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Review

Evolving therapeutic landscape of EGFR-TKIs in NSCLC

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Abstract: Lung cancer is one of the most common cancers worldwide and the leading cause of cancer-related death. Over the past two decades, the classification of lung cancer has significantly evolved. Today, non-small cell lung cancer (NSCLC) consists of various molecular oncogenic subsets that impact both prognosis and disease management. EGFR is the first targeted oncogenic alteration identified in 2004. Since then, nearly two decades of research have enabled scientists to understand its biological function and to identify and often overcome the molecular basis of acquired resistance mechanisms to EGFR-TKIs. This article reviews the role of EGFR in NSCLC and the research progress of EGFR-TKIs in patients with EGFR mutant lung cancer, discussing potential treatment strategies for drug resistance to improve survival and achieve precision drug use.

Keywords: non-small cell lung cancer (NSCLC); epidermal growth factor receptor (EGFR); epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKI)

1. Introduction

There are about 350 occurrences of lung cancer every day, making it the most common cause of cancer-related deaths [1]. Lung cancer patients continue to have a dismal prognosis for 5-year overall survival despite breakthroughs in diagnosis and multimodal treatment [2]. Numerous genetic and epigenetic changes, such as somatic mutations and elevated gene copy numbers, are accumulated in lung cancer. Tumor suppressor genes may become inactive or oncogenes may become active as a result of these modifications. 85% of newly diagnosed cases of lung cancer are non-small cell lung cancer (NSCLC), the most common subtype. Lung squamous cell carcinoma (LUSC) and lung adenocarcinoma (LUAD) are the two most prevalent subtypes of NSCLC [2], characterized by frequent disorders of epidermal growth factor receptor (EGFR) signals [3], especially in adenocarcinoma [4]. Since the EGFR mutation was first discovered in NSCLC cells in 2004 [5], it has been among the most researched therapeutic avenues for NSCLC treatment. Furthermore, EGFR kinase small molecule inhibitors were licensed in 2003 for the management of NSCLC [6].

2. Structure and function of EGFR

The work that Cohen started in the early 1960s, when he first realized that EGF is a protein that promotes the growth of epithelial cells, is the source of the name EGFR [7]. Carpenter did not identify a particular EGF-binding receptor on target cells until ten years later [8], this receptor was subsequently dubbed EGFR. The EGFR

gene, which codes for a 170 kda Type I transmembrane growth factor receptor epidermis growth with TK activity, is found on chromosome 7's short arm [9]. HER2/ERBB2/NEU, HER3/ERBB3, HER4/ERBB4, EGFR, and other members of the receptor tyrosine kinase (RTKs) family are members of the same family as EGFR. Three domains make up EGFR: the intracellular domain, which has ATP binding sites with tyrosine sections, the transmembrane domain, and the extracellular ligand binding domain [10] (**Figure 1A**). The 621 amino acids that make up the extracellular domain are separated into four sections (exon 1–16). There are 23 amino acids in the transmembrane domain (622–644). Exons 16 and 17 of the flexible merging membrane, exons 18–24 of the tyrosine kinase domain, and exons 25–28 of the C-terminal tail make up the intracellular domain [11] **Figure 1**. The two sections of the tyrosine kinase domain are called the n-leaf and C-leaf. The space between the two leaves is home to the ATP-binding active site. The transautophosphorylation connection between the N lobe of one receptor and the C lobe of another receptor initiates the downstream signal transmission of kinase [12]. The major locations of receptor ubiquitin are lysine-rich residues found in the kinase region [13]. Furthermore, several tyrosine residues found in the C-terminal tail are self-phosphorylated following receptor activation and serve as docking sites for effector proteins to transfer signals downstream, thereby controlling signal transduction [14].

