), and Osimertinib (OR = 1.96). Furthermore, Erlotinib presents a higher risk of dyspnea compared to Gefitinib (OR = 2.03), Afatinib (OR = 2.33), and Vandetanib (OR = 1.08). Dacomitinib is associated with a higher risk of dry skin among the studied EGFR-TKIs. Vandetanib carries a higher risk of anemia compared to Gefitinib (OR = 2.56), Erlotinib (OR = 2.81), Afatinib (OR = 4.09), and Osimertinib (OR = 5.55). Conversely, Icotinib appears to be relatively safer regarding the a forementioned AEs.

TABLE 6 Toxicity estimates regarding specific all-grade AEs in network meta-analysis.

	Rash	Alopecia	Fatigue	Dry skin	Stomatitis	Anorexia	Nausea/ Vomiting	Constipation	Myalgia/ Arthralgia	AST increased
Vs. Gefitinib										
Erlotinib	1.18	3.77	1.63	1.03	1.1	1.03	0.54	0.71	3.19	0.71
Icotinib	0.69				0.69	0.85	0.58			
Afatinib	3.82	0.67	1.25	0.88	**5.49**	1.03	0.66	0.29		0.31
Dacomitinib	1.25	2.15	1.21	1.26	3.4	1.27	0.69			0.41
Osimertinib	1.16		0.81	1.24	1.33	0.48	0.31	0.32		
Vandetanib	0.58		1.68	0.63		0.97	0.48	0.43		
Chemotherapy	0.14	**15.07**	**3**	**0.08**	1.29	**2.46**	**2.95**	**2.37**	**6.84**	0.73
Vs. Erlotinib										
Icotinib	0.58				0.62	0.82	1.09			
Afatinib	3.23	0.18	0.77	0.85	**4.97**	1	1.22	0.4		0.44
Dacomitinib	1.06	0.57	0.75	1.23	3.08	1.23	1.28			0.58
Osimertinib	0.98		0.5	1.21	1.2	0.46	0.58	0.44		
Vandetanib	0.49		1.03	**0.61**		0.95	0.9	0.61		
Chemotherapy	0.12	**4**	**1.85**	**0.08**	1.17	**2.39**	**5.49**	**3.32**	2.14	1.03
Vs. Icotinib										
Afatinib	5.55				8.01	1.21	1.12			
Dacomitinib	1.82				4.97	1.5	1.18			
Osimertinib	1.69				1.94	0.56	0.53			
Vandetanib	0.84					1.15	0.83			
Chemotherapy	0.2				1.88	2.9	5.05			
Vs. Afatinib										
Dacomitinib	0.33	3.22	0.97	1.44	0.62	1.24	1.05			1.33
Osimertinib	0.3		0.65	1.42	0.24	0.47	0.48	1.09		
Vandetanib	0.15		1.34	0.72		0.95	0.74	1.5		
Chemotherapy	0.04	**22.54**	**2.39**	**0.09**	**0.23**	**2.39**	**4.49**	**8.21**		2.35

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TABLE 6 (*Continued*) Toxicity estimates regarding specific all-grade AEs in network meta-analysis.

	Rash	Alopecia	Fatigue	Dry skin	Stomatitis	Anorexia	Nausea/ Vomiting	Constipation	Myalgia/ Arthralgia	AST increased
Vs. Dacomitinib										
Osimertinib	0.93		0.67	0.98	**0.39**	0.38	0.45			
Vandetanib	0.46		1.38	**0.5**		0.77	0.7			
Chemotherapy	0.11	7	2.47	**0.06**	0.38	1.93	4.28			1.77
Vs. Osimertinib										
Vandetanib	0.5		2.07	0.51		2.04	1.55	1.37		
Chemotherapy	0.12		3.71	**0.06**	0.97	**5.15**	9.44	**7.5**		
Vs. Vandetanib										
Chemotherapy	0.24		1.79	**0.12**		2.53	6.11	5.46		
	ALT increased	Creatinine increased	Anemia	White blood cell decreased	Platelet count decreased	Dyspnea	Pneumonia	Insomnia	Chest pain	ILD
Vs. Gefitinib										
Erlotinib	1.09	1.65	0.91	0.61	0.56	2.03	1.14	0.76	8.57	0.91
Icotinib				0.58						
Afatinib	0.25	12.47	0.63	0.55	0.2	0.88	4.03			0.32
Dacomitinib	0.37									
Osimertinib	0.56		0.46	6.23	1.74					
Vandetanib			2.56			1.89				
Chemotherapy	0.97	12.25	**3.03**	**10.4**	**3.59**	1.06	0.92	0.93	**1.83**	0.77
Vs. Erlotinib										
Icotinib				0.96						
Afatinib	0.23	7.57	0.69	0.9	0.36	0.43	3.55			0.35
Dacomitinib	0.34									
Osimertinib	0.51		0.51	**10.25**	3.13					
Vandetanib			2.81			0.93				
Chemotherapy	0.89	7.44	**3.33**	**17.1**	**6.47**	**0.52**	0.81	1.22	0.21	0.84

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TABLE 6 (*Continued*) Toxicity estimates regarding specific all-grade AEs in network meta-analysis.

	Rash	Alopecia	Fatigue	Dry skin	Stomatitis	Anorexia	Nausea/ Vomiting	Constipation	Myalgia/ Arthralgia	AST increased
Vs. Icotinib										
Afatinib				0.93						
Dacomitinib										
Osimertinib				10.66						
Vandetanib										
Chemotherapy				**17.79**						
Vs. Afatinib										
Dacomitinib	1.49									
Osimertinib	2.23		0.74	**11.41**	8.8					
Vandetanib			4.09			2.15				
Chemotherapy	3.87	0.98	**4.84**	**19.05**	**18.21**	1.2	0.23			2.38
Vs. Dacomitinib										
Osimertinib	1.49									
Vandetanib										
Chemotherapy	2.59									
Vs. Osimertinib										
Vandetanib			5.55							
Chemotherapy	1.74		6.56	1.67	2.07					
Vs. Vandetanib										
Chemotherapy			1.18			0.56				

Numbers in cells are odds ratios and those in bold represent statistically significant results.

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TABLE 7 Characteristics of patients with AEs associated with EGFR-TKI in FAERS database.

	Gefitinib	Erlotinib	Afatinib	Dacomitinib	Osimertinib	Vandetanib	EGFR-TKI
	n = 7184	n = 40159	n = 5842	n = 564	n = 20103	n = 1344	n = 75196
Gender							
Female (%)	3919 (54.55)	20114 (50.09)	3089 (52.88)	248 (43.97)	11056 (55.00)	532 (39.58)	38958 (51.81)
Male (%)	2706 (37.67)	17745 (44.19)	1951 (33.40)	230 (40.78)	5979 (29.74)	675 (50.22)	29286 (38.95)
Missing (%)	559 (7.78)	2300 (5.73)	802 (13.73)	86 (15.25)	3068 (15.26)	137 (10.19)	6952 (9.25)
Age							
<18 (%)	20 (0.28)	55 (0.14)	14 (0.24)	0	7 (0.03)	18 (1.34)	114 (0.15)
18–64 (%)	2182 (30.37)	6935 (17.27)	1632 (27.94)	223 (39.54)	3738 (18.59)	618 (45.98)	15328 (20.38)
≥65 (%)	3074 (42.79)	10601 (26.40)	2281 (39.04)	220 (39.01)	7137 (35.5)	436 (32.44)	23749 (31.58)
Missing (%)	1908 (26.56)	22568 (56.20)	1915 (32.78)	121 (21.45)	9221 (45.87)	272 (20.24)	36005 (47.88)
Median (Q1,Q3)	67 (59.75)	68 (59.76)	67 (58.74)	64 (56.72)	70 (61.77)	61 (49.70)	68 (59.76)
Country							
United States (%)	294 (4.09)	26401 (65.74)	2016 (34.51)	66 (11.70)	4937 (24.56)	663 (49.33)	38134 (50.71)
Japan (%)	585 (8.14)	911 (2.27)	1120 (19.17)	26 (4.61)	1658 (8.25)	47 (3.50)	5775 (7.68)
China (%)	1103 (15.35)	1373 (3.42)	263 (4.50)	120 (21.28)	576 (2.87)	6 (0.45)	4324 (5.75)
France (%)	191 (2.66)	387 (0.96)	173 (2.96)	0	323 (1.61)	48 (3.57)	1499 (1.99)
Germany (%)	56 (0.78)	362 (0.90)	401 (6.86)	2 (0.35)	141 (0.70)	19 (1.41)	1134 (1.51)
Other (%)	4955 (68.97)	10725 (26.71)	1869 (31.99)	350 (62.06)	12468 (62.02)	561 (41.74)	24330 (32.36)
Reporter type							
Physician (%)	2662 (37.05)	10585 (26.36)	3471 (59.41)	145 (25.71)	5465 (27.18)	487 (36.24)	22815 (30.34)
Pharmacist (%)	642 (8.94)	2407 (5.99)	614 (10.51)	83 (14.72)	2619 (13.03)	99 (7.37)	6464 (8.60)
Other health-professional (%)	793 (11.04)	4360 (10.86)	409 (7.00)	7 (1.24)	446 (2.22)	104 (7.74)	6119 (8.14)
Consume (%)	1054 (14.67)	22200 (55.28)	1313 (22.48)	319 (56.56)	8108 (40.33)	543 (40.40)	33537 (44.60)
Missing (%)	2033 (28.30)	607 (1.51)	35 (0.60)	10 (1.77)	3465 (17.24)	111 (8.26)	6261 (8.33)

