The advance of the third-generation EGFR-TKI in the treatment of non-small cell lung cancer (Review)

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Abstract. Lung cancer is currently the second most common type of cancer with the second incidence rate and the first mortality rate worldwide. Non-small cell lung cancer (NSCLC) accounts for ~85% of the total number of cases of lung cancers. Concerning the treatment of NSCLC, targeted therapy has become a research hotspot in recent years because of its favorable efficacy, high selectivity and minimal adverse reactions. Among the drugs used in targeted therapy, the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) are the most common and are categorized into four generations. The use of first and second-generation drugs leads to drug resistance within 8-14 months. This resistance is primarily caused by the T790M mutation, which is the most observed mechanism. A third-generation drug has been developed to address this issue and a fourth-generation drug is expected to overcome multiple resistance mechanisms, including third-generation drug resistance. However, the fourth-generation drug has not been launched yet. At present, multiple third-generation targeted drugs have been launched globally, with three being launched in China and several being at research and clinical trial stages. The present article provides a review of the development process, mechanism of action and clinical trials of the third-generation EGFR-TKIs, aiming to provide some reference and suggestions for the clinical treatment of NSCLC and scientific research on third-generation targeted drugs.

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Contents

1. Introduction

According to the latest cancer data statistics, the incidence rate and mortality of lung cancer rank second and first in

all malignant tumors, respectively (1,2). According to the latest available data in China, lung cancer has the highest incidence and mortality rates. The histological types of lung cancer are divided into non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC), with NSCLC accounting for ~85% of the total number of lung cancer cases (3,4). Patients are often in advanced stages at the time of treatment, with limited treatment options and poor prognosis. The treatment of lung cancer has attracted widespread attention due to its low 5-year survival that is <15% (5). The treatment of lung cancer mainly includes surgical resection, radiotherapy, chemotherapy, immunotherapy and targeted therapy. Targeted therapy offers several advantages, such as high selectivity and minimal adverse reactions. With the advent of precision medicine, targeted therapy has been widely applied in the field of cancer and has become a research hotspot in recent years. Epidermal growth factor receptor (EGFR) is a tyrosine kinase receptor, which carries the most common oncogenic driving mutation in NSCLC. Mutations in this gene significantly enhance the growth and division of cancer cells. ~15% of Caucasians and 50% of Asian patients with late-stage NSCLC have mutations in the EGFR domain (6,7). Among these mutations, the deletion of exon 19 and the point mutation of exon 21 L858R accounted for 90% of EGFR mutations (8). The development of anticancer drugs targeting this specific target has greatly changed the treatment methods and their prognostic efficacy for patients with NSCLC. The EGFR target was the first target to be discovered and applied in lung cancer, and the discovery of this target is of landmark significance for the treatment of lung cancer. EGFR-targeted drugs have prolonged the survival time of patients with lung cancer from >1 year in chemotherapy to ~3 years with the current three generations of targeted therapy. The incidence of grade 3 or 4 adverse events (AEs) has also decreased from 61 to 28.7%, and the targeted therapy has significantly improved the quality of life compared with chemotherapy (9,10). The present article summarizes and reviews the development history, mechanism of action and clinical trial data of the above drugs as first-line and second-line treatments for efficacy and safety analysis, with the intent to provide new ideas and references for clinical treatment and scientific research.

2. History of the EGFR-targeted drugs

The drugs targeting the EGFR, namely EGFR tyrosine kinase inhibitor (TKI), are divided into first, second, third and fourth generations (11). The first and second-generation EGFR-TKIs are used to treat advanced NSCLC with EGFR-sensitized mutations. The first-generation drugs include gefitinib and erlotinib among others. The second-generation drugs include afatinib and dacomitinib among others. Although the objective response rate (ORR) of the first and second-generation drugs is very high, which can reach 60-70%, most patients show resistance after 8-14 months of treatment, and the average progression-free survival is 9-15 months (12). Therefore, third-generation drugs have been developed, including osimertinib and almonertinib (13,14). Currently, there are several targeted drugs of the third generation that have been introduced worldwide. Among them, three drugs, namely osimertinib, almonertinib and furmonertinib, have been authorized for use in China. The fourth-generation drugs mainly focus on fighting the acquired resistance that the C797S mutation causes, which is common in third-generation drugs. These fourth-generation drugs, such as EAI045 and CH7233163, have not yet been implemented in clinical practice.

Osimertinib is the world's first third-generation targeted drug to be launched, which was developed by AstraZeneca in the United States. In November 2015, patients with NSCLC and T790M mutations were approved by the Food and Drug Administration (FDA) for use in previous EGFR TKI treatment progression (15). Rociletinib was developed by Wuhan Chemstan Biotechnology in China and showed to be not as effective as osimertinib, and the incidence of hyperglycemia (34%) and ECG QTc prolongation (11%) in third-grade adverse reactions were relatively high. Therefore, the FDA voted to postpone the approval of the drug and ultimately terminated its development in May 2016 (16,17). Olmutinib was developed by Boehringer Ingelheim and Hammi Pharmaceuticals Co., Ltd. and was approved in May 2016 in South Korea for the treatment of patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC (18). Subsequently, due to limited efficacy and severe adverse reactions, development was discontinued. Osimertinib was approved for listing in China in March 2017 (19). Naquotinib was developed by Astellas, a Japanese company. The development of naquotinib was also discontinued due to its general efficacy and high incidence of adverse reactions in the SOLAR trial in May 2017 (16,20). In November 2018, the 2019 version of the National Comprehensive Cancer Network guidelines for NSCLC in the United States included osimertinib as the first-line treatment option for EGFR-positive patients. Almonertinib is a third-generation targeted drug developed by Jiangsu Hansoh Pharmaceutical Co., Ltd. It is the first independently developed third-generation targeted drug in China. It was launched in March 2020 and is used for the second-line treatment of patients with EGFR-sensitive mutations and EGFR T790M mutations. Lazertinib was developed by Yuhan and Janssen Biotechnology and was approved as a second-line treatment for NSCLC in South Korea in January 2021 (21). Nazartinib was developed by Novartis Pharmaceuticals and approved by the Korean Ministry of Drug and Food Safety in January 2021. Furmonertinib is an irreversible third-generation EGFR-TKI, independently developed by Shanghai Allist Pharmaceutical Company in China. Approved for marketing by NMPA in March 2021, it is used to treat patients with NSCLC who develop resistance after first or second-generation targeted drug therapy and have been found to have T790M mutations through genetic testing (22). In December 2021, the National Medical Products Administration (NMPA) approved almonertinib as the first-line treatment for patients with EGFR-mutated NSCLC (23). In June 2022, furmonertinib was approved as a first-line treatment. At present, the clinical trials of the fourth generation of targeted drugs have also achieved favorable results, and we look forward to the approval of the fourth generation of targeted drugs as soon as possible. The development process of the aforementioned drugs is shown in Fig. 1.

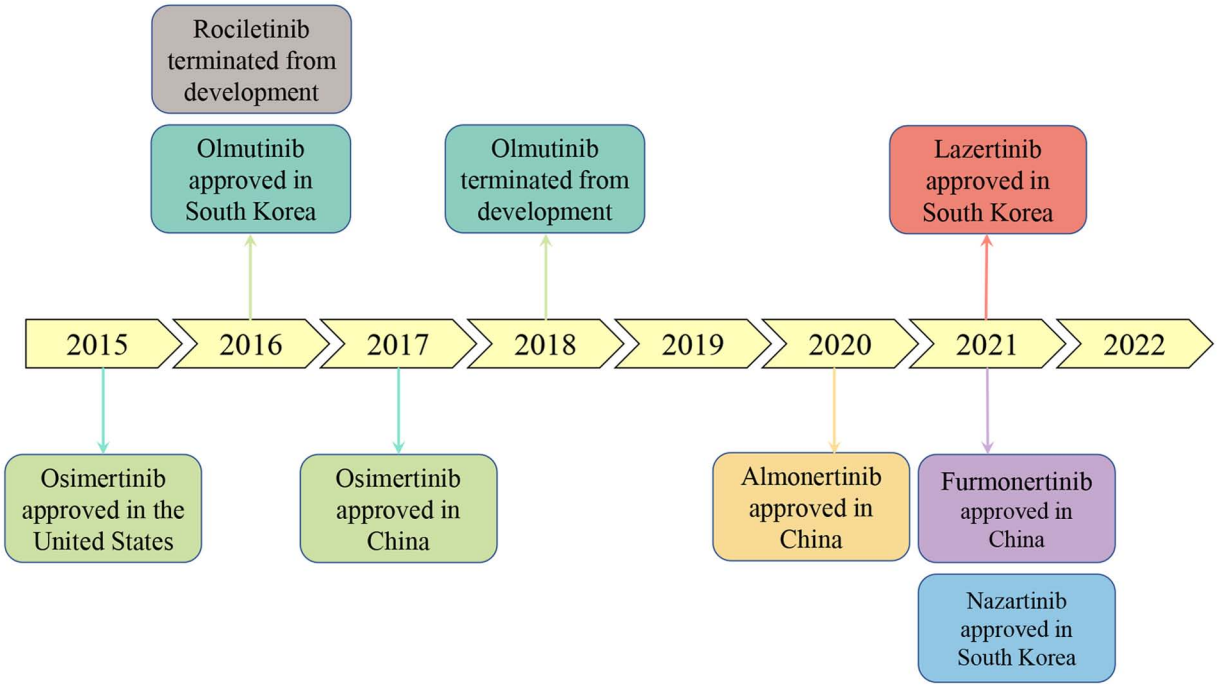

Figure 1. The development process of the targeted drugs.