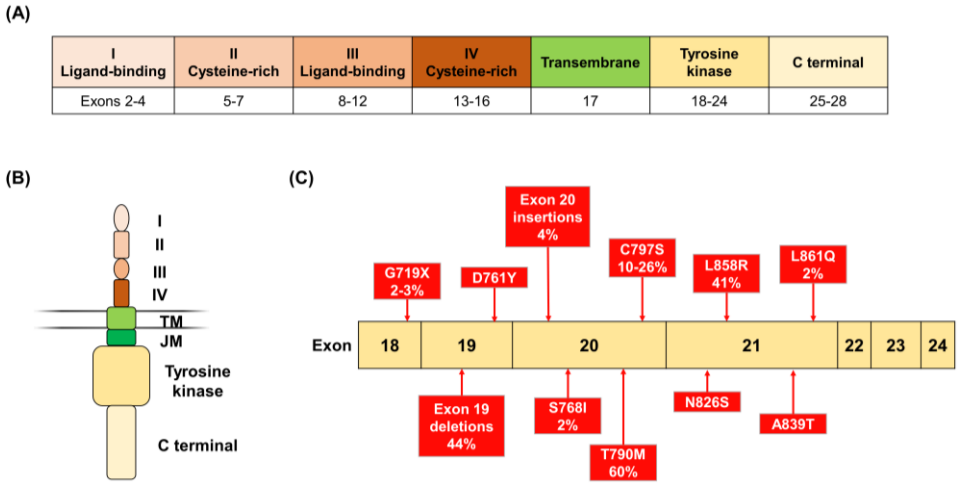

Figure 1. Diagram of EGFR protein and its mutations. **(A)** Domain structures of EGFR protein; **(B)** Diagram of EGFR over cell membrane; **(C)** Mutated sites in EGFR.

The C-helix undergoes an inward conformational shift upon binding to EGFR by EGF ligand. The enzyme is brought from an inactive state to an active conformation by this conformational shift [13]. Between the fissures in the N and C leaves, this active conformation interacts with the p ring of the active site in a significant way [15]. Driving mutations (Del19 and L858R) have been shown in early research to produce conformational changes, destroy the dormant form of EGFR, and shift the equilibrium to the active state instead of the inactive one [16]. After interacting to ligands like epidermal growth factor (EGF), this alteration causes EGFR to undergo a conformational change that is more favorable to the receptor's homologous or heterodimer formation, which activates EGFR tyrosine kinase [5]. Following its activation, the downstream substrate of activated EGFR is phosphorylated, triggering

downstream effectors and pathways that promote cell division, survival, transcription of genes, and cell cycle progression. These kinases' activation triggers a complex signaling network with numerous functions, including PI3K-AKT-mTOR pathways involved in cell survival and RAS-RAFMEK-ERK pathways involved in cell proliferation [17] (**Figure 2**).

3. Role of EGFR in NSCLC

Lung cancer is stimulated to develop and spread in large part by EGFR. Patients with EGFR mutations in NSCLC represent a unique subset of the population. There are differences in the tumor's origin, clinicopathological characteristics, prognosis, and treatment approach when compared to other patients with NSCLCr [18] **Figure 2**.

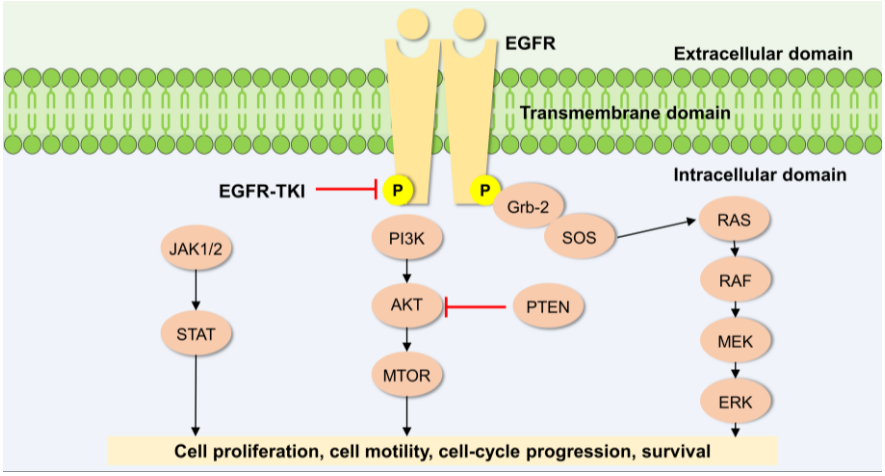

Figure 2. EGFR signalling pathway.