3.2 Disproportionality analysis

3.2.1 Descriptive analysis

Between January 2004 and June 2024, the FAERS database documented a total of 75,196 patients experiencing AEs from EGFR-TKIs, amounting to 204,092 individual event occurrences. The search process is illustrated in Figure 1. Of these cases, Gefitinib was implicated in 7,184 instances, Erlotinib in 40,159, Afatinib in 5,842, Dacomitinib in 564, Osimertinib in 20,103, and Vandetanib in 1,344. Icotinib, not identified as a direct suspect in any known events, was excluded from this study. The demographic distribution comprised 38,958 females (51.81%), 29,286 males (38.95%), with the majority aged over 65 years (23,749 individuals, 31.58%), followed by those aged between 18 and 64 years (15,328 individuals, 20.38%). The median age was 68 years. Reports predominantly originated from the United States (50.71%), followed by Japan (7.68%). Over one-third of the submissions were made by physicians (Table 7).

3.2.2 Systemic AEs

In order to analyze systemic AEs at the SOC level, we quantified the incidence of AEs and computed the ROR as an indicator of signal strength. Based on these metrics and their clinical relevance, we identified specific SOCs for further investigation as prioritized systemic AEs (Table 8). These include disorders of the Blood and Lymphatic System, Cardiac Disorders, Gastrointestinal Disorders, Renal and Urinary Disorders, Respiratory, Thoracic and Mediastinal Disorders, Nervous System Disorders, and Hepatobiliary Disorders. Osimertinib was associated with the strongest signals in Cardiac Disorders (n = 1429, ROR025 = 1.25) and Blood and Lymphatic System Disorders (n = 1034, ROR025 = 1.41); additional positive signals were noted for Respiratory and Hepatobiliary Disorders. Gefitinib exhibited the strongest signals in Respiratory, Thoracic and Mediastinal Disorders (n = 2358, ROR025 = 2.26) and Hepatobiliary Disorders (n = 576, ROR025 = 2.6), with positive signals also observed for Blood and Lymphatic System Disorders and Gastrointestinal Disorders. Afatinib showed the strongest signal in Gastrointestinal Disorders (n = 4798, ROR025 = 2.95), with a

TABLE 8 Signal profiles of AEs induced by EGFR-TKIs at the SOC level.

SOC	Gefitinib (N = 22653)		Erlotinib (N = 111361)		Afatinib (N = 21758)	
	N	ROR (95%CI)	N	ROR (95%CI)	N	ROR (95%CI)
Blood and lymphatic system disorders	452	1.19 (1.08–1.31)	2238	1.2 (1.15–1.25)	250	0.68 (0.6–0.77)
Cardiac disorders	419	0.69 (0.63–0.76)	1783	0.6 (0.57–0.62)	227	0.39 (0.34–0.44)
Gastrointestinal disorders	2432	1.29 (1.24–1.35)	14762	1.64 (1.62–1.67)	4798	3.04 (2.95–3.14)
Renal and urinary disorders	424	0.98 (0.89–1.07)	1147	0.53 (0.5–0.56)	342	0.82 (0.73–0.91)
Respiratory, thoracic and mediastinal disorders	2358	2.35 (2.26–2.46)	7737	1.51 (1.48–1.55)	1525	1.53 (1.45–1.61)
Nervous system disorders	1119	0.56 (0.52–0.59)	4794	0.48 (0.47–0.5)	897	0.46 (0.43–0.49)
Hepatobiliary disorders	576	2.82 (2.6–3.07)	918	0.9 (0.84–0.96)	179	0.9 (0.77–1.04)
General disorders and administration site conditions	3878	0.98 (0.94–1.01)	27777	1.57 (1.55–1.6)	2479	0.61 (0.58–0.63)
Eye disorders	317	0.7 (0.63–0.78)	2702	1.23 (1.18–1.28)	347	0.8 (0.72–0.89)
Congenital, familial and genetic disorders	305	4.48 (4–5.02)	90	0.26 (0.22–0.33)	130	1.97 (1.66–2.34)
Ear and labyrinth disorders	42	0.42 (0.31–0.57)	308	0.63 (0.57–0.71)	46	0.48 (0.36–0.65)
Endocrine disorders	28	0.49 (0.34–0.71)	116	0.41 (0.34–0.49)	19	0.34 (0.22–0.54)
Immune system disorders	48	0.19 (0.14–0.25)	225	0.18 (0.16–0.21)	45	0.19 (0.14–0.25)
Infections and infestations	1220	1.03 (0.97–1.09)	5116	0.87 (0.85–0.9)	1484	1.33 (1.26–1.4)
Injury, poisoning and procedural complications	602	0.24 (0.22–0.26)	4239	0.35 (0.34–0.36)	626	0.26 (0.24–0.28)
Investigations	1557	1.12 (1.07–1.18)	5276	0.76 (0.74–0.78)	834	0.61 (0.57–0.65)
Metabolism and nutrition disorders	677	1.39 (1.28–1.5)	3756	1.57 (1.52–1.63)	1108	2.42 (2.28–2.57)
Musculoskeletal and connective tissue disorders	386	0.32 (0.29–0.35)	2337	0.39 (0.38–0.41)	393	0.34 (0.3–0.37)
Neoplasms benign, malignant and unspecified	3111	5.85 (5.63–6.08)	6118	2.14 (2.08–2.19)	2639	5.07 (4.87–5.28)
Pregnancy, puerperium and perinatal conditions	5	0.05 (0.02–0.12)	21	0.04 (0.03–0.07)	1	0.01 (0–0.08)
Product issues	11	0.03 (0.02–0.05)	105	0.06 (0.05–0.07)	14	0.04 (0.02–0.07)
Psychiatric disorders	290	0.22 (0.19–0.24)	1604	0.24 (0.23–0.25)	269	0.21 (0.18–0.23)
Reproductive system and breast disorders	62	0.3 (0.24–0.39)	203	0.2 (0.18–0.23)	61	0.31 (0.24–0.4)
Skin and subcutaneous tissue disorders	1954	1.66 (1.59–1.74)	15667	2.89 (2.84–2.94)	2695	2.49 (2.39–2.59)
Social circumstances	50	0.47 (0.36–0.63)	134	0.26 (0.22–0.31)	18	0.18 (0.11–0.28)
Surgical and medical procedures	52	0.17 (0.13–0.22)	419	0.28 (0.25–0.31)	115	0.39 (0.33–0.47)
Vascular disorders	278	0.57 (0.5–0.64)	1769	0.74 (0.7–0.77)	217	0.46 (0.4–0.53)
	Dacomitinib (N = 1910)		Osimertinib (N = 41297)		Vandetanib (N = 5113)	
SOC	N	ROR (95%CI)	N	ROR (95%CI)	N	ROR (95%CI)
Blood and lymphatic system disorders	20	0.62 (0.4–0.96)	1034	1.5 (1.41–1.6)	59	0.68 (0.53–0.88)
Cardiac disorders	28	0.55 (0.38–0.79)	1429	1.31 (1.25–1.39)	113	0.83 (0.69–1)
Gastrointestinal disorders	222	1.41 (1.23–1.63)	3013	0.85 (0.82–0.88)	722	1.77 (1.63–1.91)
Renal and urinary disorders	19	0.51 (0.33–0.81)	417	0.52 (0.47–0.57)	121	1.24 (1.04–1.49)
Respiratory, thoracic and mediastinal disorders	132	1.5 (1.26–1.79)	3244	1.73 (1.67–1.79)	268	1.12 (0.99–1.27)
Nervous system disorders	69	0.4 (0.32–0.51)	1880	0.51 (0.49–0.54)	349	0.79 (0.7–0.88)
Hepatobiliary disorders	31	1.78 (1.25–2.54)	647	1.72 (1.59–1.86)	38	0.81 (0.59–1.11)
General disorders and administration site conditions	377	1.16 (1.04–1.3)	13060	2.19 (2.15–2.24)	637	0.67 (0.62–0.73)

(Continued on following page)

TABLE 8 (*Continued*) Signal profiles of AEs induced by EGFR-TKIs at the SOC level.

