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

RUIZHU SUN, ZHANSHENG HOU, YANKUI ZHANG and BO JIANG

Department of Medical Care, The Third Affiliated Hospital of Kunming Medical University, College of Clinical Oncology, Kunming Medical University, Kunming, Yunnan 650500, P.R. China

Received June 28, 2022; Accepted September 7, 2022

DOI: 10.3892/ol.2022.13528

Correspondence to: Professor Bo Jiang, Department of Medical Care, The Third Affiliated Hospital of Kunming Medical University, College of Clinical Oncology, Kunming Medical University, 519 Kunzhou Road, Xishan, Kunming, Yunnan 650500, P.R. China E-mail: jiangruonin1973@163.com

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

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.

Contents
1. Introduction
2. Drug resistance mechanisms and progress in the use of first- and second-generation EGFR-TKIs
3. Treatment of T790M-negative tumors after the development of resistance to first- and second-generation TKIs
4. Resistance mechanisms and treatment progress with osimertinib (third-generation EGFR-TKI)
5. Treatments available after the development of Osimertinib resistance
6. Summary and future perspectives

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 subse-
quent 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 trans-
duction 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 treat-
mant 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
hormans with EGFR-sensitive and T790M drug-resistant muta-
tions (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 abnor-
malities 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 prolifera-
tion (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 tyro-
sine kinase inhibitors poziotinib (51) and pyrotinib (52,53),
and the antibody conjugate drugs T-DM1 (54) and trastu-
zumab-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 cata-
lytic 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 amplifica-
tion; 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 solu-
tion 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
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.

**PIK3CA mutations.** PIK3CA mutations 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). 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
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

| 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        | Acea Biosciences                          | Advanced NSCLC with a T790M mutation after EGFR resistance                   | Declared/listed   |
| (Avitinib)    |                                          | 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 3 clinical trial |
| SH-1028       | Nanjing Sanhome Pharmaceutical Co.        | Advanced NSCLC with a T790M mutation after EGFR resistance                   | Phase 3 clinical trial |
|               |                                          | NSCLC with EGFR mutations                                                   | Phase 2 clinical trial |
| FHND9041      | Nanjing Chuangren Pharmaceutical Technology Center | Advanced NSCLC with a T790M mutation after EGFR resistance                   | Phase 3 clinical trial |
|               |                                          | NSCLC with EGFR mutations                                                   | 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      | Betther 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.
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 contended. 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 IMpower110 study, a subgroup analysis of patients following EGFR-TKI failure showed that OS benefits were obtained after addition of atezolizumab; 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).
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. 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 EGFR-L858R and KRAS-G12D 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-796s/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, EGFRc796/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 (INJ-6186372) 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-IR inhibition combined with Osimertinib can eradicates 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, JBI-04-12502, which exhibited higher efficacy, lower toxicity, and efficacy against EGFR mutations compared with the parent compound. JBI-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 JBI-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 JBI-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 a 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.

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 alezolizumab 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 cisEGFR790M-C797S mutation after Osimertinib resistance who was treated with anlotinib 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.