In NSCLC, the majority of EGFR mutations are found in the receptor tyrosine kinase domain's exons 18–21. Nearly 590 shallow hydrothermal growth factor receptor mutations have been identified to date, according to the COSMIC database. The majority of these genes are real inside the domain of tyrosine kinase [6]. 10% to 20% of individuals with lung adenocarcinomas who are Caucasian and 40% to 60% of patients from Southeast Asia will acquire EGFR mutations [19–21]. The majority of EGFR mutation-positive cancers are seen in light or nonsmokers, yet the findings are not mutually exclusive. Female patients had more EGFR mutations than male patients due to the rising incidence of nonsmoking behavior. Eighty percent of the participants in the Iressa Pan-Asian Survival Study (IPASS) trial were female, and sixty percent of the malignancies in this trial had EGFR mutations [22].

Exon 19 contains an intradeletion, exon 21 contains a single missense mutation, and exon 20 contains an intrarepetition/insertion. These are the three frequent forms of EGF RTK domain alterations (**Figure 1C**). Additionally, exons 18, 20, and 21 were found to contain rare missense mutations [23]. Tumors harboring the sensitive alterations, the intra-frame deletion of exon 19 and the L858R point mutation of exon 21, are susceptible to EGFR tyrosine kinase inhibitors (TKI). Less frequently occurring EGFR mutations include G718X, S768I, and L861Q. A unique kind of EGFR mutation—intraframe insertion of exon 20—occurs in 3 percent of lung tumors

that are not small cell. There are some innovative medications in clinical trials that target the atypical NSCLC with these uncommon mutations [24].

4. EGFR-targeted therapy of NSCLC

Inhibition of EGFR function can be achieved through two main strategies: i) inactivation of intracellular kinase signaling using TKIs, and ii) neutralization of EGFR and its ligands with antibodies. This paper mainly introduces the first strategy. FDA approved EGFR-TKIs are listed in **Figure 3**.

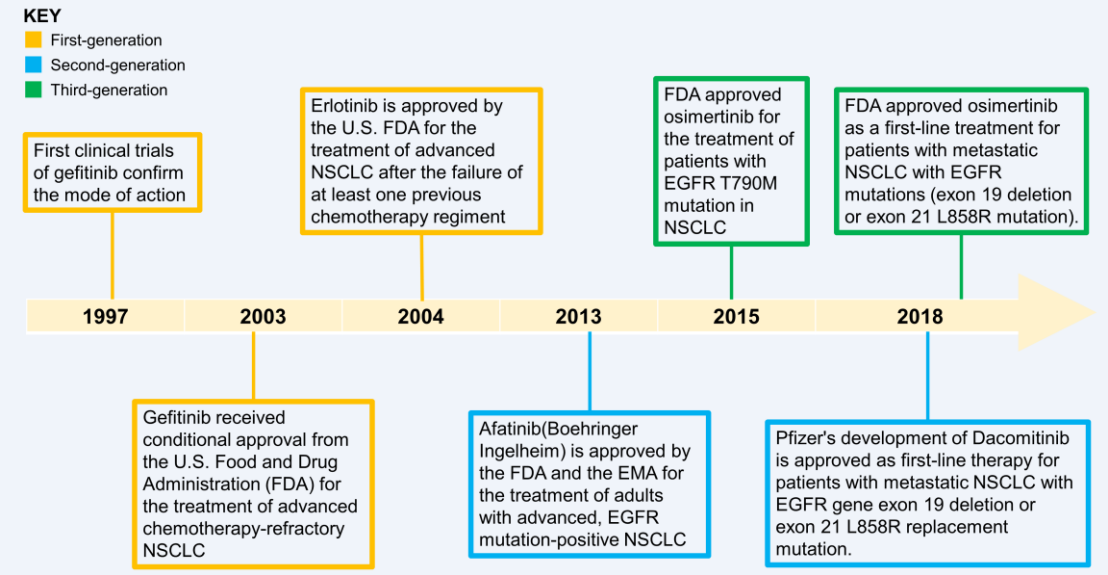

Figure 3. Timeline of three generations of EGFR-targeted drugs for the treatment of NSCLC.

