Drug resistance mechanisms and progress in the treatment of EGFR-mutated lung adenocarcinoma (Review)

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Received June 28, 2022; Accepted September 7, 2022

DOI: 10.3892/ol.2022.13528

Abstract. According to global cancer data, lung cancer was the leading cause of cancer-related death in 2020. With the diversification of treatment strategies, the survival outcomes of patients with advanced lung cancer have improved significantly, but the 5-year overall survival rate remains <20%. Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) are the preferred treatment for lung adenocarcinoma patients with EGFR-sensitive mutations; however, acquired drug resistance is inevitable. Osimertinib (a third-generation EGFR inhibitor) is the most commonly used drug for cancers with a secondary T790M mutation. Unfortunately, acquired drug resistance against third-generation drugs still emerges. The C797s mutation is the primary acquired resistance mechanism against Osimertinib. Research on fourth-generation EGFR-TKI drugs with a C797s mutation is currently at various experimental stages, and no drug has been approved for clinical use. In addition to the resistance mechanisms described above, HER2 amplification, MET amplification, PIK3A mutation, KRAS mutation, BRAF mutation, transformation to small cell lung cancer, transformation to lung squamous cell carcinoma, and EMT have been reported as mechanisms of acquired drug resistance to first-, second- and third-generation EGFR-TKIs. These mechanisms are noted in a relatively high proportion of tumors, but treatment options are limited. In recent years, immunotherapy has made progress in the treatment of several cancers, including advanced EGFR-mutated non-small cell lung cancer (NSCLC). Due to the relatively high frequency of EGFR mutation in patients with lung adenocarcinoma in China, an increased number of patients develop EGFR-TKI resistance, and subsequent treatment options are critical. This article reviews the mechanisms of drug resistance to different EGFR-TKIs and treatment progression, providing ideas for the follow-up treatment for EGFR-resistant patients.

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Key words: non-small cell lung cancer, acquired resistance mechanism, tyrosine kinase inhibitor, immunotherapy, fourth generation epidermal growth factor receptor tyrosine kinase inhibitors

Contents

1. Introduction

According to global cancer data statistics, lung cancer was the leading cause of cancer-related death in 2020 (1). Approximately 30% of cancer-related deaths in China are related to lung cancer, which remains the most common cancer type (2). Clinical statistics show that non-small cell lung cancer (NSCLC) accounts for ~85% of lung cancer cases, and lung adenocarcinoma is the most common type of NSCLC (1). Recently, with the introduction of molecular-targeted drugs and immune checkpoint inhibitors, the survival outcomes of patients with advanced lung cancer have improved greatly, but the 5-year overall survival rate of patients with lung adenocarcinoma remains less than 20% (3-5).

According to statistics, the incidence of epidermal growth factor receptor (EGFR) mutations in Caucasians is ~20% (6), whereas the rate is 44-50% among Asian nonsmoking NSCLC patients (7,8). The higher frequency of EGFR mutations appears to be beneficial for Asian lung adenocarcinoma patients. EGFR tyrosine kinase inhibitors (TKIs) are currently the first-line treatment for lung adenocarcinoma patients with EGFR-sensitive mutations (4,9-14); unfortunately, most patients develop acquired drug resistance after 10-14 months of EGFR-TKI treatment (14,15). The mechanisms of acquisition of drug resistance to first- and second-generation EGFR-TKIs

are complex, and the most important mechanism of acquired drug resistance is the secondary T790M mutation, accounting for 50-60% of all cases (16). The third-generation EGFR inhibitor Osimertinib is the most common drug used for the treatment of patients with this mutation (17). However, acquired drug resistance still emerges against third-generation drugs typically 8-10 months after receiving Osimertinib (17,18). The C797s mutation is the primary mechanism of acquired drug resistance (19). Research on fourth-generation EGFR-TKI drugs for the treatment of tumors with a C797s mutation is currently at various experimental stages, although no drug has been approved for clinical use.

Due to the relatively high frequency of EGFR mutations in patients with lung adenocarcinoma in China, an increasing number of patients develop EGFR-TKI resistance, and subsequent treatment options are critical. This article reviews the mechanisms of drug resistance and treatment progress after EGFR-TKI resistance.

2. Drug resistance mechanisms and progress in the use of first- and second-generation EGFR-TKIs

The mechanisms of acquired drug resistance against first- and second-generation EGFR-TKIs are complex and can be divided into three categories: Changes in EGFR, activation of alternative bypass or downstream pathways, and changes in the phenotype (Fig. 1).

Changes in EGFR

T790M mutation. A secondary T790M mutation is the most important mechanism of acquired drug resistance against first-generation EGFR-TKIs. The crystal structure of the ATP binding pocket is altered due to this mutation, inhibiting the binding of TKIs and ATP. Thus, downstream signal transduction cannot be inhibited by TKIs, and these drugs do not subsequently restrict tumor growth (20,21). The mechanism of action of the first-generation EGFR-TKI differs from that of the second-generation EGFR-TKI; the second-generation EGFR-TKI irreversibly binds to the ErbB receptor, resulting in a more potent effect than the first-generation drugs (22), but the mechanism of drug resistance is similar (23-25). In the ARCHER1050 study, dacomitinib had overall survival (OS) benefits relative to gefitinib in the Chinese population (median overall survival (mOS) duration was 32.5 months vs. 24.9 months, P=0.0097) (26). The LUX-Lung7 trial compared the efficacy of afatinib and gefitinib for the treatment of NSCLC patients with EGFR mutations. The results showed that the progression-free survival (PFS) duration of the afatinib group was longer than that of the gefitinib group (11.0 vs. 10.9 months; P=0.017) (11). These results suggest that compared with first-generation EGFR-TKIs, the effects of second-generation EGFR-TKIs are longer in the context of T790M.