SOC	Gefitinib (N = 22653)		Erlotinib (N = 111361)		Afatinib (N = 21758)	
	N	ROR (95%CI)	N	ROR (95%CI)	N	ROR (95%CI)
Eye disorders	24	0.63 (0.42–0.94)	521	0.63 (0.58–0.69)	117	1.16 (0.96–1.39)
Congenital, familial and genetic disorders	1	0.17 (0.02–1.22)	438	3.52 (3.21–3.87)	7	0.45 (0.21–0.94)
Ear and labyrinth disorders	9	1.08 (0.56–2.08)	95	0.53 (0.43–0.64)	21	0.94 (0.61–1.45)
Endocrine disorders	3	0.62 (0.2–1.92)	59	0.56 (0.44–0.73)	20	1.55 (1–2.4)
Immune system disorders	5	0.24 (0.1–0.57)	124	0.27 (0.23–0.32)	18	0.32 (0.2–0.51)
Infections and infestations	109	1.1 (0.9–1.33)	1426	0.65 (0.61–0.68)	247	0.92 (0.81–1.05)
Injury, poisoning and procedural complications	76	0.36 (0.29–0.46)	1615	0.36 (0.34–0.37)	244	0.44 (0.39–0.5)
Investigations	284	2.66 (2.35–3.02)	2168	0.84 (0.81–0.88)	589	1.98 (1.82–2.16)
Metabolism and nutrition disorders	35	0.84 (0.6–1.17)	995	1.11 (1.04–1.18)	168	1.53 (1.31–1.78)
Musculoskeletal and connective tissue disorders	40	0.39 (0.29–0.54)	1040	0.47 (0.44–0.5)	222	0.83 (0.73–0.95)
Neoplasms benign, malignant and unspecified	100	2.03 (1.66–2.48)	4333	4.31 (4.18–4.45)	125	0.92 (0.77–1.1)
Pregnancy, puerperium and perinatal conditions	0		2	0.01 (0–0.04)	1	0.04 (0.01–0.32)
Product issues	1	0.03 (0–0.23)	50	0.07 (0.06–0.1)	7	0.08 (0.04–0.18)
Psychiatric disorders	20	0.18 (0.11–0.27)	403	0.16 (0.15–0.18)	118	0.39 (0.33–0.47)
Reproductive system and breast disorders	5	0.29 (0.12–0.7)	53	0.14 (0.11–0.19)	27	0.59 (0.4–0.85)
Skin and subcutaneous tissue disorders	271	2.91 (2.56–3.31)	2454	1.11 (1.07–1.16)	627	2.46 (2.26–2.67)
Social circumstances	2	0.22 (0.06–0.9)	55	0.29 (0.22–0.37)	8	0.34 (0.17–0.67)
Surgical and medical procedures	11	0.43 (0.24–0.77)	58	0.1 (0.08–0.13)	94	1.38 (1.13–1.7)
Vascular disorders	16	0.39 (0.24–0.63)	684	0.77 (0.71–0.83)	146	1.34 (1.14–1.58)

The ROR (95% CI) is followed by indicators, with red denoting positive signals and green indicating negative signals. CI: confidence interval.

positive signal in Respiratory, Thoracic and Mediastinal Disorders. Vandetanib had the strongest signal in Renal and Urinary Disorders (n = 121, ROR025 = 1.04), with a positive signal in Gastrointestinal Disorders. Erlotinib was linked to the highest number of cases in Nervous System Disorders (n = 4794, ROR025 = 0.47), with positive signals in Blood and Lymphatic System Disorders, Gastrointestinal Disorders, and Respiratory Disorders. Dacomitinib demonstrated positive signals in Gastrointestinal, Respiratory, and Hepatobiliary Disorders. Figure 7 illustrates the differences in ROR025 levels across different drugs and SOCs.

3.2.3 Specific AEs

Utilizing PT criteria for the analysis of specific AEs, the FAERS database has documented over 4,982 distinct types of AEs. Based on their incidence and clinical relevance, 20 AEs warrant attention: diarrhea, rash, nausea/vomiting, fatigue, decreased appetite, dyspnea, pneumonia, asthenia, dry skin, pruritus, weight loss, stomatitis, pleural effusion, pyrexia, interstitial lung disease, acne, anemia, constipation, respiratory failure, and pulmonary embolism. Among these, Gefitinib exhibited the strongest signals for dyspnea (ROR025 = 1.16), pneumonia (ROR025 = 1.87), pleural effusion (ROR025 = 7.38), interstitial lung disease (ROR025 = 18.62), and respiratory failure (ROR025 = 3.93). Erlotinib was associated with pronounced signals for rash (ROR025 = 8.38), decreased appetite (ROR025 = 3.26), dry skin (ROR025 = 4.96), anemia (ROR025 = 1.84), and pulmonary embolism (ROR025 = 2.32). Afatinib showed prominent signals for diarrhea (ROR025 = 9.17), nausea/vomiting (ROR025 = 21.03), and fatigue (ROR025 = 4.56). Dacomitinib predominantly caused stomatitis (ROR025 = 3.73). Osimertinib's signal for interstitial lung disease (ROR025 = 13) was second only to Gefitinib and significantly higher compared to other EGFR-TKIs. Vandetanib displayed the strongest signal for acne (ROR025 = 10.56), as detailed in Table 9.

3.2.4 Onset time of AEs

Figure 8 illustrates the time to onset of AEs following the initiation of EGFR-TKI therapy, along with their median and interquartile range (IQR). Following the commencement of EGFR-TKI treatment, 43.9% of AEs occurred within 30 days, with Afatinib exhibiting the highest proportion at 65.3%. An additional 14.6% of AEs transpired between 31 and 60 days post-treatment start. Moreover, 23.1% of AEs emerged more than 181 days after initiating therapy, with Osimertinib accounting for the highest percentage at 32.5%. The shortest median time to AE onset was observed with Afatinib, at 14 days (IQR: 4–55 days), while Dacomitinib had the longest median time at 73 days (IQR: 25–246 days), followed by Osimertinib (median: 70 days, IQR:

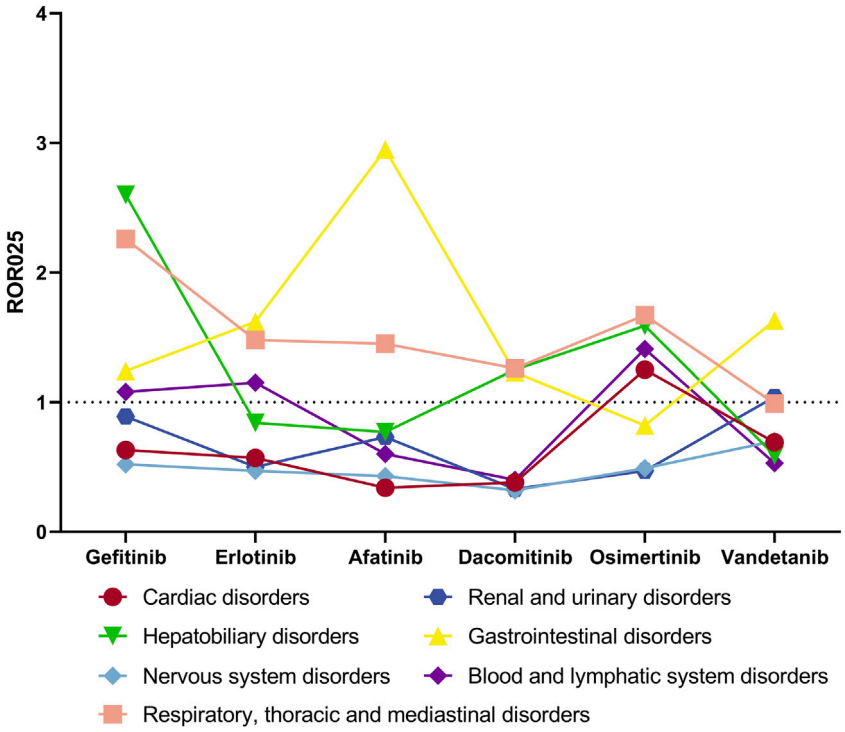

FIGURE 7
Differences in ROR025 for AEs of interest among EGFR-TKIs at SOC level.