4.1. First generation

Since most lung cancer patients had metastatic diseases at the time of diagnosis, the high death rate from the condition indicates that longer-term survival will require more efficient, methodical treatment [25,26]. In the late 1990s, patients with NSCLC were initially treated using molecular targeted treatment. Reversible EGFR TKIs include erlotinib and gefitinib. Both medications, which compete with one another for ATP binding at the catalytic sites of the enzyme EGFR tyrosine kinase, efficiently and selectively block the biochemical activity of this enzyme [27]. Both the sensitive mutant EGFR and wild-type EGFR were highly inhibited by the two medications.

In 2003, the oral EGFR TKI gefitinib was introduced, showing significant antitumor activity and favorable adverse event (AE) characteristics at a dose of 250 mg/day [28]. Gefitinib became an important treatment option for patients with advanced NSCLC, improving disease-related symptoms and inducing tumor regression in patients with persistent NSCLC after chemotherapy [29].

A phase III open-label study involving 608 patients with previously untreated advanced lung adenocarcinoma in East Asia, including non-smokers or former light smokers, compared gefitinib 250 mg/day to carboplatin plus paclitaxel. The study found that the 12-month PFS rate was 24.9% for the gefitinib group versus 6.7% for the carboplatin-paclitaxel group, demonstrating the superiority of gefitinib (hazard ratio for progression or death, 0.74; 95% CI, 0.65 to 0.85; $P < 0.001$). In patients with

positive EGFR mutations, PFS was significantly longer with gefitinib (hazard ratio for progression or death, 0.48; 95% CI, 0.36 to 0.64). Conversely, in the mutation-negative subgroup, PFS was longer with carboplatin-paclitaxel (hazard ratio for progression or death with gefitinib, 2.85; 95% CI, 2.05 to 3.98; $P < 0.001$). The study concluded that gefitinib is superior to carboplatin-paclitaxel for the initial treatment of lung adenocarcinoma in East Asian non-smokers or former light smokers, and the presence of EGFR mutations in tumors strongly predicts better outcomes with gefitinib [21].

Retrospective studies later revealed that EGFR gene mutations in a subset of patients with NSCLC were linked to a particular clinical response to the TKI gefitinib. Increased growth factor signal transduction and inhibitor sensitivity are the results of these alterations. Gefitinib-responsive lung cancer patients can be found by screening for these types of mutations [5]. After sequencing NSCLC, the receptor tyrosine kinase gene was matched to normal tissue. The majority of EGFR mutations were detected in lung adenocarcinoma cell lines allergic to gefitinib growth inhibition and in other lung cancer samples of patients who reacted to gefitinib therapy, but not in tumors or cell lines that were insensitive to the drug. These findings imply that EGFR mutation might be a predictor of gefitinib sensitivity [30]. Erlotinib is another TKI for EGFR. Following first-line or second-line chemotherapy, a randomized, placebo-controlled, double-blind trial conducted in 2005 demonstrated that it could increase the survival time of patients with NSCLC [31].

NSCLC often shows sensitivity to small molecule TKIs due to genetic alterations in the EGFR kinase domain. Despite initial therapeutic benefits observed in lung adenocarcinoma tumors with these EGFR mutations, nearly all patients eventually develop resistance to first-generation reversible ATP competitive inhibitors. This resistance is frequently attributed to the secondary T790M mutation exon 20 of the EGFR kinase domain, accounting for about half of all cases [32,33]. The T790M mutation, either alone or in combination with primary mutations in exon 19 or 21, enhances enzymatic and transformative activity,, suggesting that the therapeutic efficacy of the upcoming generation of EGFR inhibitors needs to be enhanced [34–36]. A short frame insertion in exon 20 of EGFR or the HER2 kinase domain has been identified as one of the principal drug resistance mechanisms to gefitinib and erlotinib. Consequently, the creation of alternate kinase inhibition techniques may be necessary for the treatment of lung cancer caused by EGFR exon 20 insertion [37]. The necessity for a small molecular TKI is indicated by these acquired and primary drug resistance mechanisms. This inhibitor should possess a broader activity against ERBB RTK while preserving the exceptional overall selectivity of the first-generation EGFR TKI in the human stimulation group, thus providing acceptable drug safety and tolerance.