Osimertinib is the most widely used third-generation EGFR-TKI and it can effectively and selectively inhibit tumors with EGFR-sensitive and T790M drug-resistant mutations (27), exhibiting a significant effect in NSCLC patients with brain metastases (28,29). Almonertinib (30,31) and furmonertinib (32,33) have also been approved in China, and several other third-generation EGFR-TKI inhibitors are in different stages of research and development (Table I). Lazertinib achieved a 57% overall response rate (ORR) in the T790M (+) population in a phase 2 clinical trial (34). The drug exhibited a potent beneficial effect on brain lesions, and the intracranial disease control rate in the entire population was 90.6% (35). In January 2021, the Korean Food and Drug Administration (MFDS) approved the listing of lazertinib for the treatment of patients with locally advanced or metastatic NSCLC positive for EGFR T790M mutations who previously received EGFR-TKI treatment (36). The third-generation EGFR-TKIs olmutinib (37-39) and nazartinib (40) are also approved in South Korea.

Secondary mutations. Other rare secondary mutations, such as L747S (41), D761Y (42), and T854A (43), have also been reported to be associated with gefitinib or erlotinib resistance. Due to the low incidence of these mutations, there are few *in vitro* studies and case reports showing whether Osimertinib is effective against these rare mutations (44-47).

Activation of alternative bypass or downstream pathways

Human EGFR2 gene (Her2) amplification. Activation of HER2, also known as ERBB2, triggers functional abnormalities in several downstream signaling pathways, such as the mitogen-activated protein kinase (MAPK), inosine phosphate 3-kinase (PI3K)/protein kinase B (AKT), protein kinase C (PKC), and signal transducer and transcriptional activator (STAT) pathways, resulting in uncontrolled cell proliferation (48,49). HER2 overexpression occurs in ~12% of NSCLC patients who are resistant to first- and second-generation EGFR-TKIs and usually do not co-exist with the T790M secondary mutation (50). Standard treatment for managing this drug resistance mechanism is currently not available, and there is insufficient evidence to show that existing anti-HER2 therapies are effective. The selective HER2 tyrosine kinase inhibitors poziotinib (51) and pyrotinib (52,53), and the antibody conjugate drugs T-DM1 (54) and trastuzumabe-deruxtecan (55) are potential treatment options.

MET amplification. MET is a proto-oncogene and one of the key driver genes in several types of cancer (56). The MET gene encodes c-Met [a hepatocyte growth factor (HGF) receptor], which is responsible for regulating important processes, such as cell differentiation, proliferation, migration, and apoptosis (57). Hepatocyte growth factor (HGF) binds to c-Met to phosphorylate tyrosine kinase residues in the catalytic domain; activates the downstream pathways modulated by PI3K, MAPK, and STAT3 signaling, and promotes cell transformation, cell invasion, cell proliferation, and cell cycle progression (57,58). MET amplification accounts for 2-4% of untreated NSCLC cases (59) and for 5-20% of patients with acquired drug resistance against first- and second-generation EGFR-TKIs (58,60,61). Lai *et al* (62) showed that an increased copy number of the MET gene is not equal to MET amplification; only MET amplification is a determinant of EGFR-TKI resistance in NSCLC patients.

Due to the crosstalk between MET and RTK (EGFR) signaling pathways (63), it has been proposed that the combination of MET-TKIs and EGFR-TKIs may be a solution for MET-driven EGFR-TKI resistance (64). After disease progression in the context of EGFR-TKI treatment, patients with MET amplification were treated with camatinib

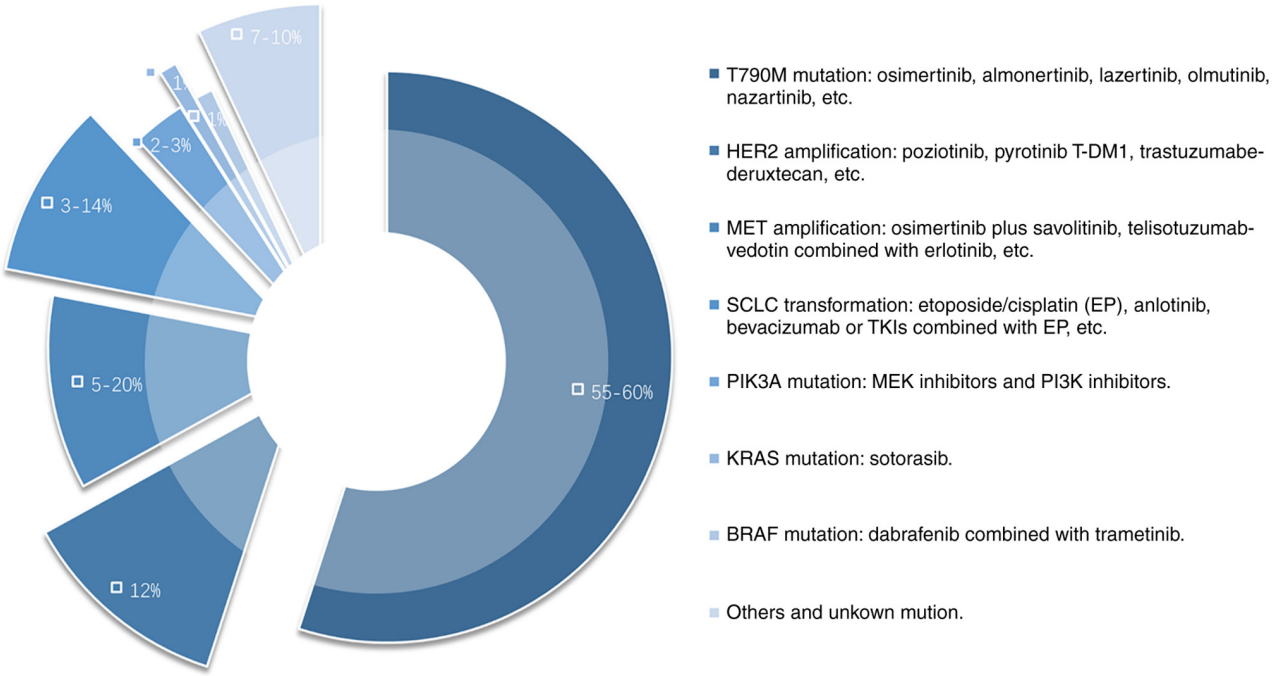

Figure 1. Mechanisms of resistance to first- and second-generation EGFR-TKIs and the corresponding therapies. EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor.

combined with gefitinib. The ORR was 29%, and the PFS was 5.5 months (65). Tepotinib combined with gefitinib prolonged the survival time compared with chemotherapy (mOS: 37.3 vs. 13.1 months) (66). Sequist *et al* (67) evaluated the efficacy of Osimertinib + savolitinib in two global expansion cohorts (part B and part D) of the Tatton study, and the results showed a higher response rate in subgroup B3 (previously untreated with third-generation EGFR-TKIs and positive for T790M) and subgroup D (previously untreated with third-generation EGFR-TKIs), with ORR values of 67 and 64% and median (m)PFS values of 11 and 9.1 months, respectively. Osimertinib combined with savolitinib is also a potential treatment approach (67). In addition to the above combination of treatments, telisotuzumab-vedotin combined with erlotinib (68), capmatinib combined with erlotinib (69), and emibetuzumab combined with erlotinib (70) also achieved certain benefits.