17–285 days). The median times to AE onset for other drugs ranged from 35 to 47 days.

We conducted a statistical analysis on the median occurrence time and interquartile ranges of systemic AEs associated with EGFR-TKIs, categorized by SOC (Figure 9). Most systemic AEs occurred within 30 days, except for Cardiac Disorders, which had a median onset time of 41 days. The second longest median onset time was observed in Nervous System Disorders at 33 days, while Gastrointestinal Disorders had the shortest median onset time at 21 days. Notably, the third quartile (Q3) for the onset time of Cardiac Disorders was 158 days, followed by Nervous System Disorders at 134 days; the Q3 for all other AEs was less than 100 days.

3.2.5 Fatality rate of AEs

Figure 10 illustrates the mortality rates of various drugs as determined by different research methodologies. The y-axis represents the proportion of deaths following AEs associated with different EGFR-TKIs in the FAERS database, ranked from highest to lowest mortality rate as follows: Osimertinib (51.66%), Dacomitinib (50.53%), Erlotinib (28.98%), Afatinib (22.53%), Gefitinib (20.6%), and Vandetanib (7.81%). The x-axis shows the pooled proportions of deaths due to AEs for different EGFR-TKIs as summarized by a NMA, with rankings from highest to lowest as Osimertinib (4.3%), Vandetanib (3.4%), Dacomitinib (2.43%), Gefitinib (1.93%), Afatinib (0.95%), and Erlotinib (0.92%). Based on this data, we conducted an exploratory study attempting to multiply the AEs mortality rates of the aforementioned EGFR-TKIs across two research settings (representing real-world data through DA and clinical trial environments via NMA). In Figure 10, this is depicted as the area of the rectangle formed by each drug's point and the origin, with the resulting product of mortality rates used to rank the EGFR-TKIs as follows: Osimertinib, Dacomitinib, Gefitinib, Erlotinib, Vandetanib, and Afatinib (Table 10).

Finally, we analyzed the data from the FAERS database to determine the number of death cases and the mortality rates of AEs across different systems. The highest mortality rate was observed in Cardiac disorders at 36.46% (n = 1099), followed by Respiratory, thoracic, and mediastinal disorders at 31.6% (n = 3300). Subsequently, the mortality rates for other AEs ranked from highest to lowest were: Renal and urinary disorders (22.89%, n = 482), Nervous system disorders (21.99%, n = 1471), Hepatobiliary disorders (19.79%, n = 405), Blood and lymphatic system disorders (19.45%, n = 641), and Gastrointestinal disorders (17.2%, n = 2682) (Figure 11).

4 Discussion

To our knowledge, this study represents the inaugural endeavor to characterize and analyze AEs associated with EGFR-TKIs by integrating two distinct methodologies. Specifically, an NMA was conducted based on RCTs comparing EGFR-TKIs either against each other or versus chemotherapy, deliberately excluding studies involving combination therapy with EGFR-TKIs to minimize confounding effects from additional medications. Trials incorporating placebo controls were also omitted due to their tendency to enroll healthier patient populations, potentially

TABLE 9 Signal profiles of AEs induced by EGFR-TKIs at the PT level.

PT	Gefitinib (N = 22653)		Erlotinib (N = 111361)		Afatinib (N = 21758)	
	N	ROR (95%CI)	N	ROR (95%CI)	N	ROR (95%CI)
Rash	534	3.3 (3.03–3.6)	6494	8.59 (8.38–8.81)	803	5.25 (4.89–5.63)
Diarrhoea	711	3.14 (2.92–3.39)	4808	4.4 (4.28–4.53)	1956	9.61 (9.17–10.06)
Nausea/Vomiting	259	0.89 (0.79–1.01)	1902	1.34 (1.28–1.41)	468	23.06 (21.03–25.28)
Fatigue	153	0.54 (0.46–0.63)	1958	1.42 (1.36–1.48)	421	5.02 (4.56–5.53)
Decreased appetite	252	2.86 (2.53–3.24)	1477	3.43 (3.26–3.62)	418	1.51 (1.38–1.67)
Dyspnoea	271	1.3 (1.16–1.47)	1273	1.24 (1.18–1.32)	232	0.85 (0.75–0.97)
Pneumonia	261	2.11 (1.87–2.38)	1087	1.78 (1.68–1.89)	226	1.7 (1.49–1.94)
Asthenia	167	1.2 (1.03–1.4)	1079	1.59 (1.5–1.69)	198	1.66 (1.44–1.91)
Dry skin	167	3.68 (3.16–4.28)	1161	5.26 (4.96–5.57)	192	1.95 (1.69–2.25)
Pruritus	148	1.08 (0.92–1.28)	990	1.48 (1.39–1.58)	184	0.92 (0.79–1.06)
Weight decreased	118	1.15 (0.96–1.37)	828	1.64 (1.53–1.76)	176	4.04 (3.48–4.69)
Stomatitis	72	3.32 (2.63–4.18)	544	5.15 (4.73–5.6)	153	5.46 (4.66–6.4)
Pleural effusion	193	8.5 (7.38–9.8)	566	5.08 (4.68–5.52)	152	6.95 (5.93–8.16)
Pyrexia	217	1.7 (1.49–1.95)	639	1.02 (0.94–1.1)	152	1.16 (0.99–1.36)
Interstitial lung disease	348	20.71 (18.62–23.04)	296	3.53 (3.15–3.96)	140	1.14 (0.97–1.35)
Acne	88	3 (2.44–3.7)	733	5.14 (4.78–5.53)	134	8.18 (6.9–9.7)
Anaemia	108	1.51 (1.25–1.83)	693	1.98 (1.84–2.14)	97	1.41 (1.16–1.73)
Constipation	54	0.71 (0.54–0.92)	532	1.42 (1.3–1.55)	90	1.23 (1–1.51)
Respiratory failure	127	4.68 (3.93–5.57)	463	3.48 (3.17–3.81)	73	2.79 (2.22–3.51)
Pulmonary embolism	78	2.15 (1.72–2.68)	453	2.54 (2.32–2.79)	53	1.52 (1.16–1.99)
PT	Dacomitinib (N = 1910)		Osimertinib (N = 41297)		Vandetanib (N = 5113)	
	N	ROR (95%CI)	N	ROR (95%CI)	N	ROR (95%CI)
Rash	82	6.13 (4.92–7.65)	494	1.66 (1.52–1.81)	154	4.25 (3.62–4.99)
Diarrhoea	78	4.13 (3.29–5.18)	856	2.05 (1.92–2.2)	266	5.32 (4.7–6.02)
Nausea/Vomiting	10	0.41 (0.22–0.76)	370	0.7 (0.63–0.77)	82	1.26 (1.01–1.57)
Fatigue	10	0.42 (0.22–0.78)	478	0.93 (0.85–1.01)	135	2.15 (1.81–2.55)
Decreased appetite	21	2.83 (1.84–4.34)	465	2.9 (2.65–3.18)	46	2.31 (1.73–3.09)
Dyspnoea	24	1.37 (0.92–2.05)	402	1.06 (0.96–1.17)	67	1.43 (1.12–1.82)
Pneumonia	15	1.43 (0.86–2.38)	280	1.23 (1.1–1.39)	36	1.28 (0.92–1.78)
Asthenia	18	1.54 (0.97–2.45)	279	1.1 (0.98–1.24)	50	1.6 (1.21–2.12)
Dry skin	12	3.13 (1.77–5.52)	201	2.42 (2.11–2.78)	35	3.41 (2.45–4.76)
Pruritus	25	2.19 (1.47–3.25)	162	0.65 (0.56–0.76)	34	1.1 (0.79–1.55)
Weight decreased	16	1.85 (1.13–3.02)	246	1.31 (1.16–1.49)	23	0.99 (0.66–1.49)
Stomatitis	12	6.58 (3.73–11.6)	170	4.31 (3.71–5.01)	18	3.67 (2.31–5.84)
Pleural effusion	13	6.76 (3.92–11.66)	327	7.91 (7.09–8.83)	6	1.16 (0.52–2.58)
Pyrexia	15	1.39 (0.84–2.32)	215	0.92 (0.81–1.05)	24	0.83 (0.56–1.24)
Interstitial lung disease	4	2.76 (1.04–7.37)	439	14.29 (13–15.71)	4	1.03 (0.39–2.75)

(Continued on following page)

TABLE 9 (*Continued*) Signal profiles of AEs induced by EGFR-TKIs at the PT level.