4.2. Second generation

The EGFR TKIs dacomitinib and afatinib are irreversible. Their quinazoline skeleton structures resemble those of gefitinib or erlotinib [38]. EGFR tyrosine kinase is irreversibly inhibited by the side chain, which is intended to attach covalently to the EGFR C797 site. In vitro, active EGFR mutation and wild-type EGFR activity were inhibited by afatinib and dacomitinib. The exon 20-T790M mutation, which has been

identified as the most frequent source of secondary drug resistance to the first-generation EGFR TKI, was also active against these TKI at greater concentrations [39]. Compared with erlotinib, gefitinib or lapatinib, afatinib had a 100-fold higher inhibitory effect on the enzyme activity of L858R-T790MEGFR and had the same effect on HER2 [40]. In a large randomized phase III trial, the two drugs were studied in patients with stage IIIB or IV lung adenocarcinoma who developed disease progression at least 12 weeks later and found tumor patients with a T790M exon 20 mutation. However, in these cohorts, there was no discernible improvement in the combined survival rate of the two medications, and it was not advised for patients with advanced NSCLC who had already undergone chemotherapy and EGFR TKIs [41,42].

Afatinib was evaluated as a first-line treatment against chemotherapy in patients with EGFR mutant malignancies in two sizable randomized phase III trials [43,44]. According to both investigations, RR, PFS, and symptoms associated with cancer are all more relieved than with chemotherapy [44,45]. Patients treated with afatinib for EGFR deletions of 19 mutations in these LUX-LONG3 and LUXLONG6 studies had higher survival times than those who began chemotherapy [43–45].

Face-to-face comparisons of EGFR-TKI were made in several randomized phase III studies. When used as second-line therapy for individuals with lung adenocarcinoma, erlotinib plus gefitinib did not significantly alter PFS in an unselected group of patients with advanced NSCLC [46]. The function of first- and second-generation EGFR-TKI in EGFR mutant populations was examined in two investigations. LUX-LONG 7 study participants were chosen at random to receive either gefitinib or afatinib. Afatinib and gefitinib were randomly assigned to 319 patients. A follow-up time of 27.3 months (IQR 15.3–33.9) was the median. PFS duration (risk ratio [HR] 0.73 [95% CI 0.57–0.95], paired 0.017; median 11.0 months in the afatinib group and 10.9 months in the gefitinib group [9.1–11.5]) and treatment failure duration (median 13.7 months for the gefitinib group [10.1–13.1], compared to 11.5 months for the afatinib group [95% CI 11.9–15.0]. HR 0.73 (paired 0.0073; 95% CI 0.58–0.92) Comparing Afatinib to Gefitinib, the former was much longer. Afatinib considerably enhanced the prognosis of newly treated patients with EGFR mutation NSCLC as compared to gefitinib [47]. Afatinib and gefitinib did not significantly differ in OS in LUX-Lung7. Updated PFS (independent evaluation), TTF, and ORR data showed a considerable improvement with afatinib [48].

In the Archer research, 452 patients with EGFR-mutant cancers received first-line treatment with either gefitinib or dacomitinib at random. Even though the two groups' RRs (72% in the gefitinib group and 75% in the dacomitinib group) were comparable. Nonetheless, the gefitinib group's PFS was only slightly shorter than the dacomitinib group's (independent review: 14.7 months vs. 9.2 months, HR: 0.59; 95% CI: 0.47–0.74). Given its remarkable improvement in PFS, dacomitinib gefitinib warrants consideration as a novel therapeutic option for this patient population [49].

To sum up, EGFR TKIs of the first generation are reversible competitive ATP inhibitors that exclusively target EGFR. Afatinib and dacomitinib, two members of the second generation of EGFR TKIs, are irreversible inhibitors of HER2 and HER4, in contrast to the first-generation TKIs [48,49].