PIK3A mutations. PIK3A can induce the phosphorylation and subsequent activation of the downstream AKT signal transduction pathway and it plays a central role in regulating tumor cell growth, reproduction, migration, and apoptosis (71). The role of PIK3CA mutations in NSCLC remains contested. Some researchers consider PIK3CA mutations to be an independent risk factor for NSCLC patient survival (72), and the survival time of patients with EGFR and PIK3CA mutations treated with EGFR-TKIs was shown to be shorter than that of people with only EGFR mutations (73). However, it has also been shown that PIK3CA mutations have no significant effect on NSCLC patient survival times (74). PIK3CA mutations are a mechanism of acquired EGFR-TKI resistance in patients with EGFR-mutated lung cancer (75). The frequency of PIK3CA mutations after EGFR-TKI resistance is 2-3% (76). Preclinical studies have found that double targeting of MEK and PI3K can effectively control the proliferation of EGFR-TKI drug-resistant NSCLC cell lines (77). Alpelisib (a PI3K inhibitor) has been approved by the Food and Drug Administration (FDA) for the treatment of breast cancer (78), but it has not been applied for NSCLC after the development of resistance to TKIs.

KRAS mutations. KRAS mutations activate downstream pathways, such as the MAPK and PI3K pathways, driving the occurrence and development of tumors (79). The proportion of KRAS mutations after the development of EGFR-TKI resistance is ~1% (76). Tanaka *et al* (80) suggested that the mechanism underlying KRASG12C-acquired drug resistance to KRAS-TKI is related to the activation of the RAS-MAPK signals and the production of KRASY96D resistance genes. The FDA approved the KRASG12C inhibitor sotorasib in May 2021 to treat NSCLC patients with KRASG12C mutations after at least one previous systematic treatment (81).

BRAF mutations. BRAF mutations increase the activity of RAF kinase, activates downstream MEK, and regulates cell growth, proliferation, differentiation, migration, and apoptosis (82). BRAFV600E is the most common BRAF mutation, accounting for 36% of all BRAF mutations (83). BRAF mutations account for only 1% of patients with acquired drug resistance to TKIs (84). Dabrafenib combined with trametinib has been approved by the FDA for the treatment of metastatic NSCLC with BRAFV600E mutations (85).

Other rare mutations. The AXL-mediated Gas6/Axl signaling pathway is associated with tumor cell growth, metastasis, invasion, EMT, angiogenesis, drug resistance, immune regulation, and stem cell maintenance (86,87). In 2012, a study found that Axl expression was upregulated in patients with acquired drug resistance to EGFR-TKIs, and EGFR-TKI sensitivity was restored after blocking Axl (88). Thus, Axl is a promising therapeutic target for patients with acquired drug resistance. Small molecule inhibitors, monoclonal antibodies, and antibody-drug conjugates targeting Axl are currently under

Table I. Research and development of third-generation EGFR inhibitors in China.

Name	Manufacturer	Indications	Development phase
MEK162	Betta Pharmaceuticals	Advanced NSCLC with a T790M mutation after EGFR resistance	Declared/listed
		Previously untreated NSCLC patients with locally advanced or metastatic EGFR sensitive mutations	Phase 2/3 clinical trial
AC0010 (Avitinib)	Acea Biosciences	Advanced NSCLC with a T790M mutation after EGFR resistance	Declared/listed
		NSCLC with EGFR mutations	Phase 3 clinical trial
BPI-7711	Beta Pharma, Inc.	Advanced NSCLC with a T790M mutation after EGFR resistance	Declared/listed
		NSCLC with EGFR mutations	Phase 3 clinical trial
ASK120067	Suzhou Aosaikang Biomedical Co.	Advanced NSCLC with a T790M mutation after EGFR resistance	Phase 1/2 clinical trial
		NSCLC with EGFR mutations	Phase 3 clinical trial
SH-1028	Nanjing Sanhome Pharmaceutical Co.	Advanced NSCLC with a T790M mutation after EGFR resistance	Phase 2 clinical trial
		NSCLC with EGFR mutations	Phase 3 clinical trial
FHND9041	Nanjing Chuangren Pharmaceutical Technology Center	Advanced NSCLC with a T790M mutation after EGFR resistance	Phase 1/2 clinical trial
YZJ-0318	Yangtze River Pharmaceutical (Group) Co.	Advanced NSCLC with a T790M mutation	Phase 1 clinical trial
MED-1007	Jiangsu Maidu Pharmaceutical Co.	Advanced NSCLC with a T790M mutation after EGFR resistance	Phase 1 clinical trial
BEBT-109	Bebtter Medicine Technology	Advanced NSCLC with a T790M mutation after EGFR resistance	Phase 1 clinical trial
TY-9591	Zhejiang Tongyuan Kang	Advanced NSCLC with a T790M mutation	Phase 1 clinical trial
TQB3456	Chiatai Tianqing	Advanced NSCLC with a T790M mutation	Phase 1 clinical trial
Lazertinib	Yuhan Corporation	Combination of amivantamab for treatment of Osimertinib resistant NSCLC	Phase 1 clinical trial
		NSCLC	Phase 3 clinical trial

NSCLC, non-small cell lung cancer; EGFR, epidermal growth factor receptor.

development (89). DS-1205 (an AXL inhibitor) combined with gefitinib (90) and BGB324 (an AXL inhibitor) combined with erlotinib (91) were evaluated, and preliminary results were promising.