PT	Gefitinib (N = 22653)			Erlotinib (N = 111361)			Afatinib (N = 21758)		
	N	ROR (95%CI)		N	ROR (95%CI)		N	ROR (95%CI)	
Acne	5	2.02 (0.84–4.86)	◉	49	0.91 (0.69–1.21)	◉	86	13.18 (10.65–16.31)	◉
Anaemia	3	0.5 (0.16–1.54)	◉	144	1.11 (0.94–1.3)	◉	8	0.5 (0.25–0.99)	◉
Constipation	5	0.78 (0.32–1.87)	◉	117	0.84 (0.7–1.01)	◉	24	1.39 (0.93–2.08)	◉
Respiratory failure	5	2.17 (0.9–5.23)	◉	141	2.84 (2.41–3.35)	◉	6	0.97 (0.44–2.17)	◉
Pulmonary embolism	8	2.61 (1.3–5.23)	◉	164	2.48 (2.13–2.89)	◉	13	1.58 (0.92–2.73)	◉

The ROR (95% CI) is followed by indicators, with red denoting positive signals and green indicating negative signals.

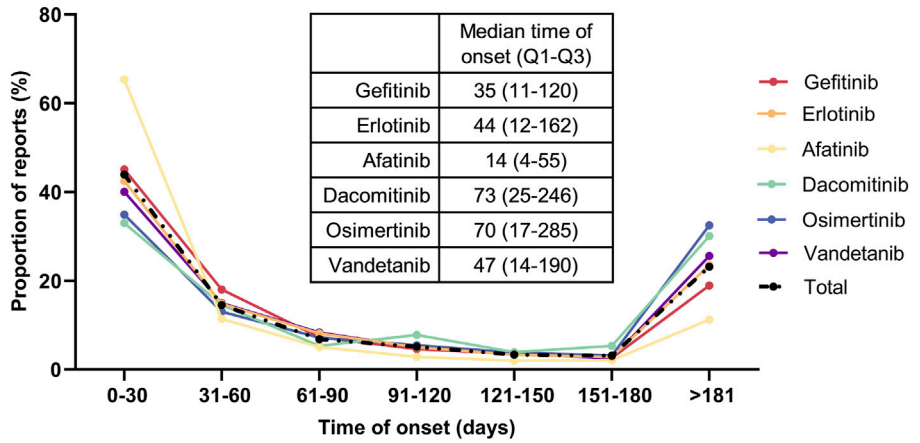

FIGURE 8
Time to onset of AEs Induced by different EGFR-TKIs.

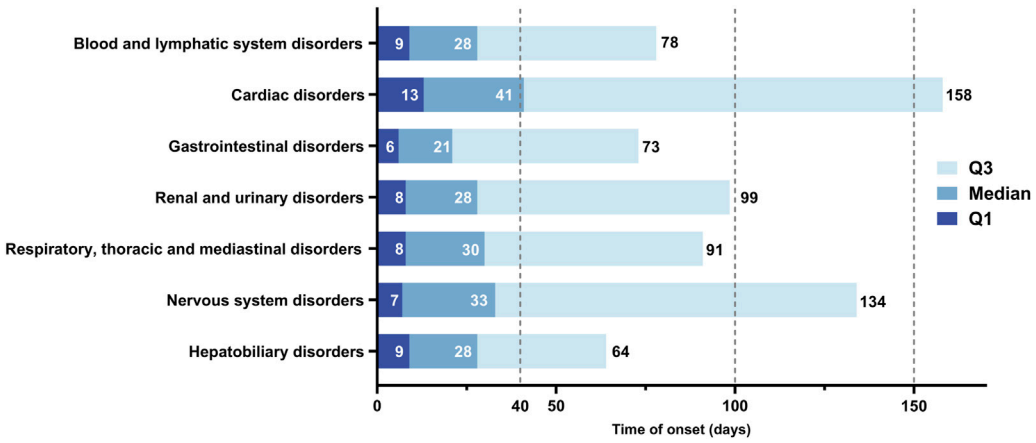

FIGURE 9
Time to onset of AEs in different systems induced by EGFR-TKIs.

diverging from real-world scenarios. Concurrently, a DA was performed utilizing the FAERS database, a repository established to facilitate the FDA's post-market surveillance of drugs and therapeutic biologics, which encompasses comprehensive and standardized reports of all AEs collected by the FDA. By merging these approaches, the FAERS dataset furnished expansive real-world

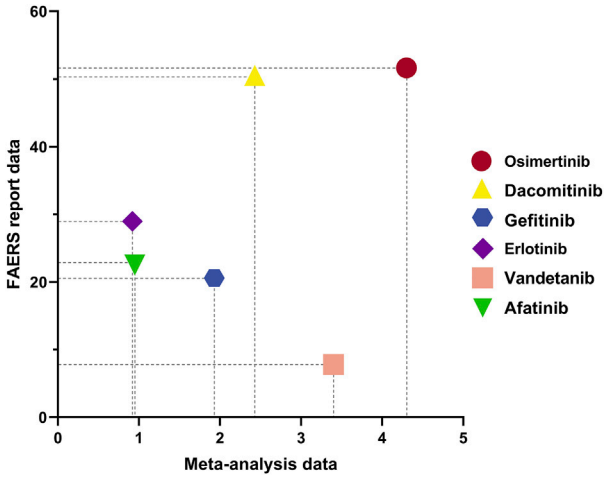

FIGURE 10
Mortality of AEs induced by different EGFR-TKIs in two research methods.

evidence, while RCTs contributed high-quality experimental data, thereby facilitating a more holistic and precise assessment of EGFR-TKI safety.

Our NMA revealed several key findings. First, over 80% of EGFR-TKI users experienced AEs, although the incidence of high-grade AEs (≥3) was relatively low at 17.7%. However, the rates for Osimertinib (37.8%) and Dacomitinib (41.6%) were significantly higher, suggesting that these drugs may require more cautious use in specific patient populations. Furthermore, DA showed that Osimertinib was not only significantly associated with Blood and lymphatic system disorders, Gastrointestinal disorders, and Renal and urinary disorders but was also the only EGFR-TKI to yield a positive signal for Cardiac disorders. This finding is particularly important for patients with a history of cardiac diseases or impaired cardiac function, as cardiovascular AEs such as QT prolongation, reduced left ventricular ejection fraction (LVEF), and heart failure can severely impact their quality of life and prognosis. Therefore, when prescribing Osimertinib, physicians should closely monitor electrocardiograms and cardiac function indicators to promptly identify and manage potential cardiovascular risks. In contrast,

TABLE 10 Mortality rates of AEs induced by different EGFR-TKIs in two research methods.

	FAERS analysis data			Meta-analysis data			AE fatality rate product area
	No. of deaths	N	Fatality Rate(%)	No. of deaths	N	Fatality Rate(%)	
Osimertinib	10385	20103	51.66	12	279	4.3	222.14
Dacomitinib	285	564	50.53	17	699	2.43	122.79
Gefitinib	1480	7184	20.6	62	3217	1.93	39.76
Erlotinib	11639	40159	28.98	27	2934	0.92	26.66
Vandetanib	105	1344	7.81	24	706	3.4	26.55
Afatinib	1316	5842	22.53	15	1571	0.95	21.4

The AE fatality rate product area is the product of the percentage mortality rate of AEs for a specific EGFR-TKI in a network meta-analysis and the percentage mortality rate of AEs in the FAERS database.