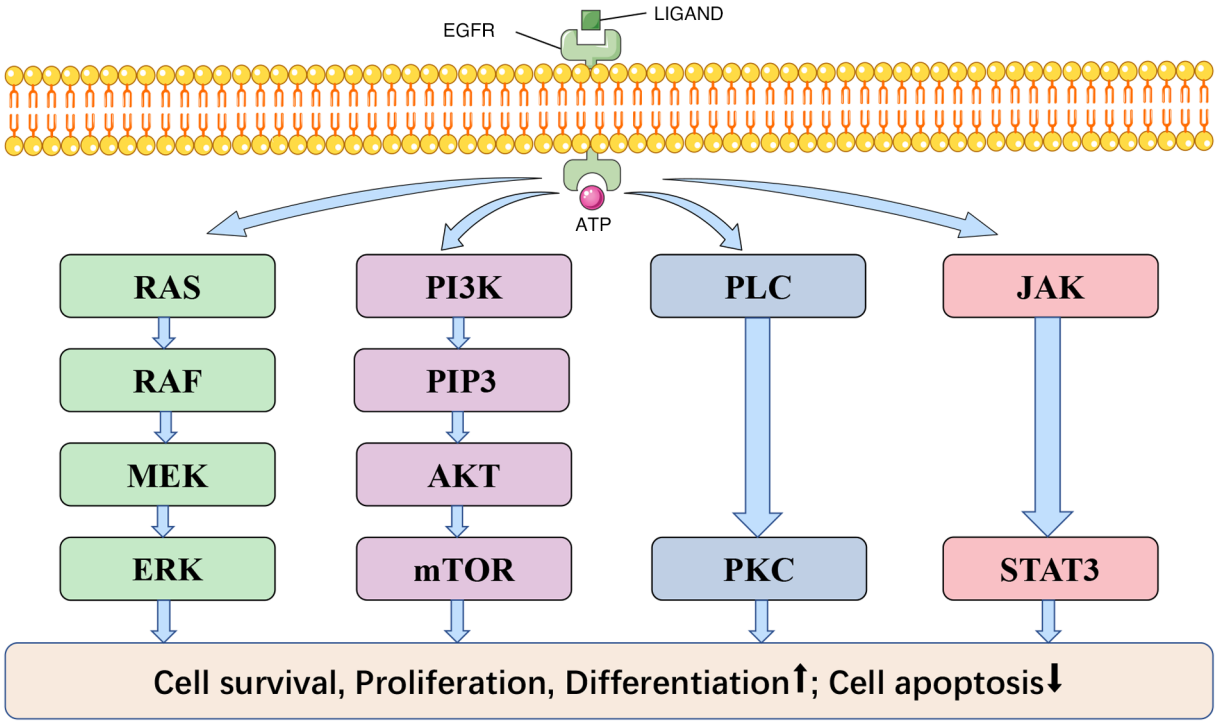

Figure 2. EGFR downstream signaling pathway.

3. Mechanism

EGFR is a member of the ERBB family, a classic cell surface signaling protein, and the most common mutated oncogene. It consists of an extracellular ligand binding domain, a hydrophobic transmembrane region anchored to the cell membrane, and a tyrosine kinase domain located within the cell (24,25). EGFR and EGF, Transforming Growth Factors α (TGF α) ligands combine to form homomorphic or heteromorphic dimers, activating the tyrosine kinase domain. ATP binds tightly to this domain and transmits signals to downstream signaling pathways (26,27). There are four common downstream signal pathways: i) PI3K/AKT; ii) RAS/RAF/MAPK; iii) JAK/STAT; and iv) PLC/PKC, respectively, as demonstrated in Fig. 2; in addition, it also includes SRC, JNK and other signaling pathways (25,27-30). EGFR plays a role in

promoting cell survival, proliferation, differentiation and inhibiting apoptosis by triggering the signal transductions aforementioned.

In NSCLC, EGFR mutations no longer rely on receptor activation, causing downstream signaling pathways to remain continuously activated, leading to the long-term existence of signals that promote proliferation, inhibit apoptosis, and ultimately lead to carcinogenesis (31). The signals transmitted by heterodimers are amplified and enhanced, exhibiting stronger carcinogenicity compared with signals transmitted by homodimers (32). Small molecule kinase inhibitors, such as first-generation targeted drugs including gefitinib and erlotinib, are reversible inhibitors that can competitively bind to the tyrosine kinase domain with ATP, leading to a decrease in EGFR's affinity for ATP, thereby blocking signal transmission, reducing proliferation, promoting apoptosis, and ultimately inhibiting tumor growth and metastasis (33). However, after a period of treatment, a T790M mutation occurred. On the one hand, the amino acid changed from threonine to a larger volume of methionine increasing steric hindrance, and resulting in weakened binding between the first-generation targeted drug and EGFR. On the other hand, the T790M mutation increased the binding ability of the L858R mutant to ATP, ultimately leading to drug resistance (34). The second generation of targeted drugs, including afatinib and dacomitinib, is an irreversible inhibitor, which cannot reach the concentration to overcome the T790M mutation in the human body. In addition, the second generation of drugs has low selectivity and combines with wild EGFR, which brings severe adverse reactions such as diarrhea and rash to patients; therefore, its clinical use is limited (35). Although the ORR of first-generation and second-generation drug therapy reached 60-70%, most patients developed resistance after 8-14 months of treatment, with an average progression-free survival of 10-14 months (12,36). The most common resistance mechanism among the others is the T790M mutation, which accounts for ~50% of all EGFR TKI resistance mechanisms in patients with NSCLC (37). However, third-generation targeted drugs have been developed for the T790M mutation, such as osimertinib, almonertinib and lazertinib (13,14). These drugs form a covalent bond with the C797 residue on the ATP binding site, which binds irreversibly and has stronger binding power (35,38). They have a weak inhibitory effect on wild EGFR, higher selectivity, and fewer adverse reactions (39). The mechanism of action and drug resistance of EGFR-TKI is revealed in Fig. 3.

4. Third-generation EGFR-TKIs

Osimertinib (also named AZD9291). The AURA17 (NCT02442349) trial is a phase 2, open-label, single-arm clinical study in the Asia Pacific population, evaluating the efficacy and safety of osimertinib as a second-line treatment for patients with EGFR T790M mutation who had previously progressed with EGFR-TKI or after chemotherapy (40). According to a data report from the European Society for Medical Oncology Asia 2018 conference, the ORR of osimertinib was 62%, the disease control rate (DCR) was 88%, and the median duration of response (mDoR) was 9.9 months, the median progression-free survival (mPFS) was 9.7 months, and the median overall survival (mOS) was 23.2 months. Grade 3 or higher AEs occurred in 35% of patients. The most common AEs were diarrhea (29.24%) and leukopenia (12.87%), with grade 3 or higher diarrhea and rash occurring in only 1% of patients. The aforementioned data was similar to the data from the AURA2 (41) and AURA3 (42) trials, both of which are global multicenter trials, indicating that osimertinib showed clinical efficacy, durability and safety similar to global data, providing data to support the use of osimertinib in patients with T790M mutation after EGFR TKI progression in the Asia-Pacific region. The global data suggest strengthening and improving the clinical application of osimertinib in China.

The FLAURA (NCT02296125) trial is a Phase 3, double-blind, randomized, multicenter clinical study, comparing the efficacy and safety of osimertinib with gefitinib or erlotinib as first-line treatment in locally advanced or metastatic EGFR sensitized NSCLC with positive mutations (43). According to the data from the FLAURA China trial, osimertinib has significantly improved in all aspects compared with the first-generation drug. The PFS was extended from 9.8 to 17.8 months for the first-generation drug, the mDoR was extended from 10.9 to 16.4 months, the ORR was increased from 70.8 to 76.1%, the DCR was increased from 95.4 to 97.2% and the mOS was extended from 25.7 to 33.1 months. The proportion of grade 3 and aforementioned AEs was 54% in the osimertinib group and 28% in the other EGFR TKIs group. The common AEs were decreased neutrophil, platelet and with blood counts, as well as rash. However, changes in the severity of these AEs did not result in any clinically significant sequelae. In addition to the aforementioned AEs, interstitial lung disease (ILD) is a potentially fatal side effect, but its incidence is only 3.3% (in the aforementioned study, the incidence of ILD was 3%), and the probability of progression to a life-threatening state was only 0.5%. There are even fewer reported and documented cases (44). In addition, in patients with central nervous system (CNS) metastasis, mPFS was not reached in the osimertinib group, while it was 13.9 months in the standard EGFR-TKI group and the hazard ratio (HR) was 0.48. CNS progression occurred in 20% of patients in the osimertinib group vs. 39% of patients in the standard EGFR-TKI group. The data for osimertinib in China were generally consistent with the global data, except for the rate of grade 3 or higher AEs. In the global data, grade ≥3 AEs were 34% in the osimertinib group and 45% in the standard EGFR-TKI group, but as aforementioned, the higher rate of AEs with osimertinib was primarily related to the reporting of laboratory abnormalities, and no new safety concerns or clinically significant sequelae were identified (45-47). From the aforementioned data, it was observed that in first-line treatment, osimertinib offers a markedly greater advantage as a third-generation targeted drug than the first-generation targeted drug. Osimertinib can not only significantly prolong the PFS, but also control the metastasis and progression in the CNS. Therefore, for patients with EGFR mutation positivity in advanced lung cancer, osimertinib has established its unshakable position in the targeted treatment of NSCLC due to its improved efficacy and permeability to CNS metastatic patients. The subjects of this experiment come from multiple centers, different countries, and different ethnicities, and the reliability of the experimental