References
1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A and Bray F: Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 71: 209-249, 2021.
2. Cao M, Li H, Sun D and Chen W: Cancer burden of major cancers in China: A need for sustainable actions. Cancer Commun (Lond) 40: 205-210, 2020.
3. Camidge DR, Doeebe RC and Kerr KM: Comparing and contrasting predictive biomarkers for immunotherapy and targeted therapy of NSCLC. Nat Rev Clin Oncol 16: 341-355, 2019.
4. Lee CK, Davies L, Wu YL, Mitsudomi T, Inoue A, Rosell R, Zhou C, Nakagawa K, Thongprasert S, Fukukoshi M, et al: Gefitinib or erlotinib vs chemotherapy for EGFR mutation-positive lung cancer: Individual patient data meta-analysis of overall survival. J Natl Cancer Inst 109: 2017.
5. Cao M, Li H, Sun D and Chen W: Cancer burden of major cancers in China: A need for sustainable actions. Cancer Commun (Lond) 40: 205-210, 2020.
6. Shi Y, Au JS, Thongprasert S, Srinivasan S, Tsai CM, Khoa MT, Lu S, Zhou C, Feng J, Ellis SH, et al: First-line afatinib for advanced EGFR-mutant NSCLC: Analysis of long-term responders in the LUX-Lung 3, 6, and 7 trials. Lung Cancer 133: 10-19, 2019.
7. Wu YL, Cheng Y, Zhou X, Lee KH, Nakagawa K, Niho S, Tsuji F, Linke R, Rosell R, Corral J, et al: Dacomitinib versus gefitinib as first-line treatment for patients with EGFR-mutation-positive non-small-cell lung cancer (ARCHER 1050): A randomised, open-label, phase 3 trial. Lancet Oncol 18: 1454-1466, 2017.
8. Ramalingam SS, Vansteenkiste J, Planchard D, Cho BC, Gray JE, Ohe Y, Zhou C, Reungwetwattana T, Cheng Y, Chewaskulyong B, et al: Overall survival with osimertinib in untreated, EGFR-Mutated advanced NSCLC. N Engl J Med 382: 41-50, 2020.
9. Shi YK, Wang L, Han BH, Li W, Yu P, Liu YP, Ding CM, Song X, Ma ZY, Ren XL, et al: First-line icotinib versus cisplatin/pemetrexed plus pemetrexed maintenance therapy for patients with advanced EGFR mutation-positive lung adenocarcinoma (CONVENIENCE): A phase 3, open-label, randomised study. Ann Oncol 28: 2443-2450, 2017.
10. Rebuzzi SE, Aliferi R, La Monica S, Minari R, Petronini PG and Tiseo M: Combination of EGFR-TKIs and chemotherapy in advanced EGFR mutated NSCLC: Review of the literature and future perspectives. Crit Rev Oncol Hematol 146: 102820, 2020.
11. Huang L and Fu L: Mechanisms of resistance to EGFR tyrosine kinase inhibitors. Acta Pharm Sin B 5: 390-401, 2015.
12. Mok TS, Wu YL, Ahn MJ, Sarassino MC, Kim HR, Ramalingam SS, Shepherd FA, He Y, Akamatsu H, Thomsen WS, et al: Osimertinib or platinum-pemetrexed in EGFR T790MPositive lung cancer. N Engl J Med 376: 629-640, 2017.
13. Thress KS, Pawelec CP, Felipe I, Cho BC, Stetson D, Dougherty B, Lai Z, Markovets A, Vivancos A, Kuang Y, et al: Acquired EGFR C797S mutation mediates resistance to AZD9291 in non-small-cell lung cancer harboring EGFR T790M. Nat Med 21: 560-562, 2015.
14. Wang S, Tsui ST, Liu C, Song Y and Liu D: EGFR C797S mutation mediates resistance to third-generation inhibitors in T790M-positive non-small-cell lung cancer. J Hematol Oncol 9: 50, 2016.
15. Lim SM, Syn NL, Cho BC and Soo RA: Acquired resistance to EGFR targeted therapy in non-small cell lung cancer: Mechanisms and therapeutic strategies. Cancer Treat Rev 65: e10, 2018.
16. Nosegno T, Tachihara M and Nishimura Y: Mechanism of resistance to epidermal growth factor receptor-tyrosine kinase inhibitors and a potential treatment strategy. Cells 7: 212, 2018.
17. Park K, Tan EH, O’Byrne K, Zhang L, Boyer M, Mok T, Hirsh V, Yang JC, Lee KH, Lu S, et al: Arafatinib versus gefitinib as first-line treatment of patients with EGFR mutation-positive non-small-cell lung cancer (LUX-Lung 7): A phase 2B, open-label, randomised controlled trial. Lancet Oncol 17: 577-589, 2016.
18. Jänne PA, Ou SJ, Kim DW, Oxnard GR, Martins R, Kris MG, Dunphy F, Nishio M, O’Connell J, Pawelec C, et al: Dacomitinib as first-line treatment in patients with clinically or molecularly selected advanced non-small-cell lung cancer: A multicentre, open-label, phase 2 trial. Lancet Oncol 15: 1434-1441, 2014.
19. Wu SG, Liu YN, Tsai MF, Chang YL, Yu CJ, Yang PC, Yang JC, Wen YF and Shih JY: The mechanism of acquired resistance to irreversible EGFR tyrosine kinase inhibitor-afatinib in lung adenocarcinoma patients. Oncotarget 7: 12404-12413, 2016.
20. Cabanero M, Sangha R, Sheffield BS, Sukhia M, Pakkal M, Kamel-Reid S, Karsan A, Ionescu D, Juergens RA, Butts C and Tsao MS: Management of EGFR-mutated non-small-cell lung cancer: Practical implications from a clinical and pathology perspective. Curr Oncol 24: 111-119, 2017.
21. Mok TS, Cheng Y, Zhou X, Lee KH, Nakagawa K, Niho S, Chawla A, Rosell R, Corral J, Migliorino MR, et al: Updated overall survival in a randomized study comparing dacomitinib with gefitinib as first-line treatment in patients with advanced non-small-cell lung cancer and EGFR-Activating mutations. Drugs 81: 257-266, 2021.
22. Soria JC, Ohe Y, Vansteenkiste J, Reungwetwattana T, Chewaskulyong B, Lee KH, Dechaphunkul A, Imamura F, Nogami N, Kurata T, et al: Osimertinib in patients with T790M-Positive advanced non-small-cell lung cancer: Data from a Randomized phase III Trial (AURA3). J Clin Oncol 36: 2702-2709, 2018.
30. Lu S, Wang Q, Zhang G, Dong X, Yang CT, Song Y, Chang GC, Reungwetwattana T, Nakagawa K, Cho BC, Cobo M, Cho EK, Kim SW, Ahn MJ, Han JY, Lee KH, Cho EK, Lee YG, Kim DW, Kim ES: Olmutinib: First global approval. Drugs 76: 1153‑1157, 2021.

31. Kim SW, Lee DH, Han JY, Lee J, Cho BC, Kang JH, Lee KH, Park K, Jӓnne PA, Kim DW, Han JY, Wu MF, Lee JS, Kang JH, Cho EK, et al: Intracranial anti‑tumor activity of lazertinib in patients with advanced EGFR T790M+ NSCLC: Updated results of phase I/II study. J Clin Oncol 37: 311‑319, 2019.

32. Cho EK, Kim JS, Min YJ, Pao W: Acquired resistance to epidermal growth factor receptor inhibitors in patients with untreated EGFR-Mutated advanced non-small-cell lung cancer. J Clin Oncol: Aug 28, 2018 (Epub ahead of print).

33. Lu S, Wang Q, Zhang G, Dong X, Yang CT, Song Y, Chang GC, Lu Y, Pan H, Chiu CH, et al: Efficacy of aumolertinib (HS-10296) in patients with advanced EGFR T790M+ NSCLC: Updated post‑national medical products administration approval results from the APOLLO registration trial. J Thorac Oncol 17: 411‑422, 2022.

34. Lu S, Wang Q, Zhang G, Dong X, Yang C, Song Y, Chang GC, Lu Y, Pan H, Chiu CH, et al: Efficacy of aumolertinib (HS-10296) in patients with pretreated EGFR T790M-positive locally advanced or metastatic non-small cell lung cancer (NSCLC). Ann Oncol 32: S962, 2021.

35. Shi Y, Hu X, Zhang S, Lv D, Wu L, Yu Q, Zhang Y, Liu L, Wang X, Cheng Y, et al: Efficacy, safety, and genetic analysis of furmotoninib (AST2818) in patients with EGFR T790M mutated non-small-cell lung cancer: A phase 2b, multicentre, single-arm, open-label study. Lancet Respir Med 9: 829‑839, 2021.

36. Deeks ED: Furmotoninib: First approval. Drugs 81: 1775‑1780, 2021.

37. Ahn MJ, Han JY, Kim SW, Ki Hyeong Lee S, Kim DW, Lee YG, Cho EK, Lee GW, Lee JS, Kim JH, et al: Lazertinib, a 3rd generation EGFR-TKI, in patients with EGFR-TKI resistant NSCLC: Updated results of phase I/II Study. Abstract #9037, May 31‑June 4, 2019.