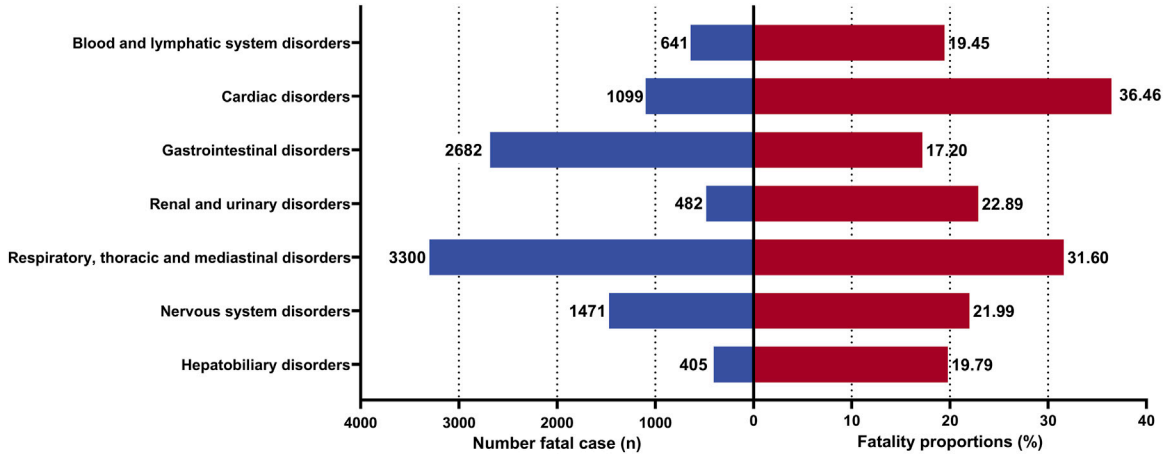

FIGURE 11
Mortality of AEs in different systems induced by EGFR-TKIs.

Dacomitinib was more frequently associated with Respiratory, thoracic and mediastinal disorders, Nervous system disorders, and Hepatobiliary disorders. These AEs can also negatively affect patients' health and quality of life. Hence, when using Dacomitinib, physicians should also monitor the respiratory, nervous, and hepatobiliary systems and tailor treatment plans based on the patient's specific conditions and potential risks.

We further employed two methods to delve into the specific AEs associated with different EGFR-TKIs. On one hand, we calculated RORs based on FAERS data; on the other, we aggregated data from randomized controlled trials to assess the incidence rates of specific AEs induced by various EGFR-TKIs. In both research approaches, rankings were derived from respective datasets, revealing an overlap of ten out of the top twenty AEs, encompassing Rash, Nausea/Vomiting, Fatigue, Dyspnea, Pneumonia, Dry Skin, Stomatitis, Anorexia, Interstitial Lung Disease (ILD), and Anemia. Among these prevalent and critically concerning AEs, some like Rash, Nausea/Vomiting, Fatigue, Dry Skin, Stomatitis, and Anorexia may ameliorate through dose adjustment or symptomatic treatment. Conversely, others such as Dyspnea, Pneumonia, ILD, and Anemia could necessitate treatment interruption or cessation, severely impacting prognosis or causing irreversible physiological alterations, including unintended mortality, particularly warranting vigilance towards respiratory complaints and diseases. Beyond common AEs, META analysis highlighted additional top twenty AEs including Alopecia, Constipation, Myalgia/Arthralgia, Elevated AST, Elevated ALT, Increased Creatinine Levels, Leukopenia, Thrombocytopenia, Insomnia, and Chest Pain. Meanwhile, FAERS data underscored ROR-prominent AEs comprising Diarrhea, Asthenia, Pruritus, Weight Loss, Pleural Effusion, Pyrexia, Acne, Constipation, Respiratory Failure, and Pulmonary Embolism. This discrepancy suggests that clinical trial reports tend to emphasize laboratory test abnormalities, whereas physician- or patient-reported outcomes lean towards subjective experiences. It underscores the necessity not only to prioritize these AEs to prevent potential severe consequences but also to intensify laboratory monitoring during EGFR-TKI therapy to ensure timely detection of AEs, thereby mitigating diagnostic omissions and associated risks.

Research based on the FAERS database has revealed the temporal distribution characteristics of AEs during EGFR-TKI treatment. The study found that most AEs occur within 60 days of treatment initiation, with no significant differences observed among various EGFR-TKIs. However, within the first 30 days of treatment, Afatinib had the highest proportion of AEs, while after 180 days of treatment, Osimertinib exhibited the highest proportion. Further analysis showed that gastrointestinal disorders had the shortest median onset time at 21 days, whereas cardiac disorders had the longest median onset time at 41 days. Additionally, the ROR for gastrointestinal disorders caused by Afatinib was significantly higher than that for other EGFR-TKIs, and the ROR for cardiac disorders caused by Osimertinib was markedly higher than that for other EGFR-TKIs. These findings indicate that Afatinib is associated with a higher incidence of gastrointestinal AEs, which generally occur early in the treatment course. Conversely, Osimertinib may lead to a higher incidence of cardiac disorders, which usually occur later in the treatment process. This discovery underscores the importance of carefully considering the risk of cardiac disorders when selecting an EGFR-TKI for clinical practice, especially during long-term treatment.

Research based on the FAERS database has revealed the temporal distribution patterns of AEs during EGFR-TKI therapy. It was found that most AEs occur within the first 60 days of treatment, with no significant differences observed among various EGFR-TKIs. However, Afatinib had the highest proportion of AEs occurring within the first 30 days of treatment, whereas Osimertinib had the highest proportion of AEs after 180 days of treatment. Further analysis showed that gastrointestinal disorders had the shortest median time to occurrence at 21 days, while cardiac disorders had the longest at 41 days. Additionally, Afatinib-induced gastrointestinal disorders had a significantly higher ROR025 than other EGFR-TKIs, and Osimertinib-induced cardiac disorders had a notably higher ROR025 compared to other EGFR-TKIs. This suggests that Afatinib is associated with a higher incidence of gastrointestinal AEs, which typically occur early in the treatment period. Conversely, Osimertinib may be associated with a higher incidence of cardiac disorders, which tend to occur later. This finding underscores the need for careful consideration of cardiac risk, particularly during long-term treatment, when selecting an EGFR-TKI in clinical practice.

We conducted an exploratory study on the mortality rate associated with AEs. First, discrepancies in mortality rates between the FAERS database and RCTs included in the META-analysis primarily arise from differences in data collection methods. The FAERS database relies on spontaneous reporting, which may include more complex and severe cases, leading to higher mortality rates. In contrast, RCTs are conducted under stringent conditions with a relatively homogeneous patient population. Additionally, variations in patient demographics, medication usage, and statistical methodologies could further influence the results. Second, an analysis of death cases due to AEs across different systems within the FAERS database revealed that respiratory system-related AEs had the highest number of deaths, while cardiovascular AEs had the highest mortality rate. Respiratory issues may be linked to drug-induced damage to lung cells, whereas cardiovascular events, once occurred, have a high mortality rate possibly due to interference with cardiac cell function. Third, we combined data from the FAERS database and RCTs for the first time to compare the mortality rates of different EGFR-TKI-related AEs. Although the statistical interpretation might be limited, the multiplicative results were consistent with expectations, indicating that both datasets reflect similar drug risks. Notably, Osimertinib was associated with the highest mortality rate among EGFR-TKIs, especially for cardiovascular-related AEs. This suggests potential cardiovascular safety concerns with Osimertinib and corroborates previous findings about its association with delayed cardiac AEs. Therefore, it is imperative to enhance long-term monitoring and follow-up of patients treated with Osimertinib to promptly detect and manage cardiovascular issues, thereby preventing patient mortality due to cardiovascular AEs.

5 Limitations

This study, despite employing a variety of analytical methods, has certain limitations. Firstly, the spontaneous reporting nature of

FAERS data may introduce bias into the results. Secondly, NMA is constrained by the quality and heterogeneity of the included studies, which may potentially affect the accuracy of the outcomes. Additionally, factors such as heterogeneity within patient populations and insufficient consideration of individual differences may impact the generalizability and comprehensiveness of the findings.

6 Conclusion

This study employed a comprehensive approach combining NMA and DA from the FAERS database to examine AEs associated with EGFR-TKIs. The results indicated that different EGFR-TKIs are associated with distinct AE profiles, predominantly characterized by relatively mild events such as Rash and Nausea. However, Osimertinib and Dacomitinib exhibited higher rates of high-grade AEs, with Osimertinib showing a significant association with cardiac disease risk. Additionally, AEs were frequently observed at the onset of treatment, but Osimertinib was found to cause more delayed AEs and had the highest mortality rate among these events. Therefore, when prescribing EGFR-TKIs, physicians should thoroughly assess patient conditions and closely monitor for AEs, especially cardiac function, regularly, to ensure patient safety.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

Ethics statement

Ethical approval was not required for the study involving humans in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and the institutional requirements.