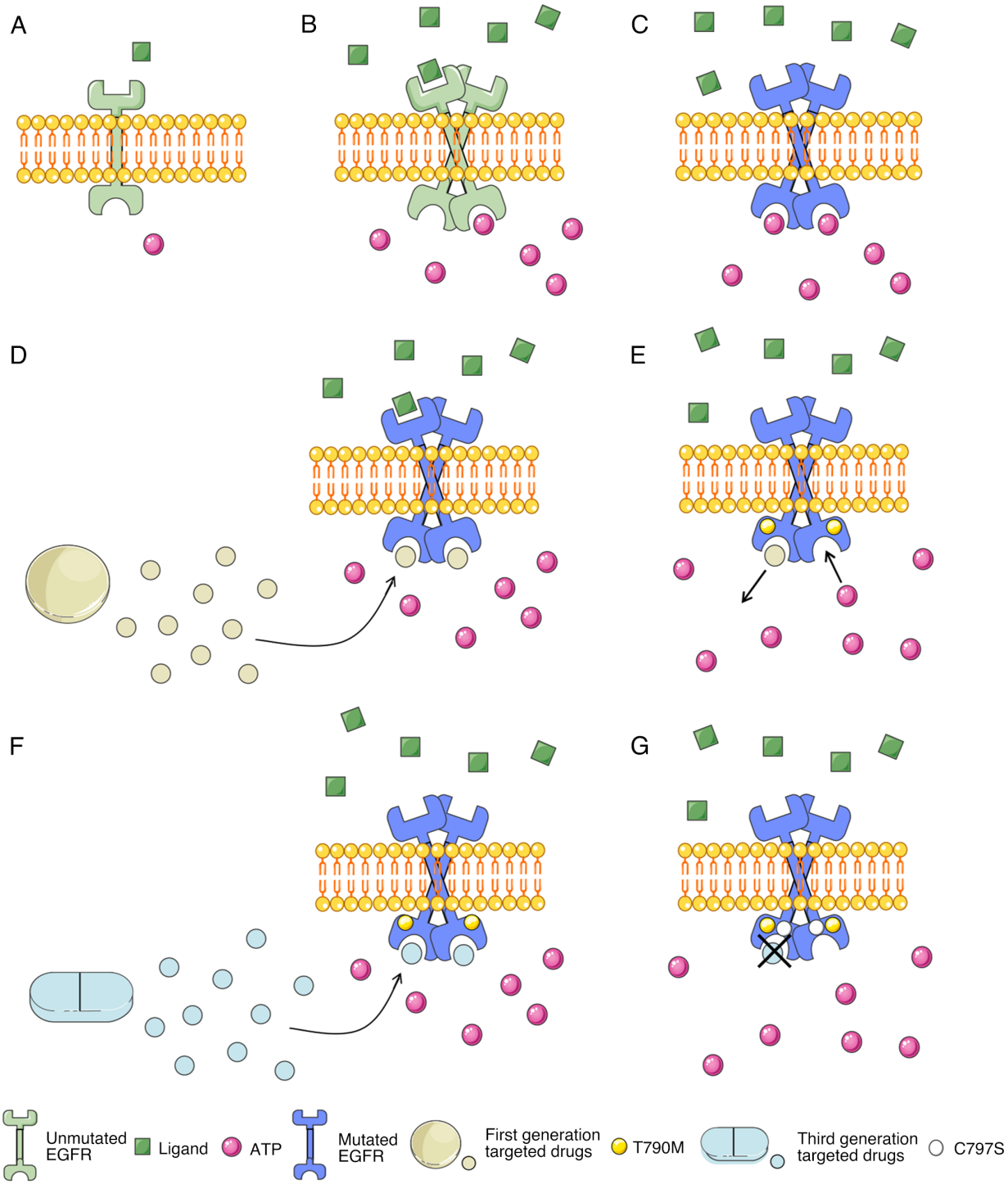

Figure 3. Mechanisms of EGFR action and resistance mechanisms of first-generation and third-generation targeted drugs. (A) EGFR, its ligands and ATP. (B) After binding to its ligand, EGFR is activated to form a dimer. (C) EGFR mutations, which no longer depend on receptor activation, causes the downstream signaling pathway to be continuously activated and eventually leads to carcinogenesis. (D) The first-generation targeted drugs competitively bind to the tyrosine kinase domain of ATP, reducing the binding capacity of this domain to ATP. (E) EGFR T790M mutation, the binding ability of the first generation of targeted drugs is weakened, ATP binding ability is enhanced, and drug resistance occurs. (F) The third generation of targeted drugs binds irreversibly to C797 residue. (G) EGFR C797S mutation and resistance to third-generation targeted drugs occurred.

results is higher and more convincing. The overall data of the FLAURA trial in China revealed a consistent trend with global data, which has great reference value for the clinical application and scientific research of osimertinib in China.

Almonertinib (also named HS-10296). The APPLLO (NCT02981108) trial was a phase 2, open-label, single-arm clinical study in China, evaluating the efficacy and safety of almonertinib as a second-line treatment for patients with T790M mutations after disease progression treated with first and second-generation EGFR-TKI (48,49). In the aforementioned study, the ORR of almonertinib was 68.9%, DCR was 93.4%, mDoR was 15.1 months, PFS was 12.4 months and mOS had not yet been reached. The most common AEs

were the elevation of blood creatine phosphokinase (CPK) level (20.9%), rash (13.9%), and aspartate transaminase (AST, 12.3%), among which 16.4% were patients with ≥grade 3 AEs. In addition, almonertinib also has a favorable blood-brain barrier permeability, which has a favorable therapeutic effect on patients with CNS metastasis. The CNS-ORR was 60.9%, CNS-DCR was 91.3%, CNS-mDoR was 12.5 months and CNS-mPFS was 11.8 months. It can be concluded that almonertinib is a third-generation targeted drug with excellent efficacy, strong tolerability, and improved CNS activity compared with the first and second-generation drugs. Based on this result, almonertinib was approved in China for the treatment of patients with NSCLC and EGFR T790M mutation. The limitations of the aforementioned study include the lack of a control group and participants from a single ethnic group, highlighting the need for further research.

The AENEAS (NCT03849768) trial was a phase 3, double-blind, randomized clinical study in China, comparing the efficacy and safety of almonertinib and gefitinib as first-line treatment for NSCLC EGFR mutation-positive patients (49-51). The ORR and DCR of almonertinib were 73.8 and 93.0%, respectively, similar to those of the gefitinib group (72.1 and 96.7%, respectively). However, almonertinib significantly prolonged the patient's mPFS and mDoR, with mPFS extending from 9.9 to 19.3 months, and mDoR extending from 8.3 to 18.1 months, both extending for nearly 10 months. The mOS of both experimental groups had not yet been reached. The most common AEs were elevated blood CPK (35.5%), elevated AST (29.9%) and elevated alanine transaminase (ALT) (29.4%). Among them, 36.4% of patients in the almonertinib group had AEs of grade 3 or above and 35.8% of patients had AEs common to gefitinib. Notably, almonertinib significantly reduced the incidence of skin and gastrointestinal AEs and improved the quality of life of patients by inhibiting wild-type EGFR. In addition, almonertinib also had favorable efficacy in patients with CNS metastasis, with a CNS-mPFS of 15.3 months, which is >7 months than the gefitinib group (8.2 months), winning patients a longer survival period and more treatment opportunities. Compared with osimertinib, although the mOS of CNS in the osimertinib group was not reached, the favorable CNS activity of almonertinib was also demonstrated by the decrease in the HR of almonertinib compared with osimertinib, which dropped from 0.48 to 0.38. The aforementioned data indicated that in first-line treatment, almonertinib can exert greater advantages than the first-generation targeted drug gefitinib. In conclusion, almonertinib is a third-generation EGFR TKI with favorable efficacy and tolerability. The limitation of this trial was that the participants were all of the same ethnicity, whilst there may be certain differences between different countries and ethnicities. Additional research is required before it can be promoted on a global scale.

Furmonertinib (also named AST2818). The ALSC003 (NCT03452592) trial was a phase 2, open-label, single-arm clinical study in China, evaluating the efficacy and safety of furmonertinib as a second-line treatment in patients with advanced NSCLC and EGFR T790M mutation (52). The clinical trial demonstrated that the ORR of furmonertinib was 74%, DCR was 94%, mPFS was 9.6 months and mDoR was 8.3 months, whereas mOS was not reached. For patients with CNS metastasis, furmonertinib also had favorable efficacy, with 66% CNS-ORR and CNS-100% DCR. During treatment, 26% of patients experienced grade 3 or above AEs, with the most common being increased γ-glutamyltransferase, AST and ALT. In terms of mPFS, furmonertinib and osimertinib exhibited similar results, but both were inferior to almonertinib. In terms of CNS efficacy, furmonertinib and almonertinib are both third-generation EGFR TKIs with favorable blood-brain barrier permeability activity. The data indicated that furmonertinib has favorable efficacy and safety as a second-line treatment of progression after first-generation or second-generation drug treatment in patients with NSCLC. The limitation of this clinical trial lies in the absence of a control group and a single-subject population. Further verification is required due to potential variations among different countries and races.