PTEN negatively regulates the PTEN/PI3K/Akt signaling pathway and regulates cell growth, apoptosis, and migration (92). Studies have shown that patients with EGFR mutations with PTEN deletions have significantly shorter PFS durations than those without PTEN deletions (6 vs. 18 months) (93). According to Xun *et al* (92), the deletion of PTEN in lung cancer promotes the carcinogenic function of STMN1 (overexpression of which is related to tumor growth, metastasis, and poor survival) through the PI3K/AKT pathway. Other reported drug resistance mechanisms include loss of neurofibromin 1 activity (94), amplification of the CT10 homologous oncogene of v-crk avian sarcoma virus (95), a multistep mechanism involved in the insulin-like growth factor 1 receptor (IGF1R) pathway (96), and the fibroblast growth factor (FGF) 2/FGF receptor 1 (FGFR1) autocrine growth pathway (97). As these drug resistance mutations are rare, no drugs targeting them have been approved.

EGFR compound mutations and co-mutations. Compound mutations indicate the presence of more than one EGFR mutation, either common or uncommon, within the same tumor. Attili *et al* (98) found high heterogeneity in the incidence of compound mutations (4-26% of total EGFR mutant cases), with the variance possibly due to the different testing methods adopted, and the specific mutations considered. In various combinations, compound EGFR mutations containing either exon 21 p. L858R or exon 19 deletions were common (99). The response rate of those tumors with compound mutations to EGFR-TKIs compared with those with single mutations is contested. Rossi *et al* (100) found a longer mOS in the compound mutation group than in the single rare mutation group (33.6 vs. 12 months; P=0.473), whereas Jiang *et al* (101) concluded that patients in the single mutation group exhibited a

longer mOS than those in the co-mutation group (ORR: 64.6% vs. 27.4%, P<0.001). More prospective randomized clinical trials (RCTs) are required to reconcile these differences.

A co-mutation is defined as the coexistence of an EGFR mutation along with one or more other gene mutations. The co-mutation incidence rate was 66.0% in the retrospective study of Jiang (101). Co-mutations, including TP53 (102,103), HER family genes (104), KRAS, MET, and ROS1, are typically considered to be associated with poor prognosis (105,106).

Histological transformations

Transformation to SCLC. Among the patients who did not maintain a response to EGFR-TKI treatment, 3-14% had tumors that showed morphological transformation to SCLC (61,107). Although the tumors that transformed into SCLC had persistent EGFR activation, immunohistochemical analysis showed that EGFR expression decreased sharply (108). EGFR-TKI-resistant lung adenocarcinoma and SCLC share a common clonal origin. Significant inactivation of Rb and TP53 (a common mutation of classical SCLC) was found in patients with SCLC after the development of drug resistance (108-110). In addition, PIK3CA (111) mutations and TERT amplification (112) were also observed. The specific mechanisms involved in this transition and TKI resistance have not been determined. In addition to the above mutations, other studies have suggested that the transformation may be related to EMT (113,114). A retrospective analysis of this mechanism of drug resistance showed that the etoposide/cisplatin regimen is currently the most effective treatment (115). In this retrospective study, patients treated with anlotinib also achieved an ORR of 66.7% and an mPFS duration of 6.2 months. Another small-sample study reported longer PFS durations were obtained with bevacizumab or other TKIs combined with chemotherapy (116).

Transformation to lung squamous cell carcinoma (SCC). In recent years, several cases of transformation of EGFR-mutated NSCLC to SCC have been reported (117-121), and some reports indicate the association between the T790M mutation and SCC transformation (122,123). As this morphological transformation is rare, the mechanism is unclear, although it has been shown that it may be related to changes in the PI3K/AKT/mTOR pathway during EGFR-TKI therapy (124). For patients with drug-resistant lung SCC, the prognosis is usually poor, and the mOS is only ~3.5 months (120). It is difficult to choose follow-up treatments due to the low incidence; Liao *et al* (121) reported the case of a patient who received almonertinib for 6 months after detection of the SCC phenotype. At the time of writing the study, the patient was continuing almonertinib monotherapy and the disease was stable.

EMT. EMT is a process in which epithelial cells lose polarity and adhesion to gain increased migratory ability, and in the process exhibit a mesenchymal phenotype characterized by decreased E-cadherin and increased vimentin expression as well as stem cell-like features (125,126). EMT is considered one of the possible mechanisms of acquired drug resistance to EGFR-TKIs (127). Increased expression of Aurora kinase A (AURKA) can induce EMT and contribute to the occurrence of acquired EGFR-TKI resistance (128). Nilsson *et al* (129) found that activation of the YAP and FOXM1 axes serves as a driver of EMT-related EGFR-TKI resistance. It has also been confirmed that reversing EMT can restore sensitivity to EGFR-TKI drugs (116). The AURKA inhibitor alisertib can restore the sensitivity of drug-resistant cells to EGFR-TKIs and partially reverse the EMT process (130). It has also been found that Bruton's tyrosine kinase (BTK) mediates dryness and EMT characteristics, and the BTK inhibitor acalabrutinib can enhance the effect of gefitinib and Osimertinib in TKI-resistant NSCLC cells (131).

3. Treatment of T790M-negative tumors after the development of resistance to first- and second-generation TKIs

Regarding the aforementioned drug resistance mechanisms, although researchers have performed extensive treatment-related research, no drugs specifically developed for acquired drug resistance mechanisms have been approved and marketed given the low incidence of these causative mutations. For the first- and second-generation TKI drug-resistant T790M-negative population, platinum-containing dual-drug chemotherapy is currently recommended, but its benefits are limited (132). Other treatment options are being explored and are summarized below.

Immunotherapy. The relationships between EGFR mutations, EGFR-TKIs, and immunotherapy efficacy are contested. A meta-analysis of large RCTs showed that patients with EGFR mutations showed no significant benefit from immunotherapy (133,134). In people with PD-L1 expression levels <50%, the use of EGFR-TKI inhibitors resulted in a better PFS rate and ORR (135). However, studies have also shown that for patients with EGFR mutations, the proportion of patients with PD-L1 expression levels ≥50% increased after EGFR-TKI treatment, and the mPFS resulting from subsequent treatment with PD-1 antibodies was longer than that of patients with low PD-L1 expression (7.1 vs. 1.7 months; P=0.0033) (136). These results indicate that EGFR-TKI drugs appear to have a positive effect on the tumor microenvironment (TME).