38. Kim SW, Ahn MJ, Han JY, Lee KH, Cho EK, Lee GW, Kim DW, Kim JH, Lee KH, et al: Intracranial anti-tumor activity of lazertinib in patients with advanced NSCLC who progressed after prior EGFR TKI therapy: Data from a phase I/II study. Am Soc Clin Oncol 38: 9571, 2020.

39. Dhillon S: Lazertinib: First approval. Drugs 81: 1107‑1113, 2021.

40. Kim ES: Omutinib: First global approval. Drugs 76: 1153‑1157, 2016.

41. Kim DW, Lee DH, Han JY, Lee J, Cho BC, Kang JH, Lee KH, Cho EK, Kim JS, Min YJ, et al: Safety, tolerability, and anti-tumor activity of olmutinib in non-small cell lung cancer with T790M mutation: A single arm, open label, phase 1/2 trial. Lung Cancer 135: 66‑72, 2020.

42. Park K, Jänne PA, Kim DW, Han JY, Wu MF, Lee JS, Kang JH, Lee DH, Cho BC, Yu CJ, et al: Omutinib in T790M-positive non-small cell lung cancer after failure of first-line epidermal growth factor receptor-tyrosine kinase inhibitor therapy: A global, phase 2 study. Cancer Discov 12: 1407‑1416, 2021.

43. Tan DS, Leigh NB, Riely GJ, Yang JC, Sequist LV, Wolf J, Seto T, Felip E, Aix SP, Jonnmaa M, et al: Safety and efficacy of nazaritinib (EGF816) in adults with EGFR-mutant non-small-cell lung carcinoma: A multicentre, open-label, phase 1 study. Lancet Respir Med 8: 561‑572, 2020.

44. Meneses M, Wollberg A, de Stanchina E, Ohashi K, Janjigian YY, Spytzler PJ, Melnick MA, et al: HER2 amplification: A potential mechanism of acquired resistance to EGFR inhibition in EGFR-mutant lung cancers that lack the second-site EGFR T790M mutation. Cancer Discov 2: 922‑933, 2012.

45. Elamini YY, Robichaux JP, Carter BW, Altan M, Gibbons DL, Fossella FV, Lam VK, Patel AB, Negrao MV, Le, X, et al: Poziotinib for patients With HER2 Exon 20 mutant non-small-cell lung cancer: Results from a phase II trial. J Clin Oncol 40: 702‑709, 2022.

46. Song Z, Lv D, Chen SQ, Huang J, Li Y, Ying S, Wu X, Hua F, Wang W, Xu C, et al: Pyrotinib in patients with HER2-Amplified advanced non-small cell lung cancer: A prospective, multicenter, single-arm trial. Clin Cancer Res 28: 461‑467, 2022.

47. Zhou C, Li X, Wang Q, Gao G, Zhang Y, Chen J, Shu Y, Hu Y, Fan Y, Fang J, et al: Pyrotinib in HER2-Mutant advanced lung adenocarcinoma after platinum-based chemotherapy: A multicenter, open-label, single-arm, phase II Study. J Clin Oncol 38: 2753‑2761, 2020.

48. Li BT, Shen R, Buonocore D, Olah ZT, Ni A, Ginsberg MS, Ulanger GA, Offin M, Feldman D, Hembrough T, et al: Ado-Trastuzumab emtansine for patients with HER2-Mutant lung cancers: Results from a phase II basket trial. J Clin Oncol 36: 2523‑2537, 2018.

49. Pasquini G and Giaccone G: C-MET inhibitors for advanced non-small cell lung cancer. Expert Opin Investig Drugs 27: 367‑375, 2018.

50. Engelman JA, Zejnullahu K, Mitsudomi T, Song Y, Hyland C, Park D, Lindeman N, Gale CM, Zhao X, Christensen J, et al: MET amplification leads to gefitinib resistance in lung cancer by activating ERBB3 signaling. Science 316: 1039‑1043, 2007.

51. Capece R, Happonen R, Lai GG, Lim TH, Lim J, Liew PJ, Kwang XL, Nahar R, Aung ZW, Takano A, Lee YY, Lau DP, et al: Clonal MET amplification as a determinant of tyrosine kinase inhibitor resistance in epidermal growth factor receptor-mutant non-small-cell lung cancer. J Clin Oncol 26: 1182‑1184; author reply 1184‑1186, 2008.

52. Beasley MB, O’Connor KE, Wyllie J, Bhana S, Toohey J, Miller VA and Ladanyi M: Differential receptor‑mutant lung adenocarcinomas with acquired resistance to gefitinib or erlotinib. Proc Natl Acad Sci USA 104: 20932‑20937, 2007.

53. Pao W, Preacox LA, Di Cosimo S, Zanconato F, Gari S, Goldzweig CL, Miller VA, Patel AB, Lehman M, et al: Efficacy, safety, and genetic analysis of pyrotinib in patients with advanced EGFR mutant NSCLC harboring HER2 amplification. JAMA Oncol 2: 1280‑1287, 2016.

54. Pasquini G and Giaccone G: C-MET inhibitors for advanced non-small cell cancer. Expert Opin Investig Drugs 27: 367‑375, 2018.

55. Pasquini G and Giaccone G: C-MET inhibitors for advanced non-small cell cancer. Expert Opin Investig Drugs 27: 367‑375, 2018.

56. Pasquini G and Giaccone G: C-MET inhibitors for advanced non-small cell cancer. Expert Opin Investig Drugs 27: 367‑375, 2018.

57. Pasquini G and Giaccone G: C-MET inhibitors for advanced non-small cell cancer. Expert Opin Investig Drugs 27: 367‑375, 2018.

58. Pasquini G and Giaccone G: C-MET inhibitors for advanced non-small cell cancer. Expert Opin Investig Drugs 27: 367‑375, 2018.