The FLAG (FURLONG, NCT03787992) trial was a phase 3, double-blind, randomized clinical study in China, comparing the efficacy and safety of furmonertinib and gefitinib as first-line treatment for patients with locally advanced or metastatic EGFR mutated NSCLC (53,54). ORR was similar to furmonertinib vs. gefitinib (89 vs. 84%), and DCR was 96 vs. 93%. The mPFS for furmonertinib was 20.8 months, while that for gefitinib was 11.1 months. Compared with gefitinib, furmonertinib extended the mPFS by nearly 10 months. The mDoR was also significantly prolonged in the furmonertinib group from 11.0 to 19.7 months in the gefitinib group. In the trial, 11% of patients in the furmonertinib group experienced ≥grade 3 AEs, while 18% were in the gefitinib group. Among them, the most common AE of higher than grade 3 in the furmonertinib group was ECG QTc interval prolongation and diarrhea. In addition, furmonertinib has excellent effects on patients with CNS metastasis, with 89% CNS-ORR, 96% CNS-DCR, 19.7 months CNS-DoR and 18.0 months CNS-mPFS. The mPFS of furmonertinib was higher than that of osimertinib and almonertinib, and the HR was the lowest among the three, which was sufficient to prove the favorable efficacy of furmonertinib. At the same time, furmonertinib had favorable safety, and CNS penetration activity was also improved compared with the almonertinib group. The aforementioned data indicated that, compared with first-generation EGFR TKIs, furmonertinib has a significant therapeutic effect on patients with advanced EGFR-positive mutations, and has favorable effects on patients with CNS metastasis. The AEs were reduced compared with gefitinib, providing an emerging treatment option for patients with EGFR-positive NSCLC in recent years. The limitations of this trial were similar to those of the AENEAS trial with almonertinib and there was a problem of a single-subject population that requires further research.

Olmutinib (also named HM61713). The ELUXA1 (NCT02485652) trial was a phase 2, open-label, single-arm, multicenter clinical study, evaluating the efficacy and safety of olmutinib as a second-line treatment in patients with T790M-positive NSCLC (55). In this trial, the ORR of olmutinib was 51.9%, DCR was 86.4%, mDoR was 12.7 months, mPFS was 9.4 months and mOS was 19.7 months. The data indicated that the efficacy of olmutinib was acceptable, but 48.2% of patients have experienced more than grade 3 drug-related AEs. Due to the high incidence of AEs and

severe skin toxicity (including toxic epidermal necrolysis and Stevens-Johnson syndrome), further ELUXA trials were discontinued (56). In April 2018, the development of olmutinib was terminated (16).

Lazertinib (also named YH25448). The LASER201 (NCT03046992) trial was a phase 1/2, open-label, single-arm, multicenter clinical study, evaluating the efficacy and safety of lazertinib as a second-line treatment in patients with EGFR mutation-positive advanced NSCLC (57,58). The results demonstrated that the ORR of lazertinib was 55.3%, DCR was 89.5%, mDoR was 17.7 months and mPFS was 11.1 months, while mOS was not reached. Among patients with CNS metastasis, the ORR was 85.7%, DCR was 100%, mDoR was 15.1 months and PFS was 26.0 months. The most surprising aspect of the data was the mPFS of patients with CNS metastasis, which exceeds 2 years. Lazertinib exhibited a very favorable blood-brain barrier penetration effect. Grade 3 or higher AEs occurred in 34.6% of the patients in the trial. The most common AEs were rash (38.5%), pruritus (34.6%), paresthesia (33.3%), headache (28.2%) and muscle spasms (28.2%). In conclusion, lazertinib had a manageable safety profile and durable antitumor activity, especially CNS activity, with the longest mPFS among the third-generation EGFR TKIs.

The LASER301 (NCT04248829) trial was a phase 3, double-blind, randomized, multicenter clinical study, comparing the efficacy and safety of lazertinib and gefitinib as first-line treatment for patients with NSCLC and EGFR mutations (59). The ORR was 76% in both lazertinib and gefitinib groups. DCR was 93.9%. mDoR was 19.4 months in the lazertinib group and 8.3 months in the gefitinib group. mPFS was 20.6 months and 9.7 months, respectively, and mOS was not reached. In patients with baseline brain metastases, mPFS was 16.4 months with lazertinib and 9.5 months with gefitinib. Treatment-related AEs of grade 3 or greater occurred in 41% of the patients in the lazertinib group and 44% of those in the gefitinib group. The most common AEs were paresthesia (39%), rash (36%), pruritus (27%) and diarrhea (26%). This trial identified that, compared with gefitinib, lazertinib significantly improved PFS and had favorable activity in patients with brain metastases, with a manageable safety profile. The efficacy of lazertinib was similar to that of osimertinib, almonertinib and furmonertinib, and all of them provide improved survival benefits to patients. This trial was the second, after osimertinib, to successfully compare a third-generation EGFR-TKI with a first-generation EGFR TKI as first-line therapy for patients with EGFR-positive mutations. This trial included both Asian and non-Asian populations, and the results were more representative. At the same time, the two subgroups also showed a consistent trend, which provides strong support for the application of the drug in China in the future. More surprisingly, according to the latest research results released at the time of writing, the combination of lazertinib and amivantamab is expected to break the resistance of Osimertinib (60).

Nazartinib (also named EGF816). The NCT02108964 trial was a phase 2, open-label, single-arm, multicenter clinical study, evaluating the efficacy and safety of nazartinib in the first-line treatment of patients with NSCLC (61). The research revealed that the ORR of nazartinib was 69.0%, DCR was 91.0%, mDoR was 25 months and mPFS was 18 months, while mOS was not reached. In addition, the drug showed favorable efficacy in patients with brain metastasis, with CNS-ORR of 67%, CNS-mDoR of 15 months, and CNS-mPFS of 17 months. In this trial, 31% of patients experienced grade 3 or above AEs, with the most common being macular papules (11%), elevated lipase (11%) and hypokalemia (7%). Nazartinib demonstrated favorable efficacy and controllable safety, and it can also be well controlled in those patients with baseline brain metastases and is a promising third-generation EGFR TKI, which is worth further research and development.

NCT03529084 is a phase 3, open-label, randomized, multicenter clinical study, comparing the efficacy and safety of nazartinib vs. gefitinib or erlotinib as first-line treatment in patients with locally advanced or metastatic NSCLC carrying EGFR-activated mutations. However, the study was withdrawn before the subjects were enrolled.

Rociletinib (also named CO1686). The TIGER-2 trial (NCT02147990) was a phase 2, open-label, single-arm, multicenter clinical study, evaluating the safety and efficacy of rociletinib as second-line EGFR TKI in patients with mutant EGFR NSCLC. The research evidenced that rociletinib has an improved therapeutic effect when received orally at a dose of 500 mg compared with a dose of 625 mg. The ORR of the 500 mg dose group was 34.0%, DCR was 76.3%, mDoR was 9.1 months and mPFS was 5.9 months. Compared with other third-generation targeted drugs, the therapeutic effect of this drug was not significant.

The TIGER-1 (NCT02186301) trial was a phase 2/3, open-label, randomized, multicenter clinical study, comparing the efficacy and safety of rociletinib vs. erlotinib as first-line treatment for advanced or metastatic NSCLC with EGFR mutations. Multiple sets of data for the 500 mg group could not be calculated due to the unavailability of the upper limit, but mPFS and mDoR were worse in both the 500 and 625 mg groups than in the erlotinib group, which is a relatively unexpected result. Due to the high incidence of hyperglycemia (34%) and QT prolongation (11%) among the tertiary adverse reactions of rociletinib, and the lower efficacy compared with other third-generation targeted drugs, the FDA postponed the approval of the drug with a 12:1 vote. After the results of the TIGER-3 (17) trial were released, the drug was ultimately discontinued in May 2016 due to the high incidence of AEs (8,16).

Other third-generation targeted drugs. The NCT02330367 trial of abivertinib (AC0010) was a phase 1/2, open-label, single-arm, clinical study in China, evaluating the efficacy and safety of abivertinib as second-line treatment in patients with NSCLC who had previously received treatment and had EGFR T790M mutations. The ORR was 52.2%, DCR was 88.0%, mDoR was 8.5 months, mPFS was 7.5 months, mOS was 24.9 months, and treatment-related AEs of grade 3 or above were 32.6% (62,63). The most common AEs were elevated ALT (7.0%), elevated AST (4.8%), diarrhea (4.4%) and neutropenia (3.5%). The aforementioned data indicated that abivertinib had favorable therapeutic effects, especially

mOS, which had the longest mPFS among the drugs aforementioned. The NCT03856697 trial was a phase 3, double-blind, randomized, clinical study in China, comparing the efficacy and safety of abivertinib vs. gefitinib as first-line standard treatment EGFR-TKI in advanced NSCLC with sensitive EGFR mutations, but no results have been published yet.