According to the IMpower150 study, a subgroup analysis of patients following EGFR-TKI failure showed that OS benefits were obtained after addition of atrizumab; this is the only study that has confirmed OS benefits from immunotherapy after the development of EGFR-TKI resistance (137). Another ongoing phase II study also showed that the addition of atezolizumab to the bevacizumab regimen improved the disease control rate (DCR) and PFS outcome (138). In the single-arm II phase study by Lam *et al* (139), a 9.4-month PFS duration was obtained using a quadruple combination of atezolizumab, bevacizumab, carboplatin, and pemetrexed. A total of 42.5% of the patients were resistant to first- and second-generation EGFR-TKIs. The incidence of treatment-related adverse events was 37.5% (15/40), which is within the range of controllable adverse events. Thus, this combination appears to be a feasible treatment.

CT18 is the first prospective immunotherapy study in patients with lung adenocarcinoma with EGFR mutations. The results showed good clinical benefits (ORR=50%, mPFS=7 months, OS=23.5 months) in T790M-negative patients with acquired drug resistance after treatment with toripalimab combined with carboplatin and pemetrexed (140).

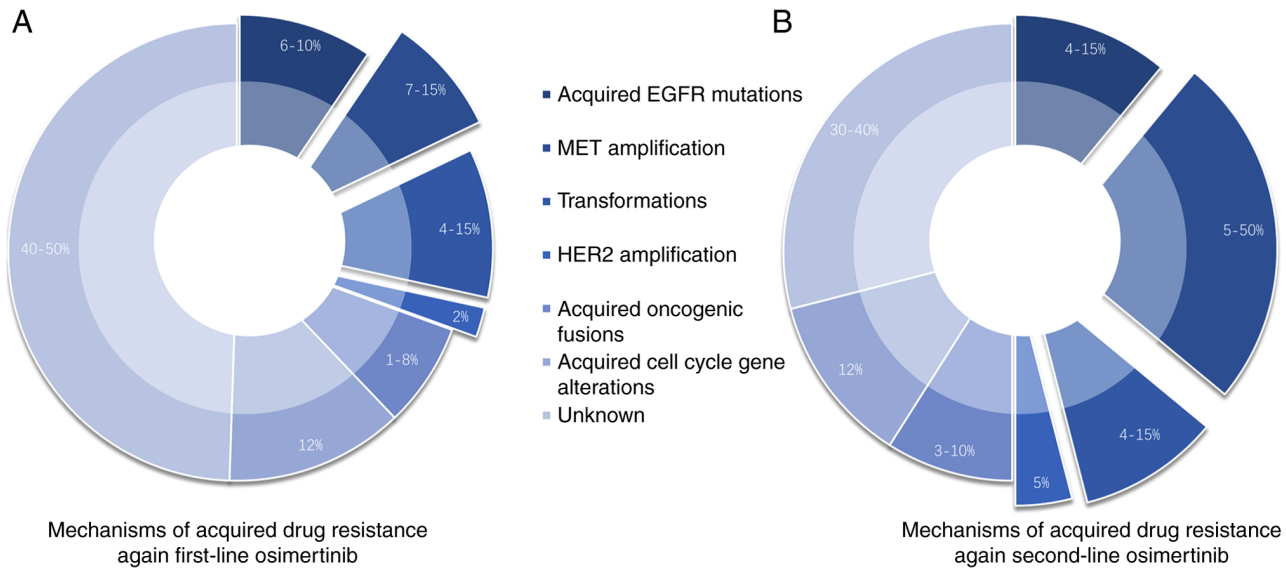

Figure 2. Mechanism of acquired drug resistance against Osimertinib. (A) The mechanism of acquired drug resistance against first line Osimertinib. (B) The mechanism of acquired drug resistance against second line Osimertinib.

A phase III RCT (TREASURE) is underway, evaluating toripalimab plus chemotherapy as second-line treatment in patients with EGFR-mutant-advanced NSCLC who were previously treated with EGFR-TKIs; patients with failed first-line EGFR-TKIs and those who did not harbor T790M mutation were enrolled. (141). ORIENT-31 was a randomized, double-blind, multicenter, phase III RCT that evaluated the efficacy and safety of the combination of sintilimab and bevacizumab for treating EGFR-mutated SCLC after EGFR-TKI treatment. The study found that patients in the quadruple drug group had prolonged mPFS (6.9 vs. 4.3 months) and median duration of efficacy (8.3 vs. 7.0 months) outcomes compared to those in the chemotherapy group (142).

A phase II RCT conducted by Hayashi *et al* (143) compared nivolumab (NIVO) with carboplatin + pemetrexed for treating EGFR-TKI-resistant patients; NIVO did not exhibit an advantage over chemotherapy (mPFS 1.7 months vs. 5.6 months, mOS 20.7 vs. 19.9 months). Therefore, more prospective trials are needed to verify the feasibility of immunotherapy in patients with EGFR resistance.

Treatment regimens containing pemetrexed. Pemetrexed is an anti-folic acid drug that can interfere with folic acid metabolism, resulting in aberrant DNA synthesis in tumor cells (144). A cancer registration cohort analysis from Taiwan showed that pemetrexed may be suitable as a first choice for chemotherapy in patients undergoing chemotherapy after progression with EGFR-TKI treatment (145). A 2018 meta-analysis showed that second-line drugs combined pemetrexed chemotherapy resulted in a longer PFS and OS duration than therapy with pemetrexed (146). In a phase II study, researchers compared cisplatin plus pemetrexed against pemetrexed alone in patients with drug resistance and found no significant difference in PFS and OS outcomes between the two groups. The efficacy of pemetrexed in NSCLC patients with disease progression after first-line EGFR-TKI treatment was not improved by adding cisplatin (147).