59. Pasquini G and Giaccone G: C-MET inhibitors for advanced non-small cell cancer. Expert Opin Investig Drugs 27: 367‑375, 2018.

60. Pasquini G and Giaccone G: C-MET inhibitors for advanced non-small cell cancer. Expert Opin Investig Drugs 27: 367‑375, 2018.

61. Pasquini G and Giaccone G: C-MET inhibitors for advanced non-small cell cancer. Expert Opin Investig Drugs 27: 367‑375, 2018.

62. Pasquini G and Giaccone G: C-MET inhibitors for advanced non-small cell cancer. Expert Opin Investig Drugs 27: 367‑375, 2018.

63. Dulak AM, Gubish CT, Stabile LP, Henry C and Siegfried JM: MET amplification leads to gefitinib resistance in lung cancer by activating ERBB3 signaling. Science 316: 1039‑1043, 2007.

64. Pasquini G and Giaccone G: C-MET inhibitors for advanced non-small cell cancer. Expert Opin Investig Drugs 27: 367‑375, 2018.

65. Pasquini G and Giaccone G: C-MET inhibitors for advanced non-small cell cancer. Expert Opin Investig Drugs 27: 367‑375, 2018.
65. Wu YL, Zhang L, Kim DW, Liu X, Lee DH, Yang JC, Ahn MJ, Vansteenkiste JF, Su WC, Felip E, et al: Phase I/II study of capmatinib (INC280) plus erlotinib after failure of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor therapy in patients with EGFR-Mutated, MET factor-dysregulated non-small-cell lung cancer. J Clin Oncol 36: 3101-3109, 2018.

66. Wu YL, Cheng Y, Zhou J, Lu S, Zhang Y, Zhao J, Kim DW, Soo RA, Kim SW, Pan H, et al: Tepotinib plus gefitinib in patients with EGFR-mutant non-small-cell lung cancer with MET overexpression or MET amplification and acquired resistance to previous EGFR inhibitor (INSIGHT study): An open-label, phase Ib/2, multicentre, randomised trial. Lancet Respir Med 8: 1123-1134, 2020.

67. Wang Y, Wang Y, Li J, Li J and Che G: Clinical significance of concurrent PIK3CA mutations in EGFR mutant non-small cell lung cancer. J Cancer Res 11: 3189‑3200, 2021.

68. Byers LA, Gold KA and Peguero JA: Ph I/II study of oral selective AXL inhibitor bemcentinib (BGB324) in combination with erlotinib in patients with advanced EGFRm NSCLC: End of trial update. Wolters Kluwer Health, 2021.

69. Xun G, Hu W and Li B: PTEN loss promotes oncogenic function of STAT3 via PI3K/AKT pathway in lung cancer. Sci Rep 11: 14318, 2021.

70. Ai X, Li Y, Chen R, Gu D and Mao Y: P53. 07 mutation profile of BRAF in Chinese non-small cell lung cancer patients. J Thorac Oncol 16: S1149, 2021.

71. Camidge DR, Moran T, Demedts I, Grosch H, Mileham K, Zhang SS, Nagasaka MJLCT and Therapy: Spotlight on Sotorasib (AMG 510) for KRASp.G12C positive non-small cell lung cancer. Lung Cancer (Auckl) 12: 115-122, 2022.
102. Wang R, Pan S and Song X: Research Advances of EGFR-TKI Co-mutation in advanced non-small cell lung cancer. Zhongaohui Fei Ai Za Zhi 25: 174‑182, 2022 (In Chinese).

103. Wang G, Zeng ZH, Deng LL, Yang Y and Lu C: Prognostic value of TP53 co-mutation status combined with EGFR mutation in patients with lung adenocarcinoma. J Cancer Res Clin Oncol 146: 2851‑2859, 2020.

104. Cheng Y, Ma L, Liu Y, Zhu J, Xin Y, Liu X, Wang Y, Zhang T, Yang C, Wang S, et al.: Comprehensive characterization and clinicopathological significance of co-mutant genomic alterations in EGFR-mutant NSCLC treated with EGFR kinase inhibitors. Lung Cancer 145: 63‑70, 2020.

105. Zhang Y, Li S, Lyu Z, Cai J, Zheng N, Li Y, Xu T and Zeng H: The co-mutation of EGFR and tumor-related genes leads to a worse prognosis and a higher level of tumour mutational burden in Chinese non-small cell lung cancer patients. J Thorac Dis 14: 185‑193, 2022.

106. Li HS, Liu CM and Wang Y: Limited role of KRAS mutation in guiding immunotherapy in advanced non-small-cell lung cancer. Future Oncol 18: 2433‑2443, 2022.

107. Marcoux N, Gettinger SN, O'Kane G, Arbour KC, Neal JW, Lockerman EL, Garcia AR, Katayama R, Costa C, Ross KN, et al.: RB loss in resistant EGFR mutant lung adenocarcinomas that transform to small-cell lung cancer. Nat Commun 6: 6377, 2015.

108. Lee KY, Lee K, Kim S, Youk J, Park S, An Y, Yeam B, Kim DW, Heo DS, et al.: Clonal history and genetic predictors of transformation into small-cell lung cancers from lung adenocarcinomas. J Clin Oncol 35: 3063‑3074, 2017.

109. Offin M, Chan JM, Tenet M, Rizvi HA, Shen R, Riely GJ, Hedman Y, Quintanilla-Villalonga A, Persson A, et al.: Concurrent R1156C and TP53 alterations define a subset of EGFR-Mutant lung cancers at risk for histologic transformation and inferior clinical outcomes. J Thorac Oncol 14: 1784‑1793, 2019.

110. Wang CY, Lee MH, Kao YR, Hsiao SH, Hong SY and Wu CW: Detection of acquired TERT amplification in addition to predisposing EGFR mutations in EGFR-mutant NSCLC patients. J Cancer Res Clin Oncol 146: 2851‑2859, 2020.

111. Su KY, Chang YL, Wu CT, Hsu CC, Su CT, Lin CH and Hsu CL: FGFR2-DNA copy number change contributes to drug resistance in EGFR-mutant NSCLC. Biochim Biophys Acta Mol Cell Res 1868: 119016, 2021.