The SOLAR (NCT02588261) trial of naquotinib (ASP8273) was a phase 3, open-label, randomized multicenter clinical study, comparing the efficacy and safety of naquotinib vs. gefitinib or erlotinib as first-line treatment. In this trial, the ORR of naquotinib was 33.0%, DCR was 62.0%, mDoR was ~9.2 months, mPFS was ~9.3 months, and drug-related grade 3 or above AEs were 46.0%. However, the ORR of the gefitinib or erlotinib group was 47.9% and PFS was 9.6 months. The DCR and mDoR were similar in both groups. From the results, it can be easily observed that the efficacy of naquotinib is limited and even cannot reach that of the gefitinib or erlotinib group, and the toxicity is significant. Therefore, the trial was terminated by the independent disease monitoring committee in May 2017. However, in a Phase 2 study (64), it was found that the ORR and DCR of naquotinib were 45 and 94%, indicating acceptable efficacy. However, the number of participants in the study was relatively small and there may be some deviation. The drug has currently been discontinued.

The NCT03812809 trial of rezivertinib (BPI-7711) was a phase 2, open-label, single-arm clinical study in China, evaluating the efficacy and safety of rezivertinib as second-line treatment in patients with NSCLC who had advanced and confirmed EGFR-sensitive mutations and EGFR T790M positive mutations after previous EGFR-TKI treatment (65). The results revealed that the ORR of rezivertinib was 64.6%, DCR was 89.8%, mDoR was 12.5 months, mPFS was 12.2 months and mOS was 23.9 months. The proportion of grade 3 and above AEs in the trial was 19.9%. In addition, rezivertinib also demonstrated favorable efficacy in patients with CNS metastasis, with CNS-ORR of 69%, CNS-DCR of 100% and CNS-mPFS of 16.6 months. In conclusion, as a second-line treatment, rezivertinib showed favorable antitumor effect, high safety and favorable CNS penetration activity. Rezivertinib is a third-generation EGFR TKI with great development potential in the future. The NCT03866499 trial is a randomized, double-blind, phase 3 trial that evaluated the efficacy and safety of rezivertinib compared with gefitinib as a first-line treatment in NSCLC patients with advanced EGFR mutations. The trial is expected to be completed by October 2023.

In addition, there are various third-generation targeted drugs, including mavelertinib (PF-06747775) (65), limertinib (ASK120067) (66,67), befotertinib (D-0316) (68), olafertinib (CK-101/RK518), keynatinib (16), SH-1028 (69,70) and TAS-121 (71), which are all under development and trial.

5. Comparison of drug efficacy and clinical plan recommendations

By comparing the phase 2 and second-line treatment trials of third-generation targeted drugs such as the AURA17 trial and the APOLLO trial, it was found that the data on mPFS and grade 3 and above AEs of almonertinib were more prominent than those of other third-generation drugs; especially mPFS, which was extended by 2.7 months compared with osimertinib and 9.8 months compared with furmonertinib. The probability of grade 3 and above AEs is currently the lowest among the drugs mentioned in the present review, which was 8.6% lower than osimertinib and 31.8% lower than olmutinib. The ORR and DCR of furmonertinib are more prominent and the ORR of this drug is the only one that exceeds 70% of the other drugs discussed in the present review. The mDoR of lazertinib was extended by 7.8 months compared with osimertinib, 2.6 months compared with almonertinib, and 9.4 months compared with furmonertinib. In addition, lazertinib has excellent efficacy in patients with CNS metastasis and the CNS-mPFS is markedly longer than other drugs. Abivertinib and rezivertinib have also shown favorable efficacy through longer OS, and rezivertinib has relatively fewer AEs. Therefore, for patients with NSCLC who can receive second-line treatment, almonertinib, with its accuracy, efficiency, and low toxicity, is expected to become the first choice for patients with T790M mutations who progress after treatment. In addition, for patients with CNS metastasis, lazertinib exhibited excellent blood-brain barrier penetration efficacy in the LASER201 trial, with >2 years of mPFS. If subsequent or larger trials can confirm these results, lazertinib may bring greater benefits to patients with brain metastasis and become the first choice for such patients. China can also consider introducing and applying lazertinib to domestic patients. The comparison of the efficacy and safety of the aforementioned drugs as second-line treatment for NSCLC is demonstrated in Fig. 4 and Table I. The comparison of the AEs of the aforementioned drugs as second-line treatment for NSCLC is listed in Table III.

By comparing phase 3 and first-line treatment trials with third-generation targeted drug trials such as the FLAURA and AENEAS, the results revealed that third-generation targeted drugs have improved efficacy, safety, CNS permeability and greater advantages compared with first-generation targeted drugs. In the case of third-generation EGFR-TKIs, osimertinib still holds a very important position as the first-line treatment for NSCLC, and ORR, DCR and OS all show favorable efficacy. The mPFS of both almonertinib and furmonertinib was slightly longer than that of osimertinib, with almonertinib extending by 1.5 months and furmonertinib extending by 3 months. In addition, furmonertinib also has excellent therapeutic effects on patients with CNS metastasis, with an ORR increase of 22% compared with osimertinib and an mPFS increase of 2.7 months compared with almonertinib. The biggest advantage of furmonertinib is the extremely low incidence of AEs, with 11% of patients experiencing grade 3 or above AEs, which is currently the lowest known rate, with a 17% decrease compared with osimertinib and a 25.4% decrease compared with almonertinib. The development of naquotinib was terminated due to its low efficacy and high adverse reaction rate. The similarity between the aforementioned third-generation targeted drug trials is that the control group consists of first-generation targeted drugs and the experimental group contains third-generation targeted drugs. The authors of the present review found by comparing the data that osimertinib, almonertinib and furmonertinib have similar results and comparable efficacy. For patients with CNS metastasis, furmonertinib is the best choice. In addition, the lower incidence of AEs with furmonertinib leads to the conclusion that all three drugs are effective in patients receiving regular first-line treatment for NSCLC, while furmonertinib is preferable in patients with CNS metastasis and those with

Table I. Comparison of the efficacy of the third generation EGFR-TKIs as second-line treatment.

	mPFS (month)	mOS (month)	≥3 AEs (%)	CNS-mPFS (month)
Osimertinib	9.7	23.2	35	-
Almonertinib	12.4	NA	16.4	11.8
Furmonertinib	9.6	NA	26	-
Olmutinib	9.4	19.7	48.2	-
Lazertinib	11.1	NA	34.6	26.0
Abivertinib	7.5	24.9	32.6	-
Rezivertinib	12.2	23.9	19.9	16.6
Befotertinib	16.6	NA	29.3	NA
Limertinib	11.0	NA	34.6	9.7

mPFS, median progression-free survival; mOS, median overall survival; AEs, adverse events; NA, not applicable.

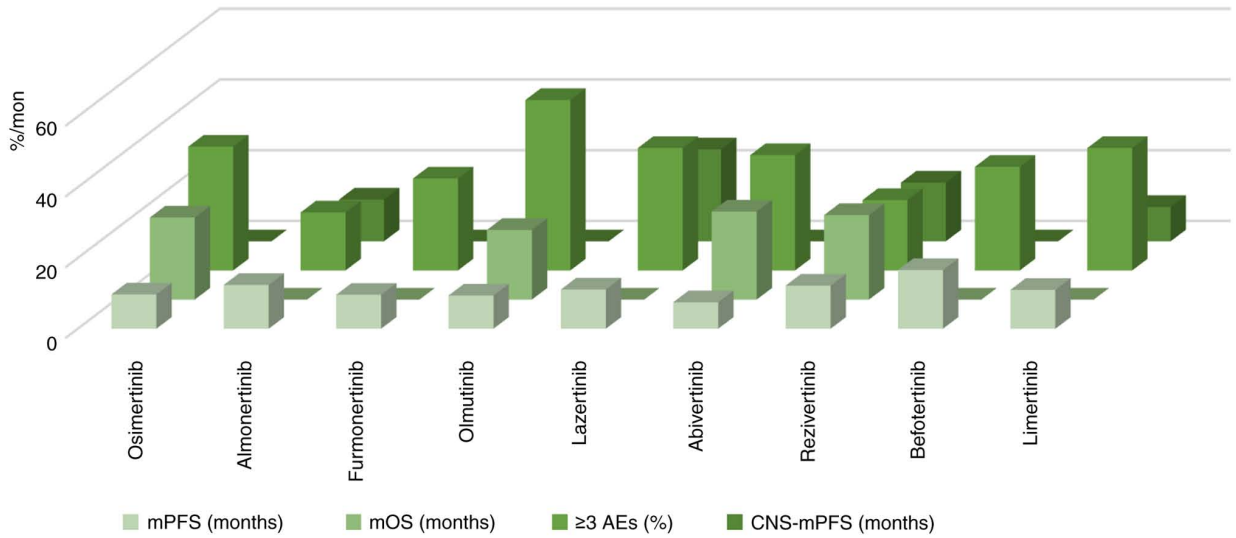

Figure 4. Comparison of the efficacy and safety of third generation EGFR tyrosine kinase inhibitors when used as second-line treatment. mPFS, median progression-free survival; mOS, median overall survival; AEs, adverse events; CNS, central nervous system.

underlying diseases that cannot tolerate AEs. Due to the limitations of cross-comparison of data derived from different trials, further research and verification is needed. The comparison of the efficacy and safety of the aforementioned drugs as first-line treatment for NSCLC is shown in Fig. 5 and Table II. The comparison of the AEs of the aforementioned drugs as first-line treatment for NSCLC is presented in Table IV.