Author contributions

JS: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Software, Validation, Visualization, Writing–original draft, Writing–review and editing. XL: Conceptualization, Data curation, Investigation, Resources, Supervision, Writing–review and editing. MG: Conceptualization, Data curation, Formal Analysis, Methodology, Visualization, Writing–review and editing. JY: Conceptualization, Data curation, Validation, Visualization, Writing–review and editing. TC: Data curation, Formal Analysis, Investigation, Methodology, Validation, Visualization, Writing–review and editing. YJ: Data curation, Project administration, Supervision, Writing–review and editing. JL: Data curation, Formal Analysis, Validation, Writing–review and editing. YZ: Conceptualization, Data curation, Funding acquisition, Project administration, Resources, Software, Supervision, Visualization, Writing–review and editing. LW: Conceptualization, Project administration, Resources, Software, Supervision, Validation, Writing–review and editing.

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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.

Generative AI statement

The author(s) declare that no Generative AI was used in the creation of this manuscript.

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Anlotinib induced type 1 diabetes: a case report

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Studies have shown some tyrosine kinase inhibitors (TKIs) can influence glucose metabolism leading to either hypoglycemia or hyperglycemia which is reversable in most patients after treatment cessation. Anlotinib is a novel oral multi-target tyrosine kinase inhibitor (TKI) which has been approved for non-small cell lung cancer in China. Previous studies of anlotinib did not report it has any side effect on blood glucose, and there has been no case reporting type 1 diabetes associated with any TKI. The present case study, to our knowledge, was the first to report on an 81-year-old man with lung cancer who developed type 1 diabetes following 14 cycles treatment with TKI. The fasting plasma blood glucose and hemoglobinA1c (HbA1c) was 24.3mmol/L and 9.0%, respectively, and GADA (glutamic acid decarboxylase antibody) was more than 2000IU/ml (normal range is less than 10IU/ml) when he was diagnosed. We also conducted a literature review to explore the potential mechanism of anlotinib in inducing type 1 diabetes and recommend that self-monitoring blood glucose (SMBG) for fasting and random postprandial blood glucose at least once a week is needed for early identification of glucose dysregulation when using TKI drugs, and monthly fasting and random postprandial plasma glucose monitoring and HbA1c test every 3 months is also recommended if the SMBG protocol cannot be completed.

KEYWORDS

anlotinib, type 1 diabetes, TKI - tyrosine kinase inhibitor, VEGF - vascular endothelial growth factor, autoimmune disease

Introduction

Tyrosine kinase inhibitors (TKIs) have been at the forefront in targeted chemotherapy for cancers over the past two decades, and anlotinib is a novel oral multi-target tyrosine kinase inhibitor (TKI) which has been approved for non-small cell lung cancer in China (1, 2). Studies have shown some TKIs can influence glucose metabolism leading to either hypoglycemia or hyperglycemia, which is reversable in most patients after treatment cessation (3). TKIs such as imatinib, erlotinib, and sunitinib can improve blood glucose concentration potentially in part due to preservation of functional β cell mass and increasement of insulin sensitivity or insulin secretion. While others such as Nilotinib, ceritinib and rociletinib may raise blood glucose levels attributing to pancreatic β-cell insulin secretion impairment or development of insulin resistance and inhibition of the insulin receptor (4, 5). However, the exact mechanism by which TKIs elicit an increase or a decrease in patients largely remains unknown. TKIs with similar structure and same target such as imatinib and nilotinib have shown opposite effects on glucose metabolism, even certain TKI such as imatinib has exhibited contrasting effects on

blood glucose levels when used to treat different tumors (6, 7). Imatinib has shown glucose-lowing effects in the treatment of chronic myeloid leukemia, while in gastrointestinal stromal tumors, hyperglycemia has been reported with the use of imatinib in 0.1-1% of cases (8). In summary, TKIs exert markedly different effects on glucose metabolism depending on the specific TKI and the type of tumor being treated. Previous studies of anlotinib did not report it has any side effect on blood glucose level, and there has been no case reporting type 1 diabetes associated with any TKI, therefore, this case study is the first, to our knowledge, to report on a patient who developed type 1 diabetes following treatment with TKI.

Case presentation

An 81-year-old man without family history of diabetes or any chronic disease was diagnosed with lung adenocarcinoma (T4N2M1) in October 2020. He received gyroknife radiotherapy for left and right lung malignancies 12 times in November 2020, and 12 times for right lung malignancies in June 2021. In September 2022, the patient was administrated anlotinib 8mg orally once daily for 14 days every 3 weeks due to tumor progression. After 14 cycles treatment of anlotinib, his fasting plasma glucose was found at 26.1mmol/L and urine ketone was (+++) on July 12th 2023, then he was admitted to Endocrinology Department of Chongqing General Hospital (the blood glucose levels prior to anlotib administration and during the 14 cycles is shown in Figure 1). Other long term drug use history, anti-tumor drugs, medications known to potentially cause hyperglycemia such as steroids, records of SARS-CoV-2 vaccination or confirmed SARS-CoV-2 infection was not identified before admission. We only found history of short-term use of proton pump Inhibitors and anti-biotics before the onset of diabetes. Additionally, there were no symptoms of respiratory or gastrointestinal infections noted within one month before admission. Laboratory parameters were measured upon admission are detailed in Table 1. The patient was diagnosed with type 1 diabetes and was treated with insulin degludec in combination with insulin aspartate, and he was discharged on July 19th, 2023 with the hypoglycemic regimen (insulin degludec 5 units in the morning and insulin aspartate 4 units three times a day). The patient reported a significant increase in blood glucose levels after re-starting anlotinib one week after discharge. The highest blood glucose level recorded was 30.1 mmol/L and insulin dose was increased to maintain his glucose levels. Conversely, the blood glucose decreased significantly and the dosage of injected insulin was decreased after 14 days of anlotinib treatment (blood glucose level in the 15th and 16th cycle is shown in ure2). After two cycles of anlotnib treatment, his oncologist decided to discontinue the use of anlotinib due to tumor progression and its significant negative impact on glucose metabolism (the laboratory parameters after 16th cycle is shown in Table 1). The patient had tried afatinib, erlotinib and osimertinib before he passed way in March 1st, 2024. The follow-up blood glucose level did not reveal any significant fluctuation before his death (the follow-up blood glucose level is shown in Figure 2). Informed consent had been obtained from the patient to present all his clinical data.

Discussion

With the development and application of new generation of TKI drugs such as anlotinib with more targets, their influence on glucose metabolism is more complex and harder to predict, some previously unknown forms of type 1 diabetes may occur when using new generation of TKI drugs. We conducted a literature review to explore the potential mechanism of anlotinib in inducing type 1 diabetes in this case. Firstly, Anlotinib exerts significant inhibitory effects on angiogenesis both *in vivo* and *in vitro* (9–11). The impact on islet blood vessels presents a dual effect on type 1 diabetes development. While it can impede the proliferation of islet blood vessels, thereby reducing inflammatory cell migration and restoring normal blood glucose metabolism (11, 12). It can also exacerbate islet capillary degeneration which may lead to islet hypoperfusion and subsequent abnormal hormone secretion from islet cells (13, 14). The mean progression-free survival (PFS) of anlotinib in lung adenocarcinoma was 5.5 months (15), however the patient had

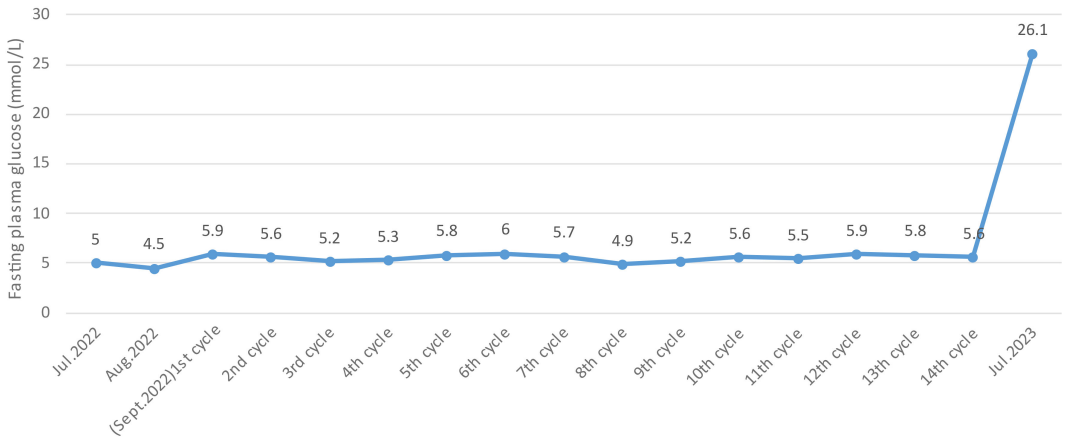

FIGURE 1
Fasting plasma glucose (before admission).