Antiangiogenic drugs. Preclinical studies have shown that vascular endothelial growth factor (VEGF) and EGFR share a common downstream signaling pathway and acquired EGFR resistance is associated with increased VEGF levels (148). *In vivo* and *in vitro* studies have confirmed that anlotinib (a small molecular multitarget tyrosine kinase inhibitor) can overcome acquired resistance to EGFR-TKIs through modulation of the FGFR1 signaling pathway (149,150). Phase II clinical trials have shown that the use of bevacizumab combined with afatinib resulted in an ORR of 22% and a PFS of 7.1 months in T790M-negative patients who developed drug resistance (151). A patient with EGFRL858R and KRASG12D mutations administered a combination of bevacizumab, camrelizumab, and pemetrexed after developing EGFR-TKI resistance achieved a benefit lasting ~17 months (152). A retrospective analysis in China revealed that the longer the duration of the previous EGFR-TKI treatment had been, the longer the PFS duration was when patients received follow-up immunotherapy combined with chemotherapy and antiangiogenic drugs (153). Due to the limitations of the above studies, additional prospective studies are needed to confirm the efficacy of antiangiogenic drugs combined with targeted therapy or immunotherapy in the future.

4. Resistance mechanisms and treatment progress with Osimertinib (third-generation EGFR-TKIs)

At present, Osimertinib is the only third-generation EGFR-TKI preparation that is widely used and that has been studied relatively extensively. Drug resistance mechanisms associated with first-line use of Osimertinib are similar to those associated with second-line therapy, but the proportion of patients developing resistance differs (Fig. 2). At present, the reported mechanisms of drug resistance can be divided into EGFR-dependent and EGFR-independent mechanisms (154,155). The mechanisms of EGFR-dependent drug resistance include EGFR mutations, amplification, deletion, and ligand overexpression as well as

tertiary EGFR mutations, whereas EGFR-independent resistance mechanisms include activation of abnormal accessory pathways, activation of downstream pathways, and histological/phenotypic transformation (156).

EGFR-dependent drug mechanisms

c797s mutation and treatment progress. The Aura3 study revealed that 49% of the patients had T790M loss, and 14% had EGFRC797S mutations, the most common mutations acquired after the development of Osimertinib resistance (154). EGFRC797S mutations include *cis* (98%) and *trans* mutations (2%). T790M and C797S mutations that occur simultaneously in the same allele are referred to as *cis* mutations, and mutations that occur in different alleles are referred to as *trans* mutations (157,158).

Recent studies have shown that a third-generation TKI combined with a first-generation EGFR-TKI can change the expression profile of drug resistance genes in lung adenocarcinoma patients with EGFR activation mutations, and T790M and *trans*-C797S triple mutations (158). Brigatinib combined with cetuximab is an effective treatment strategy for these lung adenocarcinoma patients with EGFR activation mutations and T790M and *cis*-C797S triple mutations (158,159). Chang *et al* (160) reported the case of a patient with lung adenocarcinoma with triple mutations (L858R, T790M, and *cis*-G796s/cis-C797s). After treatment failure with brigatinib combined with cetuximab, the patient responded to the combination of brigatinib, Osimertinib, and bevacizumab. Other reported treatments include Osimertinib combined with anlotinib (161), chemotherapy combined with antiangiogenic agents (162), and apatinib combined with afatinib (163). At present, fourth-generation EGFR-TKIs targeting drug-resistant T790M mutations are under development, although no drug has been approved. Fourth-generation EGFR-TKIs in clinical trials and currently undergoing research and development and are described in subsequent sections.

Other gene mutations and treatment progress. In a study where next-generation sequencing (NGS) analysis was performed on 93 samples obtained after the development of Osimertinib resistance, EGFRG796/C797, L792, and L718/G719 mutations were found in 24.7, 10.8, and 9.7% of cases, respectively (164). G724 mutations were also reported in some studies (165,166). At present, a drug that targets the aforementioned mutated genes is not available. *In vitro* studies have confirmed that L792 is still sensitive to gefitinib (167) and that tumors with the L718Q mutations remain sensitive to icotinib (168). In a patient with the EGFRG724S/19del mutation after second-line Osimertinib resistance, PFS was achieved after using afatinib for 3.8 months (169).

EGFR-independent mechanisms of drug resistance and treatment progress. EGFR-independent mechanisms of drug resistance primarily include activation of abnormal accessory and downstream pathways and histological/phenotypic transformation. Most of the mechanisms of Osimertinib drug resistance are the same as those of first- and second-generation TKIs.

MET amplification. Leonetti *et al* (155) demonstrated that the incidence of MET amplification after Osimertinib first-line treatment resistance was 7-15%, and that of MET amplification after second-line treatment resistance was 5-50%. In the B1 expansion cohort of the TATTON study (previously treated with third-generation EGFR-TKIs), a 5.5-month PFS duration was obtained with Osimertinib combined with sevotinib (67), and other therapeutic developments have been described. Zhang *et al* (170) found that MET amplification weakened the response of lung tumors to immunotherapy by inhibiting the STING signaling pathway, and that MET inhibitors combined with immune checkpoint inhibitors overcame this drug resistance; however, this information needs to be confirmed by further prospective studies. Amivantamab (JNJ-61186372) is a bispecific antibody against EGFR and MET that has been approved for the treatment of patients with EGFR exon 20 insertion mutations (171). Amivantamab can inhibit both the phosphorylation of EGFR and MET and the activation of downstream signals and has potent antibody-dependent cell-mediated cytotoxic effects (171,172). Amivantamab is inhibited by double targeting, which showed an inhibitory effect on several types of mutations secondary to EGFR-TKI resistance (C797S mutations, MET amplification, previous resistance to Osimertinib) (173).

HER2 amplification and PIK3CA mutation. HER2 amplification is one of the mechanisms of Osimertinib resistance (174). The AURA3 study showed that HER2 amplification was detected in 5% (4 out of 73) of second-line Osimertinib-resistant patients (157). In the FLAURA study, HER2 amplification occurred in 2% of first-line Osimertinib-resistant patients (175). PIK3CA mutations occur in patients with Osimertinib resistance, and T790M mutations may be retained or lost. Moreover, PIK3CA mutations showed different incidences in different studies (176,177).