The ARCHER 1050 trial compared the efficacy and safety of dacomitinib and gefitinib as first-line treatment for patients with EGFR mutation-positive NSCLC (72). In this trial, the ORR was similar to dacomitinib and gefitinib (75 vs. 72%), with mPFS of 14.7 and 9.2 months, and mDoR of 14.8 and 8.3 months, respectively. In this regard, the efficacy of dacomitinib is markedly improved compared with gefitinib, and the drug shows greater benefit in the Asian subgroup than in the non-Asian subgroup, which is also the basis for the use of dacomitinib as the first-line treatment for patients with EGFR mutations. However, grade 3 or higher AEs occurred in 63% of the patients in the dacomitinib group and 41% in the gefitinib group. The LUX-Lung7 trial compared the efficacy and safety of afatinib with those of gefitinib as first-line treatment

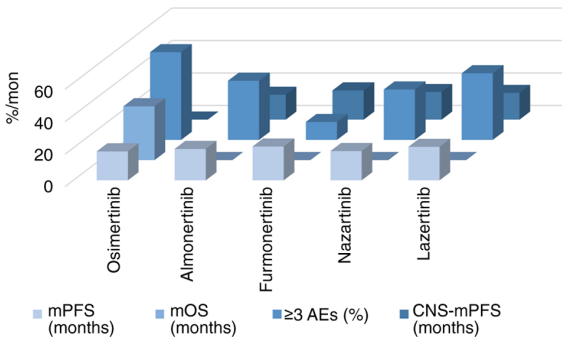

Figure 5. Comparison of the efficacy and safety of third generation EGFR tyrosine kinase inhibitors when used as first-line treatment. mPFS, median progression-free survival; mOS, median overall survival; AEs, adverse events; CNS, central nervous system.

for patients with EGFR mutation-positive NSCLC (73). In this trial, afatinib was associated with some improvement in ORR (70 vs. 56%), DCR (91 vs. 87%), mPFS (11.0 vs. 10.9 months), mDoR (10.1 vs. 8.4 months) and mOS (27.9 vs. 25.0 months), but

Table II. Comparison of the efficacy of third-generation EGFR-TKIs as first-line therapy.

	mPFS (month)	mOS (month)	≥3 AEs (%)	CNS-mPFS (month)
Osimertinib	17.8	33.1	54	NA
Almonertinib	19.3	NA	36.4	15.3
Furmonertinib	20.8	NA	11	18.0
Nazartinib	18	NA	31	17
Lazertinib	20.6	NA	41	16.4

mPFS, median progression-free survival; mOS, median overall survival; AEs, adverse events; CNS, central nervous system; NA, not applicable.

Table III. Comparison of adverse events when third-generation EGFR-TKIs were used as second-line therapy.

	Osimertinib	Almonertinib	Furmonertinib	Lazertinib	Abivertinib	Rezivertinib
Leukopenia	12.87	4.51	-	-	-	7.1
Diarrhea	29.24	0	-	28.2	61.2	7.5
Nausea	9.36	6.15	-	16.7	17.2	-
Vomiting	8.19	0	5	11.6	16.7	10.6
Neutrophil count decreased	7.02	5.74	6	-	23.3	18.6
Platelet count decreased	11.11	9.43	6	-	24.2	23.0
White blood cell count decreased	12.28	12.3	12	-	25.6	27.9
Rash	7.60	13.9	-	38.5	37.0	8.8
Pruritus	12.28	10.7	-	34.6	-	8.8
Increased blood creatine	-	20.9	-	-	-	8.4
Increased alanine aminotransferase	-	11.9	15	12.8	64.8	11.9
Increased aspartate aminotransferase	-	12.3	16	14.1	57.3	16.4
Prolonged electrocardiogram	-	-	15	-	19.4	5.3

the improvement was not significant. Rates of grade 3 or higher AEs were also similar, 57% with afatinib and 52% with gefitinib. Although the efficacy of dacomitinib and afatinib is improved compared with the first-generation EGFR TKIs, the incidence of grade 3 and above AEs of these two drugs was higher than that of the first-generation EGFR TKIs. Therefore, the clinical utilization rate of the second-generation EGFR TKIs decreases significantly after the emergence of the third-generation EGFR TKIs.

6. Advantages and disadvantages of the third-generation EGFR-TKIs

Osimertinib is the first third-generation targeted drug to be marketed, which is highly specific and selective compared with the first and second-generation EGFR TKIs. In addition, osimertinib also can penetrate the blood-brain barrier and has a favorable effect on patients with brain metastases. However, patients using osimertinib may experience a white blood cell count decrease, which may lead to the development of infectious diseases, especially bacterial infections. In addition, rash AE is also not to be ignored. According to the current data, almonertinib and furmonertinib have improved efficacy and few AEs compared with Osimertinib; however, the data on these two drugs are only available in China and there is a lack of global data, which represents a limitation. The AEs of furmonerftinib and almonertinib mainly regard the increase of blood CPK, ALT and AST, which may cause liver injury. The efficacy of lazertinib and osimertinib were comparable and the first-line trial of lazertinib included both Asian and non-Asian subgroups, making it more reliable; however, paresthesia differed from the other grade >3 AEs with lazertinib and the incidence of pulmonary embolism was relatively high. As a second-line treatment, nazartinib has significant CNS activity, but first-line results are not yet available. The advantages and disadvantages of other drugs will not be discussed in the present review.

7. Prospects

In summary, numerous trials revealed that the third-generation EGFR-TKIs have absolute advantages over the first generation. The third-generation EGFR-TKIs have favorable efficacy,

Table IV. Comparison of adverse events when third-generation EGFR-TKIs were used as first-line therapy.

	Osimertinib	Almonertinib	Furmonertinib	Lazertinib
Leukopenia	17	-	-	-
Neutropenia	17	-	-	-
Diarrhea	24	16.4	27	26
Nausea	14	10.7	-	-
Vomiting	14	-	-	-
Neutrophil count decreased	24	13.6	11	-
Platelet count decreased	28	22	9	-
White blood cell count decreased	41	23.8	15	-
Rash	37	23.4	17	36
Pruritus	-	6.5	-	27
Increased blood creatine	-	35.5	4	-
Increased alanine aminotransferase	9	29.4	29	15
Increased aspartate aminotransferase	16	29.9	26	11
Prolonged electrocardiogram	10	10.7	9	-

controllable safety and strong drug activity against CNS metastasis in the treatment of patients with advanced EGFR mutations and T790M mutations in NSCLC. However, each drug also has its advantages and disadvantages, and suitable drugs should be selected according to the different conditions of patients. In addition, various third-generation EGFR-TKIs, including limertinib (ASK120067), rezivertinib (BPI-7711) and abivertinib (AC0010), are also under intense research and experimentation. In the future, more effective targeted drugs will emerge, providing more choices for NSCLC. But whether it is the first, second or third-generation drugs, drug resistance will occur after a period of treatment. At present, there are solutions for drug resistance, such as third-generation combination with first-generation or second-generation targeted drug therapy, such as osimertinib combined with gefitinib (NCT03122717), osimertinib combined with dacomitinib (NCT03810807) and nazartinib combined with gefitinib (NCT03292133); the combination of EGFR third-generation targeted drugs with other targeted drugs, such as osimertinib and anlotinib (74); fourth-generation targeted drugs, such as EAI045 (75), OBX02-011 (76), LS-106 (77) and CH7233163 (78). The research on the mechanism of third-generation drug resistance is currently mainly focused on osimertinib and there is very little research on other drug resistance mechanisms. Therefore, the research on drug resistance mechanisms and response strategies after drug resistance remain urgent challenges that need further attention. Further research and exploration by medical and scientific researchers are needed to provide improved solutions for individualized and precise treatment of tumors.

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Availability of data and materials