TABLE 1 Laboratory parameters on admission to Endocrinology Department of Chongqing General Hospital and after the 16th cycle of anlotinib treatment.

Parameter	Value		Normal range
	on admission to Endocrinology Department of Chongqing General Hospital	after the 16th cycle of anlotinib treatment	
GADA (IU/ml)	> 2000	–	< 10
ICA (COI)	43.4	–	< 1
IAA (CDI)	< 1	–	< 1
Fasting blood glucose (mmol/L)	24.3	8.7	3.9-6.1
Fasting insulin (uIU/L)	0.83	–	4.03-23.5
FastingC-peptide (ng/ml)	0.13	–	0.3-3.73
Hemoglobin A1c, HbA1c(%)	9.0	8.1	4.5-6.3
Hemoglobin (g/L)	96	113	130.00-175.00
Serum albumin (g/L)	27.2	30.4	40-55
TC (mmol/L)	4.17	4.39	<5.20
TG (mmol/L)	0.67	0.58	0.00-1.70
LDL-C (mmol/L)	2.43	2.15	<3.37
Crea (umol/L)	87.7	90.1	57.0-111.0
AST (U/L)	16	17.8	15.0-40.0
ALT (U/L)	11.6	12.3	9.0-50.0
TSH (mIU/L)	5.32	–	0.3-5.5
FT3 (pmol/L)	4.41	–	3.08-7.00
FT4 (pmol/L)	18.0	–	11.57-22.36
pancreatic amylase (U/L)	63.6	–	35.0-135.0
lipase (U/L)	14.5	–	8.0-53.0

GADA, glutamic acid decarboxylase antibody; ICA, insular cellular antibody; IAA, insulin autoimmune antibody; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride; AST, aspartate transaminase; ALT, alanine aminotransferase; TSH; thyroid stimulating hormone; FT3, free triiodothyronine; FT4, free thyroxine

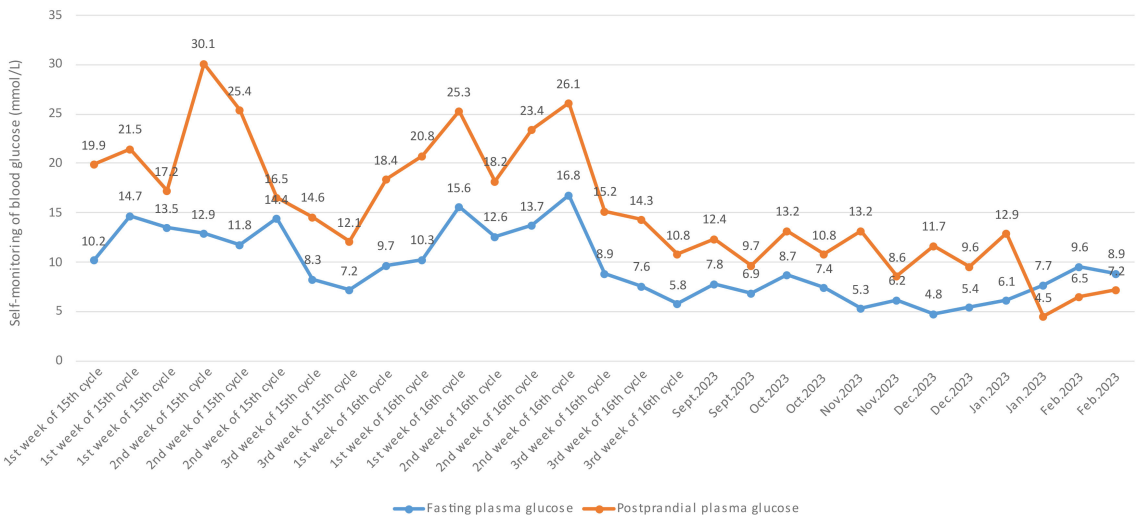

FIGURE 2
Fasting and random postprandial plasma glucose (after discharge).

received anlotinib treatment for nearly 10 months before hyperglycemia was noticed in our case. Consequently, it is hypothesized that the potential harm resulting from prolonged anlotinib use, which excessively inhibits normal islet capillaries, outweighs the benefits of blocking increased blood supply, ultimately leading to abnormal insulin secretion and diabetes development. Secondly, Type 1 diabetes is an autoimmune disease caused by the immune-mediated destruction of insulin-producing pancreatic β cells (16). It is hypothesized that the neoantigen released by the tumor might be similar with Glutamic Acid Decarboxylase 65 (GAD65) expressed by panreatic β cells in this case, therefore, activated T cell induced by the neoantigen might also destruct β cells through molecular mimicry. Anlotinib treatment can break immune tolerance of tumor microenvironment and inhibit tumor growth by enhancing CD8+ T cell infiltration which is dependent from the anti-angiogenesis effect (17). The enhanced anti-tumor immune response might also trigger the increased auto-immune attack to pancreatic β cells Which accelerated β cell reserve depletion, resulting the late-onset of type1 diabetes of this patient, it might also explain the phenomenon of blood glucose fluctuation during the last 2 cycles of anlotinib treatment (18, 19). Besides, recent evidence suggests anlotinib's immunomodulatory effects may paradoxically amplify pre-existing autoimmunity. therefore, its capacity to enhance CD8+ T-cell infiltration could theoretically facilitate islet-directed immune attacks if the patient in our case was genetically predisposed (20). Thirdly, TKIs have been shown to have direct toxic effects on various organs and systems in the body including the pancreas. The toxicity of TKIs is attributed to their active metabolites, which are generated when TKIs interact with metabolic enzymes in the human body (5, 21, 22). It is hypothesized that the direct toxic effects of TKIs active metabolites on islet beta cells may play a role in the development of type 1 diabetes in this case. Future studies could leverage zebrafish xenotransplant models which successfully employed in TKI efficacy evaluation to dissect tissue-specific toxicity profiles (23).Fourthly, as a multi-target TKI with potent VEGFR2/FGFR/PDGFR inhibition, anlotinib's metabolic impacts may differ from single-target agents which may have a significant impact on 14 endogenous metabolic pathways including glucose metabolism. This interference can lead to fluctuations in endogenous metabolites, causing both increases and decreases that result in side effects (5, 24). It is postulated that prolonged disruption of these metabolic pathways may negatively affect glucose metabolism and potentially contribute to the onset of type 1 diabetes in our case (7, 8).

In conclusion, to the best of our knowledge, the present case study was the first to report on a case of type 1 diabetes induced by anlotinib. The patient's oncologist failed to identify the blood glucose dysregulation early although he regularly monitored fasting plasma glucose. Therefore, we recommend fasting blood glucose and HbA1c test to fully evaluate blood glucose before using TKI drugs. If the blood glucose is abnormal, diabetes-related autoantibodies should be further tested. We also recommend that SMBG for fasting and random postprandial blood glucose at least once a week is needed for early identification of glucose dysregulation when using TKI drugs. If the SMBG protocol can not be completed, we recommend to monitor fasting and random postprandial plasma glucose at least once o month and HbA1c every 3 months at outpatient clinics (25). In addition, further research is needed to explore the correlation and underlying mechanisms between TKI drugs and glucose metabolism.

Limitation

We did not do SARS-CoV-2 antibodies test at the onset of diabetes to completely exclude the possibility of asymptomatic virus infection which might lead to the development of diabetes. We did not do type 1 diabetes high-risk genes (e.g. human leukocyte antigen, HLA-DR4/DQ8) or related autoantibodies tests before anotinib treatment to know whether the patient was susceptible for ty1 diabetes, either. HbA1c was not tested before using anlotinib to exclude the possibility that post-prandial blood glucose had already met the diagnostic criteria of diabetes before treatment. Either Pancreatic imaging to assess islet inflammation or T cell receptor library analysis which might help us explore the mechanism of the type1 diabetes in this case was not done.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

JC: Writing – original draft, Writing – review & editing. DX: Writing – original draft, Writing – review & editing. LK: Writing – original draft, Writing – review & editing.

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Publisher's note

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