Changes in other bypass pathways. Abnormal FGFR expression can lead to the activation of the FGFR cancer-related signaling pathway effectors (PI3K/AKT, STAT, and MAPK) and affect cell proliferation, survival, metabolism, and migration as well as the cell cycle (178). *In vitro* studies found that hypoxia can lead to acquired resistance to EGFR-TKIs by increasing the expression of FGFR1 (179). The combined use of EGFR-TKIs and FGFR1 inhibitors (BGJ398) may represent a potential therapeutic strategy for the management of NSCLC (179,180). Upregulation of IGF1R is one of the mechanisms of drug resistance to EGFR-TKIs, including Osimertinib (181-183). In cells resistant to Osimertinib that exhibit low levels of AXL expression, short-term IGF-1R inhibition combined with Osimertinib can eradicate tumors and prevent regrowth (184).

Histology/bypass transformation. Histological transformation from lung adenocarcinoma to SCLC, SCC and EMT was also observed in patients with Osimertinib resistance (177,185). Platinum-containing dual-drug chemotherapy is still recommended for these patients.

5. Treatments available after the development of Osimertinib resistance

Fourth-generation EGFR-TKI inhibition. Drug resistance to third-generation targeted drugs (Osimertinib) is a dilemma faced by several lung cancer patients who receive targeted

therapy. To date, the FDA has not approved targeted therapy for progression after treatment with Osimertinib. Thus, the research and development of fourth-generation EGFR-TKI drugs have become a focus recently, and several drugs have shown good results in clinical trials.

EAI045 is the first fourth-generation EGFR-TKI drug. EAI045 combined with cetuximab significantly reduced the tumor size in mice carrying L858R/T790M/C797S mutations, but no obvious effect was observed with single-agent use (186). To improve the activity of EAI045 and the ability to use the drug as a single agent, To *et al* (187) modified EAI045 and obtained a new allosteric inhibitor, JBJ-04-12502, which exhibited higher efficacy, lower toxicity, and efficacy against EGFR mutations compared with the parent compound. JBJ-04-12502 inhibits the triple-drug resistance mechanism of patients with L858R/T790M/C797S mutations, the double mutation of EGFR-T70M, and the L858R drug resistance mutation. The therapeutic effect of JBJ-04-12502 in combination with Osimertinib is more potent, although it is still in the research and development stage (188). CH7233163 is a fourth-generation EGFR-TKI inhibitor developed by Roche Chugai Pharmaceuticals for patients with a Del19 mutation. After the application of CH7233163 in Del19/L858R/T790M, L858R/T790M mutant, and Del19 mice, a substantial reduction in tumor volume was observed (189). The prospect of CH7233163 appears to be more promising than that of JBJ-04-12502.

Both BLU-945 and BLU-701 are fourth-generation EGFR-TKI inhibitors developed by Blueprint Medicines. Both can resist EGFR activation mutations (del19, 21L858R) as well as T790M and C797S drug resistance mutation activity (190,191). BLU-945 combined with Osimertinib or gefitinib provided a more significant tumor elimination effect in n NSCLC mouse model (192). BLU-701 also exhibited intracranial antitumor activity, and both BLU-701 alone and in combination with BLU-945 showed strong antitumor activity (193).

TQB3804 is a fourth-generation oral EGFR-targeted drug developed by the Zhengda Tianqing Pharmaceutical Group. It not only solves Osimertinib resistance caused by d746750 (19del)/T790M/C797S and L858R/T790M/C797S, but is also effective against the d746-750/T790M and L858R/T790M double mutations associated with resistance to first- and second-generation TKIs (194). Correlative clinical trials (NCT04128085 and NCT04180150) are currently underway (195).

BBT-176 is an innovative EGFR-TKI developed by Bridge Biotherapeutics in Korea. BBT-176 showed strong anticancer activity in xenotransplantation animal models carrying triple mutations Del19/T790M/C797S and L858R/T790M/C797S (196). Moreover, BBT-176 in combination with the anti-EGFR antibody cetuximab showed significantly enhanced activity (197).

The EGFR and MET bispecific antibody amivantamab is also classified as a fourth-generation EGFR-TKI. This drug is effective against the EGFR exon 20 insertion mutation (primary drug resistance mutation) (198), C797S mutation, and MET amplification after the acquisition of Osimertinib resistance. Amivantamab combined with Lazertinib effectively overcomes Osimertinib resistance. In 45 patients with Osimertinib resistance, the disease control rate reached 60% with a median follow-up period of 4 months (199). All the above drugs, except for amivantamab, which has been approved for the treatment of the NSCLC EGFR exon 20 insertion mutation, remain in different stages of research and development or clinical trials. Thus, it will be several years before these drugs are available for clinical use.

U3-1402. U3-1402 is an antibody-drug conjugate (ADC) developed by Daiichi Co., Ltd., which consists of patritumab acting on HER3 antibodies and the cytotoxic drug DX-8951 (Exitecan, a topoisomerase inhibitor). U3-1402 is effective against different drug resistance mechanisms against EGFR-TKIs, as demonstrated in phase I trial results published in 2019 (200). Another phase I study included 57 patients with EGFR-TKI resistance. The DCR was 68% in 44 patients who had previously received Osimertinib and platinum-containing chemotherapy. The mPFS reached 8.2 months (201). ADC drugs have considerable potential for solving the problem of resistance to Osimertinib.

Osimertinib rechallenge. Soo *et al* (202) showed no benefit regarding PFS in patients with T790M-positive NSCLC when treated with Osimertinib combined with bevacizumab compared with Osimertinib monotherapy. However, in a small-sample retrospective study, after the development of Osimertinib resistance, Osimertinib combined with bevacizumab showed certain benefits. The study compared the efficacy and safety of Osimertinib combined with bevacizumab against chemotherapy combined with bevacizumab in patients with Osimertinib resistance. The mPFS duration of the two groups was 7.0 vs. 4.9 months, and the mOS was 12.6 vs. 7.1 months, respectively; the difference was statistically significant (203).

The COMPEL study was a randomized, double-blind phase III clinical study that evaluated the efficacy and safety of chemotherapy plus Osimertinib or chemotherapy plus placebo in advanced NSCLC patients with progressive EGFR mutations after first-line treatment with Osimertinib. The study is currently underway and will be published in September 2024 (204).