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Authors' contributions

ZC, HC and YW were the major contributors in writing and editing the manuscript. XJ and LS provided direction and guidance throughout the preparation of this manuscript. JC, JY, CL, XS and YZ analysis and organized the data. All authors read and approved the final version of the 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. Siegel RL, Miller KD, Fuchs HE and Jemal A: Cancer statistics, 2022. CA Cancer J Clin 72: 7-33, 2022.
3. Xia C, Dong X, Li H, Cao M, Sun D, He S, Yang F, Yan X, Zhang S, Li N and Chen W: Cancer statistics in China and United States, 2022: Profiles, trends, and determinants. Chin Med J (Engl) 135: 584-590, 2022.
4. Miller KD, Nogueira L, Mariotto AB, Rowland JH, Yabroff KR, Alfano CM, Jemal A, Kramer JL and Siegel RL: Cancer treatment and survivorship statistics, 2019. CA Cancer J Clin 69: 363-385, 2019.
5. Herbst RS, Morgensztern D and Boshoff C: The biology and management of non-small cell lung cancer. Nature 553: 446-454, 2018.
6. Sun C, Gao W, Liu J, Cheng H and Hao J: FGL1 regulates acquired resistance to Gefitinib by inhibiting apoptosis in non-small cell lung cancer. Respir Res 21: 210, 2020.
7. Leonetti A, Sharma S, Minari R, Perego P, Giovannetti E and Tiseo M: Resistance mechanisms to osimertinib in EGFR-mutated non-small cell lung cancer. Br J Cancer 121: 725-737, 2019.
8. Andrews Wright NM and Goss GD: Third-generation epidermal growth factor receptor tyrosine kinase inhibitors for the treatment of non-small cell lung cancer. Transl Lung Cancer Res 8 (Suppl 3): S247-S264, 2019.
9. Simeone JC, Nordstrom BL, Patel K and Klein AB: Treatment patterns and overall survival in metastatic non-small-cell lung cancer in a real-world, US setting. Future Oncol 15: 3491-3502, 2019.
10. Mok TS, Wu YL, Thongprasert S, Yang CH, Chu DT, Saijo N, Sunpaweravong P, Han B, Margono B, Ichinose Y, *et al*: Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med 361: 947-957, 2009.
11. Tran PN and Klempner SJ: Profile of rociletinib and its potential in the treatment of non-small-cell lung cancer. Lung Cancer (Auckl) 7: 91-97, 2016.
12. He J, Huang Z, Han L, Gong Y and Xie C: Mechanisms and management of 3rd-generation EGFR-TKI resistance in advanced non-small cell lung cancer (Review). Int J Oncol 59: 90, 2021.
13. Tan CS, Kumarakulasinghe NB, Huang YQ, Ang YLE, Choo JR, Goh BC and Soo RA: Third generation EGFR TKIs: Current data and future directions. Mol Cancer 17: 29, 2018.
14. Remon J, Steuer CE, Ramalingam SS and Felip E: Osimertinib and other third-generation EGFR TKI in EGFR-mutant NSCLC patients. Ann Oncol 29 (suppl_1): i20-i27, 2018.
15. Cooper AJ, Sequist LV and Lin JJ: Third-generation EGFR and ALK inhibitors: Mechanisms of resistance and management. Nat Rev Clin Oncol 19: 499-514, 2022.
16. Nagasaka M, Zhu VW, Lim SM, Greco M, Wu F and Ou SI: Beyond osimertinib: The development of third-generation EGFR tyrosine kinase inhibitors for advanced EGFR+ NSCLC. J Thorac Oncol 16: 740-763, 2021.
17. Yang JC, Reckamp KL, Kim YC, Novello S, Smit EF, Lee JS, Su WC, Akerley WL, Blakely CM, Groen HJM, *et al*: Efficacy and safety of rociletinib versus chemotherapy in patients with EGFR-Mutated NSCLC: The results of TIGER-3, a phase 3 randomized study. JTO Clin Res Rep 2: 100114, 2020.
18. Kim ES: Olmutinib: First global approval. Drugs 76: 1153-1157, 2016.
19. H L, H X and H Y: Research on the third-generation epidermal growth factor receptor tyrosine kinase inhibitor drugs and their patents. Chin J N Drugs 31: 1553-1559, 2022.
20. Kelly RJ, Shepherd FA, Krivoshik A, Jie F and Horn L: A phase III, randomized, open-label study of ASP8273 versus erlotinib or gefitinib in patients with advanced stage IIIB/IV non-small-cell lung cancer. Ann Oncol 30: 1127-1133, 2019.
21. Dhillon S: Lazertinib: First approval. Drugs 81: 1107-1113, 2021.
22. Deeks ED: Furmonertinib: First approval. Drugs 81: 1775-1780, 2021.
23. Koch AL, Vellanki PJ, Drezner N, Li X, Mishra-Kalyani PS, Shen YL, Xia H, Li Y, Liu J, Zirkelbach JF, *et al*: FDA approval summary: Osimertinib for adjuvant treatment of surgically resected non-small cell lung cancer, a collaborative project orbis review. Clin Cancer Res 27: 6638-6643, 2021.
24. Prenzel N, Fischer OM, Streit S, Hart S and Ullrich A: The epidermal growth factor receptor family as a central element for cellular signal transduction and diversification. Endocr Relat Cancer 8: 11-31, 2001.
25. Levantini E, Maroni G, Del Re M and Tenen DG: EGFR signaling pathway as therapeutic target in human cancers. Semin Cancer Biol 85: 253-275, 2022.
26. Ward RA, Anderton MJ, Ashton S, Bethel PA, Box M, Butterworth S, Colclough N, Chorley CG, Chuaqui C, Cross DA, *et al*: Structure- and reactivity-based development of covalent inhibitors of the activating and gatekeeper mutant forms of the epidermal growth factor receptor (EGFR). J Med Chem 56: 7025-7048, 2013.
27. Dong RF, Zhu ML, Liu MM, Xu YT, Yuan LL, Bian J, Xia YZ and Kong LY: EGFR mutation mediates resistance to EGFR tyrosine kinase inhibitors in NSCLC: From molecular mechanisms to clinical research. Pharmacol Res 167: 105583, 2021.
28. Wee P and Wang Z: Epidermal growth factor receptor cell proliferation signaling pathways. Cancers (Basel). 9: 52, 2017.
29. Huang L and Fu L: Mechanisms of resistance to EGFR tyrosine kinase inhibitors. Acta Pharm Sin B 5: 390-401, 2015.
30. Liu Q, Yu S, Zhao W, Qin S, Chu Q and Wu K: EGFR-TKIs resistance via EGFR-independent signaling pathways. Mol Cancer 17: 53, 2018.
31. Soejima K, Yasuda H and Hirano T: Osimertinib for EGFR T790M mutation-positive non-small cell lung cancer. Expert Rev Clin Pharmacol 10: 31-38, 2017.
32. Sigismund S, Avanzato D and Lanzetti L: Emerging functions of the EGFR in cancer. Mol Oncol 12: 3-20, 2018.
33. Sabbah DA, Hajjo R and Sweidan K: Review on epidermal growth factor receptor (EGFR) structure, signaling pathways, interactions, and recent updates of EGFR inhibitors. Curr Top Med Chem 20: 815-834, 2020.
34. Yun CH, Mengwasser KE, Toms AV, Woo MS, Greulich H, Wong KK, Meyerson M and Eck MJ: The T790M mutation in EGFR kinase causes drug resistance by increasing the affinity for ATP. Proc Natl Acad Sci USA 105: 2070-2075, 2008.
35. Cross DA, Ashton SE, Ghiorghiu S, Eberlein C, Nebhan CA, Spitzler PJ, Orme JP, Finlay MR, Ward RA, Mellor MJ, *et al*: AZD9291, an irreversible EGFR TKI, overcomes T790M-mediated resistance to EGFR inhibitors in lung cancer. Cancer Discov 4: 1046-1061, 2014.
36. Wu L, Ke L, Zhang Z, Yu J and Meng X: Development of EGFR TKIs and options to manage resistance of Third-generation EGFR TKI osimertinib: Conventional ways and immune checkpoint inhibitors. Front Oncol 10: 602762, 2020.
37. Lamb YN: Osimertinib: A review in previously untreated, EGFR Mutation-positive, advanced NSCLC. Target Oncol 16: 687-695, 2021.
38. Singh M and Jadhav HR: Targeting non-small cell lung cancer with small-molecule EGFR tyrosine kinase inhibitors. Drug Discov Today 23: 745-753, 2018.
39. Patel H, Pawara R, Ansari A and Surana S: Recent updates on Third generation EGFR inhibitors and emergence of Fourth generation EGFR inhibitors to combat C797S resistance. Eur J Med Chem 142: 32-47, 2017.
40. Zhou C, Wang M, Cheng Y, Li H, Wang J and Wu YL: AURA17 study of osimertinib in Asia-Pacific patients (pts) with EGFR T790M-positive advanced non-small cell lung cancer (NSCLC): Updated phase II results including overall survival (OS). Ann Oncol 29: IX157, 2018.
41. Goss G, Tsai CM, Shepherd FA, Bazhenova L, Lee JS, Chang GC, Crino L, Satouchi M, Chu Q, Hida T, *et al*: Osimertinib for pretreated EGFR Thr790Met-positive advanced non-small-cell lung cancer (AURA2): A multicentre, open-label, single-arm, phase 2 study. Lancet Oncol 17: 1643-1652, 2016.
42. Papadimitrakopoulou VA, Mok TS, Han JY, Ahn MJ, Delmonte A, Ramalingam SS, Kim SW, Shepherd FA, Laskin J, He Y, *et al*: Osimertinib versus platinum-pemetrexed for patients with EGFR T790M advanced NSCLC and progression on a prior EGFR-tyrosine kinase inhibitor: AURA3 overall survival analysis. Ann Oncol 31: 1536-1544, 2020.
43. Cheng Y, He Y, Li W, Zhang HL, Zhou Q, Wang B, Liu C, Walding A, Saggese M, Huang X, *et al*: Osimertinib versus comparator EGFR TKI as First-line treatment for EGFR-mutated advanced NSCLC: FLAURA China, A randomized study. Target Oncol 16: 165-176, 2021.
44. Wu L, Zhong W, Li A, Qiu Z, Xie R, Shi H and Lu S: Successful treatment of EGFR T790M-mutant non-small cell lung cancer with almonertinib after osimertinib-induced interstitial lung disease: A case report and literature review. Ann Transl Med 9: 950, 2021.
45. Soria JC, Ohe Y, Vansteenkiste J, Reungwetwattana T, Chewaskulyong B, Lee KH, Dechaphunkul A, Imamura F, Nogami N, Kurata T, *et al*: Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. N Engl J Med 378: 113-125, 2018.
46. Leighl NB, Karaseva N, Nakagawa K, Cho BC, Gray JE, Hovey T, Walding A, Rydén A and Novello S: Patient-reported outcomes from FLAURA: Osimertinib versus erlotinib or gefitinib in patients with EGFR-mutated advanced non-small-cell lung cancer. Eur J Cancer 125: 49-57, 2020.