112. Weng CH, Chen LY, Lin YC, Shih YJ, Lin YC, Tseng YR, Chiu AC, Yeh YH, Liu C, Lin YT, et al.: Epithelial‑mesenchymal transition (EMT) beyond EGFR mutation: transformational mechanisms. Cancers (Basel) 10: 455‑468, 2019.

113. Brabletz S, Schuhwerk H, Brabletz T and Steffl M: Dynamic EMT: A multi-tool for tumor progression. EMBO J 40: e108647, 2021.

114. Zhu X, Chen L, Liu L and Niu X: EMT-Mediated Acquired Resistance to EGFR-TKI in NSCLC: Mechanisms and strategies. Front Oncol 11: 1044, 2019.

115. Spritzler J, Arvanitis L, Fricke J, Pharaon R, Baroz AR, et al.: Clinical outcomes of patients with T790M mutation receiving EGFR-TKI treatment. J Thorac Oncol 10: e86‑e88, 2015.

116. Longo L, Mengoli MC, Bertolini F, Bettelli S, Manfredini S and Rossi G: Synchronous occurrence of squamous-cell carcinoma 'transformation' and EGFR exon 20 S768I mutation as a novel mechanism of EGFR-mutated lung adenocarcinoma. Lung Cancer 103: 24‑26, 2017.

117. Duggan DDG, Kailoor N, Zhang J, Neskey M and William WN Jr: Squamous-cell transformation in a patient with lung adenocarcinoma receiving erlotinib: Co-occurrence with T790M mutation. Cancer Treat Rev 44: 34‑36, 2015.

118. Kim Y, Lee J, Cho I, Park KY, Kim Y, Lee SH, Choi Y, Han J, Ahn JS, et al.: EGFR mutation and clinical outcomes of 455 EGFR-mutant lung adenocarcinomas. Lung Cancer 134: 7‑15, 2019.

119. Wang W, Xu C, Chen H, Jia J, Wang L, Feng H, Wang H, et al.: Understanding lineage plasticity as a path to targeted therapy failure in EGFR-Mutant non-small cell lung cancer patients. J Cancer Res Clin Oncol 146: 2851‑2859, 2020.
137. Reck M, Teg T, Nishio M, Jotte R, Cappuzzo F, Li Z, Guo H, Lu Y, Hu J, Luo H and Gu W: Chemotherapy with pemetrexed-related toxicity. Drug Saf 44: 1271-1281, 2021.

138. Jiang T, Wang P, Zhang J, Zhao Y, Zhou J, Fan Y, Shu Y, Liu X, Zhang H, He J, Guo Y et al: A multicenter phase II study of toripalimab with chemotherapy in patients with EGFR mutant advanced NSCLC patients resistant to EGFR TKIs: Efficacy and biomarker analysis. Am Soc Clin Oncol 66: 355, 2020.

139. Li Z, Hu Y, Hu J, Luo H and Gu W: Chemotherapy with or without pemetrexed as second-line regimen for advanced non-small-cell lung cancer patients who have progressed after first-line EGFR TKIs: A systematic review and meta-analysis. Onco Targets Ther 11: 3697-3703, 2018.

140. Le X, Nilsen O, Reck M, Jiang T, Ma L, Chen R, Wang F, Ma LL, Yuan MM, Chen RR and Gao R: Concurrent use of anlotinib overcomes acquired resistance to EGFR-TKIs in patients with advanced EGFR-mutant non-small-cell lung cancer. Thorac Cancer 11: 254-258, 2020.

141. Jiang T, Wang P, Zhang J, Zhao Y, Zhou J, Fan Y, Shu Y, Liu X, Zhang H, He J, Guo Y et al: A phase II study of toripalimab, pemetrexed and carboplatin for metastatic EGFR mutated NSCLC after TKI failure. Lung Cancer 159: 18-26, 2021.

142. Ren S, Zhang J, Zhao Y, Zhou J, Fan Y, Shu Y, Liu X, Zhang H, He J, Guo Y et al: Toripalimab plus chemotherapy in patients with EGFR mutant advanced NSCLC patients resistant to EGFR TKIs: A multi-center phase II study. Signal Transduct Target Ther 6: 355, 2021.

143. Jiang T, Wang P, Zhang J, Zhao Y, Zhou J, Fan Y, Shu Y, Liu X, Zhang H, He J, Guo Y et al: Toripalimab plus chemotherapy as second-line treatment in previously EGFR-TKI treated patients with EGFR-mutant-advanced NSCLC: A multicenter phase-II trial. Signal Transduct Target Ther 6: 355, 2021.

144. Su S, Wu L, Jian H, Cheng Y, Wang Q, Fang J, Wang Z, Hu Y, Sun M, Han Y, Han Y. 2020: V99-2021: Phase III study of sunitinib with or without IBI305 plus chemotherapy in patients with EGFR mutated nonsquamous NSCLC who progressed after EGFR-TKI therapy. Ann Oncol 33: 111-112, 2022.

145. Hayashi H, Sugawara S, Fukuda Y, Fujimoto D, Miura S, Ota K, Lam TC, Tsang KC, Choi HC, Lee VH, Lam KO, Chiang CL, Lam KO, et al: Analysis of resistance mechanisms to osimertinib in patients with EGFR T790M advanced NSCLC from the AURA3 study. Ann Oncol 29: vi741, 2021.

146. Piotrowska Z, Nagy R, Fairclough S, Lanman R, Marcoux N, Gettinger S, Ovonikoto T, Ramalingam S and Sequist L: Characterizing the genomic landscape of EGFR C797S in lung cancer using cDNA next-generation sequencing. J Thorac Oncol 12: S1767, 2017.

147. Wang X, Zhou L, Yin JC, Wu X, Shao YW and Gao B: Lung adenocarcinoma harboring EGFR 19del/C797S/T790M triple mutations responds to brigatinib and Anti-EGFR antibody combination therapy. J Thorac Oncol 14: e58-e85, 2019.