Immunotherapy. The ORIENT-31 study included patients who were T790M-negative after first- and second-generation EGFR-TKI treatment and patients who received third-generation EGFR-TKI treatment. The results showed that the PFS duration was significantly prolonged in patients treated with sintilimab combined with bevacizumab and chemotherapy compared with that of patients treated with chemotherapy alone (142). This study was the first to confirm that PD-1 inhibitors combined with antivascular drugs and chemotherapy significantly improved PFS outcomes in EGFR-mutant non-squamous NSCLC patients with progression after EGFR-TKI treatment, providing options for the follow-up treatment of drug-resistant patients after targeted treatment.

In a single-arm phase II study of patients administered a quadruple combination of atezolizumab, bevacizumab, carboplatin, and pemetrexed, the PFS duration was 9.4 months; 57.5% of these patients had been treated with Osimertinib (139). The IMpower150 study is currently the only randomized

prospective phase III clinical trial that demonstrated OS benefits in NSCLC patients in an EGFR-sensitive mutation subgroup (137), showing that the addition of atezolizumab to the standard therapy of bevacizumab and chemotherapy represents a novel treatment option.

Other treatment options. According to the subgroup analysis of the ALTER0303 study (205), patients with EGFR mutations exhibited PFS and OS benefits following treatment with anlotinib. Zhou *et al* (161) also reported on the case of a patient with a cisEGFRT790M-C797S mutation after Osimertinib resistance who was treated with amlotinib combined with Osimertinib and achieved partial remission that persisted for 9 months. The use of afatinib combined with bevacizumab has also been reported; it improved the patient's symptoms and was continued as the treatment for 12 months (206).

6. Summary and future perspectives

The 21st century is the era of targeted cancer treatment, and several promising options for lung adenocarcinoma patients are available. Although novel treatments provide survival benefits to varying degrees, the problem of drug resistance inevitably leads to disease progression. It has been demonstrated that tumors become increasingly molecularly heterogeneous following targeted therapy (5,207). There is a large body of literature implicating intratumoral heterogeneity as a major driver of drug resistance (208,209). NGS and single-cell RNA sequencing (scRNA-seq) are used to study the genetic and molecular characteristics of tumor development at various stages (210), revealing the heterogeneity of tumor cells and monitoring the progress of tumor development.

Maynard *et al* (211) performed scRNA-seq of metastatic lung adenocarcinoma using 49 clinical biopsies obtained from 30 patients before and during targeted therapy and found that the components of the TME differ at the stages of TKI naïve, residual disease (RD), and progression. A more inflammatory phenotype was observed in RD following targeted therapy that was characterized by T cell infiltration and decreased infiltration of immunosuppressive macrophages (211). In addition, various immunosuppressive cell states characterize progressive disease. Therefore, researchers have proposed that if deployed at the appropriate time, treatments that target a specific cell state or prevent further adaptation may help improve patient survival by constraining continued tumor evolution toward complete drug resistance (211).

In recent years, modified T-cell therapy, particularly those that use chimeric antigen receptor (CAR)-T cells, has attracted growing interest in various solid tumors with the clinical success of chimeric antigen receptor CAR T-cell therapy in hematological malignancies (212,213). The CAR T strategy aims to isolate T cells from the peripheral blood of patients or other donors and genetically engineer T cells with CAR structures to equip them with the capability of recognizing specific antigens on the tumor cell surface. After infusion back into patients, these 'super' T cells recognize and eliminate the cancer cells that express specific target antigens (214). The major difference between CAR T cells and tumor-specific T cells is that the former cells are not limited by the major histocompatibility complex (215,216). It is critical to identify targeted tumor-associated antigens (TAAs). Ideal TAAs are highly and selectively expressed in solid tumors, but weakly expressed or absent in normal tissues (217).

The lung adenocarcinoma-associated TAAs currently being investigated in clinical trials on CAR-T cells include mesothelin (MSLN), mucin 1 (MUC1), carcinoembryonic antigen (CEA) EGFR, PD-L1, prostate stem cell antigen (PSCA), disialoganglioside GD2 (GD2), and c-Met (218-222).

For EGFR-mutated LUAD, EGFR is definitely an optimum TAA. A phase I clinical trial of EGFR-targeting CAR T-cell therapy to treat patients with EGFR-positive relapsed/refractory NSCLC achieved initial success (NCT01869166). The results showed that none of the patients exhibited significant toxic side effects after anti-EGFR CAR-T-cell therapy, 2 patients achieved partial remission, and 5 patients had stable disease for 2-8 months (223). This result provides preliminary evidence that EGFR-targeting CAR T therapy is safe and feasible in certain cases of relapsed/refractory NSCLC. Currently, there are two ongoing phase I clinical trials in patients with lung cancer on C-X-C chemokine receptor type 5 modified EGFR-targeted CAR-T cells (NCT05060796 and NCT04153799).

Although CAR-T-cell therapies have achieved great success in hematological malignancies, the study of lung cancer is still in the early exploration stage. Numerous clinical trials have progressed slowly and have achieved very limited efficacy, and several challenges and hurdles remain, such as on-target/off-tumor toxicity, CAR-T cell trafficking and infiltration into the tumor, TME heterogeneity, immune suppression, and cytokine release syndrome (224-226). Recently, Vasic *et al* (227) found that allogeneic double-negative CAR-T cells inhibit tumor growth with no off-tumor toxicity in either a lung cancer xenograft model or B-cell acute lymphoblastic leukemia (B-ALL) was observed. Therefore, double-negative CAR-T cells may serve as a patient-accessible form of CAR-T cell therapy.

Due to China's large population and relatively high EGFR mutation rate, the identification of the best treatment after the development of EGFR-TKI resistance has become an urgent problem. EGFR-TKIs have been continuously developed and are currently in their fourth generation of iteration, and this process is accompanied by the continuous optimization of pharmacological mechanisms, the emergence of novel drug resistance mechanisms, and the development of solutions to these new drug resistance mechanisms. Although it may take considerably more research to conquer cancer, significant levels of drug research and development remain ongoing.

Acknowledgements

Not applicable.

Funding

The present study was supported by the Wu Jieping Medical Foundation of China (grant no. 320.6750.2021-22-8).

Availability of data and materials

Not applicable.

Authors' contributions

RS conceived the article, performed the literature search and drafted the manuscript. ZH and YZ contributed their knowledge on this topic and were involved in planning the structure of this review. BJ made critical modifications to the content within the manuscript. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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