47. Reungwetwattana T, Nakagawa K, Cho BC, Cobo M, Cho EK, Bertolini A, Bohnet S, Zhou C, Lee KH, Nogami N, *et al*: CNS response to osimertinib versus standard epidermal growth factor receptor tyrosine kinase inhibitors in patients with untreated EGFR-mutated advanced non-small-cell lung cancer. J Clin Oncol: Jco2018783118, 2018 doi: 10.1200/JCO.2018.78.3118 (Epub ahead of print).
48. 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 registrational trial. J Thorac Oncol 17: 411-422, 2022.
49. Shirley M and Keam SJ: Aumolertinib: A review in non-small cell lung cancer. Drugs 82: 577-584, 2022.
50. Lu S, Dong X, Jian H, Chen J, Chen G, Sun Y, Ji Y, Wang Z, Shi J, Lu J, *et al*: AENEAS: A randomized phase III trial of aumolertinib versus gefitinib as First-line therapy for locally advanced or metastaticnon-small-cell lung cancer with EGFR exon 19 deletion or L858R mutations. J Clin Oncol 40: 3162-3171, 2022.
51. Benjamin DJ and Nagasaka M: Freeing the competition: Will aumolertinib (AENEAS) have a fighting chance against osimertinib (FLAURA)? J Clin Oncol 41: 742-744, 2023.
52. 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 furmonertinib (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.
53. Shi Y, Chen G, Wang X, Liu Y, Wu L, Hao Y, Liu C, Zhu S, Zhang X, Li Y, *et al*: Furmonertinib (AST2818) versus gefitinib as first-line therapy for Chinese patients with locally advanced or metastatic EGFR mutation-positive non-small-cell lung cancer (FURLONG): A multicentre, double-blind, randomised phase 3 study. Lancet Respir Med 10: 1019-1028, 2022.
54. Shi Y, Chen G, Wang X, Liu Y, Wu L, Hao Y, Liu C, Zhu S, Zhang X, Li Y, *et al*: Central Nervous system efficacy of furmonertinib (AST2818) versus gefitinib as first-line treatment for EGFR-mutated NSCLC: Results from the FURLONG study. J Thorac Oncol 17: 1297-1305, 2022.
55. Park K, Jänne PA, Kim DW, Han JY, Wu MF, Lee JS, Kang JH, Lee DH, Cho BC, Yu CJ, *et al*: Olmutinib 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 127: 1407-1416, 2021.
56. Murtuza A, Bulbul A, Shen JP, Keshavarzian P, Woodward BD, Lopez-Diaz FJ, Lippman SM and Husain H: Novel Third-generation EGFR tyrosine kinase inhibitors and strategies to overcome therapeutic resistance in lung cancer. Cancer Res 79: 689-698, 2019.
57. Lee J, Hong MH and Cho BC: Lazertinib: On the Way to Its Throne. Yonsei Med J 63: 799-805, 2022.
58. Cho BC, Han JY, Kim SW, Lee KH, Cho EK, Lee YG, Kim DW, Kim JH, Lee GW, Lee JS, *et al*: A Phase 1/2 Study of Lazertinib 240 mg in patients with advanced EGFR T790M-positive NSCLC after previous EGFR tyrosine kinase inhibitors. J Thorac Oncol 17: 558-567, 2022.
59. Cho BC, Ahn MJ, Kang JH, Soo RA, Reungwetwattana T, Yang JC, Cicin I, Kim DW, Wu YL, Lu S, *et al*: Lazertinib versus gefitinib as First-line treatment in patients with EGFR-mutated advanced non-small-cell lung cancer: Results from LASER301. J Clin Oncol 41: 4208-4217, 2023.
60. Cho BC, Kim DW, Spira AI, Gomez JE, Haura EB, Kim SW, Sanborn RE, Cho EK, Lee KH, Minchom A, *et al*: Amivantamab plus lazertinib in osimertinib-relapsed EGFR-mutant advanced non-small cell lung cancer: A phase 1 trial. Nat Med 14: 023-02554, 2023.
61. Tan DSW, Kim SW, Ponce Aix S, Sequist LV, Smit EF, Yang JCH, Hida T, Toyozawa R, Felip E, Wolf J, *et al*: Nazartinib for treatment-naive EGFR-mutant non-small cell lung cancer: Results of a phase 2, single-arm, open-label study. Eur J Cancer 172: 276-286, 2022.
62. Zhou Q, Wu L, Hu P, An T, Zhou J, Zhang L, Liu XQ, Luo F, Zheng X, Cheng Y, *et al*: A Novel Third-generation EGFR Tyrosine kinase inhibitor abivertinib for EGFR T790M-mutant Non-small cell lung cancer: A multicenter phase I/II study. Clin Cancer Res 28: 1127-1135, 2022.
63. Wang F and Zhou Q: The challenges of Third-generation EGFR tyrosine kinase inhibitors in the therapy of advanced NSCLC. J Thorac Oncol 17: 481-486, 2022.
64. Azuma K, Nishio M, Hayashi H, Kiura K, Satouchi M, Sugawara S, Hida T, Iwamoto Y, Inoue A, Takeda K, *et al*: ASP8273 tolerability and antitumor activity in tyrosine kinase inhibitor-naïve Japanese patients with EGFR mutation-positive non-small-cell lung cancer. Cancer Sci 109: 2532-2538, 2018.
65. Cho BC, Goldberg SB, Kim DW, Socinski MA, Burns TF, Lwin Z, Pathan N, Ma WD, Masters JC, Cossons N, *et al*: A phase 1b/2 study of PF-06747775 as monotherapy or in combination with Palbociclib in patients with epidermal growth factor receptor mutant advanced non-small cell lung cancer. Expert Opin Investig Drugs 31: 747-757, 2022.
66. Shi Y, Li B, Wu L, Pan Y, Pan Z, Liu Y, Fan Y, Ji Y, Fang J, Shi Q, *et al*: Efficacy and safety of limertinib (ASK120067) in patients with locally advanced or metastatic EGFR Thr790Met-mutated NSCLC: A multicenter, single-arm, phase 2b study. J Thorac Oncol 17: 1205-1215, 2022.
67. Zhang T, Qu R, Chan S, Lai M, Tong L, Feng F, Chen H, Song T, Song P, Bai G, *et al*: Discovery of a novel third-generation EGFR inhibitor and identification of a potential combination strategy to overcome resistance. Mol Cancer 19: 90, 2020.
68. Lu S, Zhang Y, Zhang G, Zhou J, Cang S, Cheng Y, Wu G, Cao P, Lv D, Jian H, *et al*: Efficacy and safety of befotertinib (D-0316) in patients with EGFR T790M-mutated NSCLC that had progressed after prior EGFR tyrosine kinase inhibitor therapy: A phase 2, multicenter, single-arm, open-label study. J Thorac Oncol 17: 1192-1204, 2022.
69. Han L, Zhang X, Wang Z, Zhang X, Zhao L, Fu W, Liang X, Zhang Z and Wang Y: SH-1028, An irreversible Third-generation EGFR TKI, overcomes T790M-mediated resistance in non-small cell lung cancer. Front Pharmacol 12: 665253, 2021.
70. Xiong A, Ren S, Liu H, Miao L, Wang L, Chen J, Li W, Li R, Wang X, Lu Z, *et al*: Efficacy and Safety of SH-1028 in patients with EGFR T790M-positive NSCLC: A multicenter, single-arm, open-label, phase 2 trial. J Thorac Oncol 17: 1216-1226, 2022.
71. Ito K, Nishio M, Kato M, Murakami H, Aoyagi Y, Ohe Y, Okayama T, Hashimoto A, Ohsawa H, Tanaka G, *et al*: TAS-121, A selective mutant EGFR inhibitor, shows activity against tumors expressing various EGFR mutations including T790M and uncommon mutations G719X. Mol Cancer Ther 18: 920-928, 2019.
72. 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.
73. Park K, Tan EH, O'Byrne K, Zhang L, Boyer M, Mok T, Hirsh V, Yang JC, Lee KH, Lu S, *et al*: Afatinib 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.
74. Lei T, Xu T, Zhang N, Zou X, Kong Z, Wei C and Wang Z: Anlotinib combined with osimertinib reverses acquired osimertinib resistance in NSCLC by targeting the c-MET/MYC/AXL axis. Pharmacol Res 188: 106668, 2023.
75. Jia Y, Yun CH, Park E, Ercan D, Manuia M, Juarez J, Xu C, Rhee K, Chen T, Zhang H, *et al*: Overcoming EGFR(T790M) and EGFR(C797S) resistance with mutant-selective allosteric inhibitors. Nature 534: 129-132, 2016.
76. Choi YJ, Kim DS, Hoon Sung Y, Kim DH, Im K, Lee H, Lee CW, Cho J, Min J, Woo DC, *et al*: The reversible fourth-generation EGFR tyrosine kinase inhibitor OBX02-011 overcomes C797S-mediated resistance in lung cancer. Cancer Res: Jun 14, 2022 (Epub ahead of print). doi: 10.1158/0008-5472.CAN-22-0394.
77. Liu Y, Lai M, Li S, Wang Y, Feng F, Zhang T, Tong L, Zhang M, Chen H, Chen Y, *et al*: LS-106, a novel EGFR inhibitor targeting C797S, exhibits antitumor activities both in vitro and in vivo. Cancer Sci 113: 709-720, 2022.
78. Kashima K, Kawauchi H, Tanimura H, Tachibana Y, Chiba T, Torizawa T and Sakamoto H: CH7233163 overcomes osimertinib-resistant EGFR-Del19/T790M/C797S mutation. Mol Cancer Ther 19: 2288-2297, 2020.