148. Wang Y, Sun M, Han Y, Han Y, Han Y. 2020: V99-2021: Phase III study of sunitinib with or without IBI305 plus chemotherapy in patients with EGFR mutated nonsquamous NSCLC who progressed after EGFR-TKI therapy. Ann Oncol 33: 111-112, 2022.

149. de Rouw N, Piet B, Derijks HJ, van den Heuvel MM and Ten Heine M: Mechanisms, management and prevention of pemetrexed-related toxicity. Drug Saf 44: 1271-1281, 2021.

150. Zeng Y, Liu Z and Huang JA: Anlotinib can overcome acquired resistance of L858R, T790M, cis-G796s/cis-C797s by osimertinib, brigatinib, and bevacizumab combination therapy: A case report. Respir Med Case Rep 36: 101582, 2021.

151. Zhao R, Song L, Zhang W, Shao L, Li X and Li X: Combination of osimertinib and anlotinib may overcome the resistance mediated by cis in EGFR T790M/C797S in NSCLC: A case report. Onco Targets Ther 14: 2847-2851, 2021.

152. Yang Y, Xu H, Ma L, Yang L, Yang G, Zhang S, Ai X, Zhang S and Wang Y: Possibility of brigatinib-based therapy, or chemotherapy plus anti-angiogenic treatment after resistance of osimertinib harboring EGFR T790M/C797S mutations in lung adenocarcinoma patients. Cancer Med 10: 8328-8337, 2021.

153. Zhao Y, Chen Y, Huang H, Li X, Shao L and Ding H: Significant benefits of afatinib and apanitin in a refractory advanced NSCLC patient resistant to osimertinib: A case report. OncoTargets Ther 14: 3063-3067, 2021.

154. Yu Z, Yang N, Ou D, Xiang Y, Jiang T, Wu X, Bao H, Tong X, Wang X, Shao YW et al: Investigating novel resistance mechanisms to third-generation EGFR tyrosine kinase inhibitor osimertinib in non-small cell lung cancer patients. Cancer Res 24: 3097-3107, 2018.

155. Zhang Y, He B, Zhou D, Li M and Hu C: Newly emergent acquired EGFR exon 18 G724S mutation after resistance of a T790M specific EGFR inhibitor osimertinib in non-small-cell lung cancer: A case report. OncoTargets Ther 12: 51-56, 2018.

156. Schoenfeld AJ, Chan JM, Kubota D, Sato H, Rizvi H, Dumanhodh C, Jiang JC, Paik PK, Ofint C, Arcila ME et al: Tumor analyses reveal squamous transformation and off-target alterations as early resistance mechanisms to first-line osimertinib in EGFR-Mutant lung cancer. Cancer Clin Res 26: 1854-1863, 2020.

157. Fairclough SR, Kiedrowski LA, Lin JJ, Zelichov O, Tarcic G, Piotrowska Z, Nagy R, Fairclough S, Lanman R, Marcoux N, Gettinger S, Ovonikoto T, Ramalingam S and Sequist L: Characterizing the genomic landscape of EGFR C797S in lung cancer using cDNA next-generation sequencing. J Thorac Oncol 12: S1767, 2017.

158. Zeng Y, Liu Z and Huang JA: Anlotinib can overcome acquired resistance of L858R, T790M, cis-G796s/cis-C797s by osimertinib, brigatinib, and bevacizumab combination therapy: A case report. Respir Med Case Rep 36: 101582, 2021.

159. Wang X, Zhou L, Yin JC, Wu X, Shao YW and Gao B: Lung adenocarcinoma harboring EGFR 19del/C797S/T790M triple mutations responds to brigatinib and Anti-EGFR antibody combination therapy. J Thorac Oncol 14: e58-e85, 2019.

160. Zeng Y, Liu Z and Huang JA: Anlotinib can overcome acquired resistance of L858R, T790M, cis-G796s/cis-C797s by osimertinib, brigatinib, and bevacizumab combination therapy: A case report. Respir Med Case Rep 36: 101582, 2021.

161. Zhou R, Song L, Zhang W, Shao L, Li X and Li X: Combination of osimertinib and anlotinib may overcome the resistance mediated by cis in EGFR T790M/C797S in NSCLC: A case report. Onco Targets Ther 14: 2847-2851, 2021.

162. Yang Y, Xu H, Ma L, Yang L, Yang G, Zhang S, Ai X, Zhang S and Wang Y: Possibility of brigatinib-based therapy, or chemotherapy plus anti-angiogenic treatment after resistance of osimertinib harboring EGFR T790M/C797S mutations in lung adenocarcinoma patients. Cancer Med 10: 8328-8337, 2021.

163. Zhao Y, Chen Y, Huang H, Li X, Shao L and Ding H: Significant benefits of afatinib and apanitin in a refractory advanced NSCLC patient resistant to osimertinib: A case report. OncoTargets Ther 14: 3063-3067, 2021.

164. Yu Z, Yang N, Ou D, Xiang Y, Jiang T, Wu X, Bao H, Tong X, Wang X, Shao YW et al: Investigating novel resistance mechanisms to third-generation EGFR tyrosine kinase inhibitor osimertinib in non-small cell lung cancer patients. Cancer Res 24: 3097-3107, 2018.

165. Zhang Y, He B, Zhou D, Li M and Hu C: Newly emergent acquired EGFR exon 18 G724S mutation after resistance of a T790M specific EGFR inhibitor osimertinib in non-small-cell lung cancer: A case report. OncoTargets Ther 12: 51-56, 2018.

166. Schoenfeld AJ, Chan JM, Kubota D, Sato H, Rizvi H, Dumanhodh C, Jiang JC, Paik PK, Ofint C, Arcila ME et al: Tumor analyses reveal squamous transformation and off-target alterations as early resistance mechanisms to first-line osimertinib in EGFR-Mutant lung cancer. Cancer Clin Res 26: 1854-1863, 2020.