Although the effectiveness of second-generation EGFR-TKI has been beneficial to T790M-positive NSCLC patients, the improvement seems to be quite limited. This

is mainly due to the insufficient concentration of the drug because the toxicity of the drug limits the blood concentration to below the level needed to overcome the EGFRT790M mutation [50]. In the LUX-lung1 clinical trial, Adverse events (AEs) like rash, acne, and diarrhea were shown to be at least 10% more common compared to the placebo group. Of the 390 patients (38%), 150 needed to reduce the dose, and 70 (18%) stopped using afatinib because of these AEs [41].

4.3. Third generation

The Food and Drug Administration (FDA) in the United States has cleared osimertinib, CO1686, and HM61713 for clinical testing. Since osimertinib is the gold standard for first-line treatment of advanced EGFR mutation, it plays a prominent role in the treatment of EGFR-positive NSCLC worldwide. NSCLC and NSCLC with EGFR_T790M positivity following the first or second EGFR-TKI generation [51,52].

Osimertinib was authorized by the FDA in 2015 to treat patients with metastatic EGFRT790M mutant NSCLC who also had EGFR drug-resistant mutations. In 2018, the medication was authorized as a primary therapy for advanced NSCLC with EGFR mutation [53]. Osimertinib is an irreversible EGFR-TKI that can be taken orally. It acts on the central nervous system (CNS) and is selective for EGFR and T790M mutations. When compared to early EGFR-TKI, osimertinib produces more central nervous system activity because it can be better retained in cerebrospinal fluid after crossing the blood-brain barrier, despite being the substrate of several drug efflux transporters, including permeable glycoprotein (Pgp) and breast cancer resistance protein (BCRP) [54]. After first-generation EGFR-TKI treatment, AURA3, a randomized, open-label phase 3 trial, shows that Osimertinib is superior to platinum in patients with advanced NSCLC who test positive for T790M(including those with CNS metastases) With the failure of the first generation of EGFR-TKI therapy, it establishes a standard regimen for patients with EGFR(T790M) positivity and targeted therapy for brain metastases [51]. In untreated EGFR mutation-positive advanced NSCLC patients, the safety and effectiveness of Osimertinib in comparison to standard EGFR-TKI (erlotinib or gefitinib) were examined in the double-blind phase 3 FLAURA study. According to the findings, patients with an EGFR mutation who were left untreated had a median PFS of 18.9 months as opposed to 10.2 months for those receiving gefitinib or erlotinib (human resources, 0.80% confidence interval, 0.370.57%, $P < 0.001$) [52]. The median OS time (38.6 months vs. 31.8 months; hazard ratio for death 0.80; 95.05% CI, 0.64 to 1.00; $P = 0.046$) shows the similar pattern [55]. Osimertinib has CNS efficacy in patients with untreated EGFR mutant NSCLC, as evidenced by the objective remission rate (ORR) of 91% among patients with measurable brain metastasis and 68% among the first-generation EGFR-TKI group (odds ratio, 4.6 ; 95% CI 0.9–34.9 ; $P = 0.066$) [56]. The effectiveness and safety of EGFR-TKIs when used in conjunction with other targeted treatments have been the subject of additional research [57]. The safety and tolerability of Osimertinib in combination with human programmed cell death ligand-1 (PD-L1) antibody Durvalumab, savolitinib (hepatocyte growth factor receptor) inhibitor, or selumetinib (MEK inhibitor) was assessed in Phase Ib TATTON trials. The groups treated with durvalumab, savolitinib, and selumetinib had an ORR of 42% (95% confidence

interval 26% to 59%), 44% (22% to 69%), and 43% (23% to 66%), respectively [58]. ADAURA was the world first Phase III study to demonstrate a statistically significant benefit in both DFS and OS with targeted treatment in patients with EGFR-mutated stage IB-IIIA NSCLC [59]. Terms of overall survival, osimertinib reduced the risk of death by 51%，and the hazard ratio was 0 (95% CI 0.33–0.73, $p = 0.0004$) [60].