167. Fairclough SR, Kiedrowski LA, Lin JJ, Zelichov O, Tarcic G, Piotrowska Z, Nagy R, Fairclough S, Lanman R, Marcoux N, Gettinger S, Owonikoko T, Ramalingam S and Sequist L: Characterizing the genomic landscape of EGFR C797S in lung cancer using cDNA next-generation sequencing. J Thorac Oncol 12: S1767, 2017.
170. Zhang Y, Yang Q, Zeng X, Wang M, Long S, Yang B, Tu X, Wei T, Xie W, Zhang C, et al: MET amplification attenuates lung tumor response to immunotherapy by inhibiting STING. Cancer Discov 11: 2726‑2737, 2021.

171. Syed YY: Amivantamab: First approval. Drugs 81: 1349‑1353, 2021.

172. Planchard D, Loriot Y, André F, Gobert A, Auger N, Lacroix L: Amivantamab OK'd for EGFR‑Mutant NSCLC. Cancer Discov 11: 1604, 2021.

173. Neijssen J, Cardoso RM, Chevalier KM, Wiegman L, Valerius T, Anderson GM, Moores SL, Schuurman J, Parren P, Strohl WR and the Chiu M: Amivantamab (JNJ‑61186372), a bispecific antibody targeting EGFR and MET. J Biol Chem 296: 100641, 2021.

174. Planchar D, Loriot Y, André F, Gobert A, Auger N, Lacroix L: Amivantamab OK'd for EGFR‑Mutant NSCLC. Cancer Discov 11: 1604, 2021.

175. Ramalingam S, Cheng Y, Zhou C, Ohe Y, Immamura F, Cho BC, Lin M, Majem M, Shah R, Rukazenkov Y, et al: Mechanisms of acquired resistance to first‑line osimertinib: preliminary data from the phase III FLAURA study. Oncology Pro 29: vii740, 2018.

176. Oxnard GR, Hu Y, Mileham KF, Husain H, Costa DB, Tracy P, Feeney N, Sholl LM, Dahlberg SE, Redj AJ, et al: Assessment of resistance mechanisms and clinical implications in patients with EGFR T790M‑Positive lung cancer and acquired resistance to osimertinib. Tuma Oncology 4: 1527‑1534, 2018.

177. Qu F, Zhou Y and Wu WJA‑CD: A review of research progress on mechanisms and overcoming strategies of acquired osimertinib resistance. Anticancer Drugs 33: e76‑e82, 2022.

178. Beenken A and Mohammadi M: The FGF family: Biology, pathophysiology and therapy. Nat Rev Drug Discov 8: 235‑253, 2009.

179. Lu Y, Liu Y, Oeck S, Zhang GJ, Schramm A and Glazer PM: Hypoxia induces resistance to EGFR inhibitors in lung cancer cells via upregulation of FGFR1 and the MAPK pathway. Cancer Res 80: 4655‑4667, 2020.

180. Quintal‑Villalonga A, Molina‑Pinelo S, Cirauchy C, Ojeda‑Márquez L, Marrugal Á, Suarez R, Conde E, Ponce‑Aix S, Quintanal‑Villalonga A, Molina‑Pinelo S, Cirauqui C, Hsieh J, Eno M, Wilson D, Campbell J: BLU‑945, a 3rd‑generation EGFR inhibitor with intracranial activity as a single agent and in combination with BLU‑945 in models of non‑small cell lung cancer (NSCLC) driven by EGFR mutations. Mol Cell Biol 165: S37, 2022.

181. Lin X, Zhang Y, Yang L and Chen S, Tu, Dong D, Ding C, Hu L, Wu L, Zhao L, Mao J, et al: Preclinical evaluation of TQB3804, a potent EGFR C797S inhibitor. Cancer Res 79 (Suppl 13): 1320, 2019.

182. Lu Y, Lin CC, Shih JY, Yu CJ, Ho CC, Liao WY, Lee JH, Tsai TH, Lin M, Majem M, Shah R, Rukazenkov Y, et al: Mechanisms of resistance to osimertinib. Nature 534: 129‑132, 2016.

183. Makimoto G, Ninomiya K, Kubo T, Sunami R, Kato Y, Zhao Y, Wang H and He C: Drug resistance of targeted therapy with EGFR T790M mutation. Thorac Cancer 11: 140‑149, 2020.

184. Makimoto G, Ninomiya K, Kubo T, Sunami R, Kato Y, Ichihara E, Ohashi K, RAI K, Hotta K, Tabata M, et al: A novel osimertinib‑Resistant human lung adenocarcinoma cell line harbouring mutant‑specific T790M and activated IGFIR. Jpn J Clin Oncol 51: 956‑965, 2021.

185. Zhang Y, Wang H and He C: Drug resistance of targeted therapy for advanced non‑small cell lung cancer harbored EGFR mutation: From mechanism analysis to clinical strategy. J Cancer Res Clin Oncol 147: 3653‑3664, 2021.

186. Seki H, Okuyama S, Shinohara S, Ohashi K, Shiotsuki J, Tanioka K, Hidai K, Minardi W, Ibara H, Kamonori K, Matsumoto N, Asao T, et al: Activation of insulin‑like growth‑factor I‑receptor confers acquired resistance to osimertinib in non‑small cell lung cancer with EGFR T790M mutation. Thoracic Cancer 11: 140‑149, 2020.

187. Zhao Y, Wang H and He C: Drug resistance of targeted therapy for advanced non‑small cell lung cancer harbored EGFR mutation: From mechanism analysis to clinical strategy. J Cancer Res Clin Oncol 147: 3653‑3664, 2021.

188. Makimoto G, Ninomiya K, Kubo T, Sunami R, Kato Y, Ichihara E, Ohashi K, RAI K, Hotta K, Tabata M, et al: A novel osimertinib‑resistant human lung adenocarcinoma cell line harboring mutant‑specific T790M and activated IGFIR. Jpn J Clin Oncol 51: 956‑965, 2021.

189. Zhang Y, Wang H and He C: Drug resistance of targeted therapy for advanced non‑small cell lung cancer harbored EGFR mutation: From mechanism analysis to clinical strategy. J Cancer Res Clin Oncol 147: 3653‑3664, 2021.

190. Zhao Y, Wang H and He C: Drug resistance of targeted therapy for advanced non‑small cell lung cancer harbored EGFR mutation: From mechanism analysis to clinical strategy. J Cancer Res Clin Oncol 147: 3653‑3664, 2021.

191. Zhao Y, Wang H and He C: Drug resistance of targeted therapy for advanced non‑small cell lung cancer harbored EGFR mutation: From mechanism analysis to clinical strategy. J Cancer Res Clin Oncol 147: 3653‑3664, 2021.

192. Zhao Y, Wang H and He C: Drug resistance of targeted therapy for advanced non‑small cell lung cancer harbored EGFR mutation: From mechanism analysis to clinical strategy. J Cancer Res Clin Oncol 147: 3653‑3664, 2021.

193. Zhao Y, Wang H and He C: Drug resistance of targeted therapy for advanced non‑small cell lung cancer harbored EGFR mutation: From mechanism analysis to clinical strategy. J Cancer Res Clin Oncol 147: 3653‑3664, 2021.

194. Zhao Y, Wang H and He C: Drug resistance of targeted therapy for advanced non‑small cell lung cancer harbored EGFR mutation: From mechanism analysis to clinical strategy. J Cancer Res Clin Oncol 147: 3653‑3664, 2021.

195. Zhao Y, Wang H and He C: Drug resistance of targeted therapy for advanced non‑small cell lung cancer harbored EGFR mutation: From mechanism analysis to clinical strategy. J Cancer Res Clin Oncol 147: 3653‑3664, 2021.

196. Zhao Y, Wang H and He C: Drug resistance of targeted therapy for advanced non‑small cell lung cancer harbored EGFR mutation: From mechanism analysis to clinical strategy. J Cancer Res Clin Oncol 147: 3653‑3664, 2021.

197. Zhao Y, Wang H and He C: Drug resistance of targeted therapy for advanced non‑small cell lung cancer harbored EGFR mutation: From mechanism analysis to clinical strategy. J Cancer Res Clin Oncol 147: 3653‑3664, 2021.

198. Zhao Y, Wang H and He C: Drug resistance of targeted therapy for advanced non‑small cell lung cancer harbored EGFR mutation: From mechanism analysis to clinical strategy. J Cancer Res Clin Oncol 147: 3653‑3664, 2021.

199. Zhao Y, Wang H and He C: Drug resistance of targeted therapy for advanced non‑small cell lung cancer harbored EGFR mutation: From mechanism analysis to clinical strategy. J Cancer Res Clin Oncol 147: 3653‑3664, 2021.

200. Zhao Y, Wang H and He C: Drug resistance of targeted therapy for advanced non‑small cell lung cancer harbored EGFR mutation: From mechanism analysis to clinical strategy. J Cancer Res Clin Oncol 147: 3653‑3664, 2021.

201. Zhao Y, Wang H and He C: Drug resistance of targeted therapy for advanced non‑small cell lung cancer harbored EGFR mutation: From mechanism analysis to clinical strategy. J Cancer Res Clin Oncol 147: 3653‑3664, 2021.

202. Zhao Y, Wang H and He C: Drug resistance of targeted therapy for advanced non‑small cell lung cancer harbored EGFR mutation: From mechanism analysis to clinical strategy. J Cancer Res Clin Oncol 147: 3653‑3664, 2021.
206. Tamiya M, Kunimasa K, Nishino K, Matsumoto S, Kawachi H, Kuno K, Inoue T, Kuhara H, Imamura F, Goto K and Kumagai T: Successful treatment of an osimertinib-resistant lung adenocarcinoma with an exon 18 EGFR mutation (G719S) with afatinib plus bevacizumab. Invest New Drugs 39: 232-236, 2021.

207. Blakely CM, Watkins TBK, Wu W, Gini B, Chabon JJ, McCoach CE, McGranahan N, Wilson GA, Birkbak NJ, Olivas VR, et al: Evolution and clinical impact of co-occurring genetic alterations in advanced-stage EGFR-mutant lung cancers. Nat Genet 49: 1693-1704, 2017.

208. Dagogo-Jack I and Shaw AT: Tumour heterogeneity and resistance to cancer therapies. Nat Rev Clin Oncol 15: 81-94, 2018.

209. Assaraf YG, Brozovic A, Gonçalves AC, Jurkovicova D, Linē A, Machuqueiro M, Saponara S, Sarmento-Ribeiro AB, Xavier CPR and Vasconcelos MH: The multi-factorial nature of clinical multidrug resistance in cancer. Drug Resist Updat 46: 100645, 2019.

210. Zhang Y, Wang D, Peng M, Tang L, Ouyang J, Xiong F, Guo C, Tang Y, Zhou Y, Liao Q, et al: Single-cell RNA sequencing in cancer research. J Exp Clin Cancer Res 40: 81, 2021.

211. Kim DW and Cho JY: Recent advances in allogeneic CAR-T cells. Biomolecules 10: 263, 2020.

212. Patel AJ, Richter A, Drayson MT and Middleton GW: The role of B lymphocytes in the immuno-biology of non-small-cell lung cancer. Cancer Immunol Immunother 69: 325-342, 2020.

213. Xiao BF, Zhang JT, Cui XR, Lu ZM, Yu BT and Wu N: Chimeric antigen receptor T-cell therapy in lung cancer: Potential and challenges. Front Immunol 12: 782775, 2021.

214. Qu J, Mei Q, Chen L and Zhou J: Chimeric antigen receptor (CAR)-T-cell therapy in non-small-cell lung cancer (NSCLC): Current status and future perspectives. Cancer Immunol Immunother 70: 619-631, 2021.

215. Chen L, Chen F, Li J, Yang C, Wang Y, Lei Y and Huang Y: CAR-T cell therapy for lung cancer: Potential and perspective. Thorac Cancer 13: 889-899, 2022.

216. Vasic D, Lee JB, Leung Y, Khatri I, Na Y, Abate-Daga D and Zhang L: Allogeneic double-negative CAR-T cells inhibit tumor growth without off-tumor toxicities. Sci Immunol 7: eabl3642, 2022.

This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0) License.