T790 M-positive NSCLC can now be treated with rociletinib (CO-1686), the first medication of its kind to enter clinical development. It inhibits mutant EGFR specifically and irreversibly, including Ex19del and L858R, especially T790M resistance mutations in the NSCLC model, while avoiding inhibition of targeted toxicity observed by wt. EGFR, but cannot inhibit exon 20 insertion (Ex20ins) [61,62]. Both the phase I/II TIGER-X trial and the phase II, open-label, multicenter TIGER-2 trial assessed the safety and effectiveness of CO-1686 in patients who had previously received treatment for EGFR mutant NSCLC. In all, 130 patients took part in the TIGER-X research. The estimated median PFS duration of the 46 assessable T790M patients was 13.1 months (95% CI, 5.4–13.1), and the ORR was 59% (95% CI, 45–73) [62]. Nonetheless, the verified response rate of CO-1686 was found to be 28%–34% in the combined cohort of patients included in the TIGER-X and TIGER-2 studies, which differed significantly from the TIGER-X test's response rate. The median PFS time was revised to 6.1 months and the mature confirmation response rate was revised to 45% following independent research [63]. Osimertinib was administered to nine patients who had progressed to CO-1686, according to Sequist et al. Out of them, three cases had stable conditions, four cases had progressing diseases, and two instances had partial remission. Following CO-1686 treatment, three patients who had brain metastases also showed improved responses to osimertinib for their CNS illness [64]. On 6 May 2016, CO-1686's development was stopped since it was less effective than osimertinib and had a higher risk of adverse events (AEs) such as high-grade hyperglycemia and correction of extended QT interval [65].

In December 2015, the FDA approved olmutinib (HM61713), an oral third-generation EGFR TKI, for clinical investigation in the management of NSCLC. The third-generation EGFR TKI, which covalently binds to the receptor, showed irreversible enzymatic inhibition of activation of EGFR mutation and T790M mutation while retaining wild-type EGFR [66]. In a single-arm, open-label phase I/II trial reported in 2019, EGFR_T790M-positive patients who had failed one or more EGFR-TKIs were treated with omutinib (800 mg/day), which demonstrated an ORR of 55% (38 cases of 69 evaluable patients; 95% CI: 42.6–67.1) and an estimated median PFS was 6.9 months (95% CI: 5.6–9.7) [67]. In the phase II trial in Olmutinib, South Korea, two cases of toxic epidermal necrolysis/Stevens-Johnson syndrome were reported on 30 September 2016, one of which was fatal. Olmutinib's development was stopped on 13 April 2018 [65].

Another EGFR inhibitor that is selective is WZ4002. It is 100 times less potent than wild-type EGFR and 30–100 times more potent than EGFR_T790M when compared to quinazoline-based EGFR inhibitors in vitro. Additionally, they work well in lung cancer mouse models driven by EGFR_T790M. In the clinic, these mutant selective irreversible EGFR kinase inhibitors might be more advantageous and kinder to patients than quinazoline-based inhibitors [68]. According to one study, WZ4002

suppresses the growth of H1975 cells carrying the gatekeeper T790M mutation, but not that of HCC827ER or PC-9/HGF cells. HGF caused H1975 cells to become resistant to WZ4002, while E7050 prevented the phosphorylation of EGFR and Met as well as the downstream molecules they bind to, making H1975 cells treated with HCC827ER, PC-9/HGF, and HGF responsive to WZ4002. In severe combined immunodeficient mice, the combination therapy significantly reduced tumor growth produced by H1975–HCC827ER and PC-9/HGF cells without noticeable adverse events. Although more research in clinical trials is required, the combination of mutation-selective EGFR-TKI and Met-TKI can successfully stop the growth of erlotinib-resistant cancers brought on by the gatekeeper T790M mutation, MET amplification, and HGF overexpression [69].

Furmonertinib, a novel third-generation EGFR-TKI, has excellent clinical performance and a favorable safety profile in patients with advanced EGFR-mutated NSCLC, both with classical and CNS metastases, as well as a wide therapeutic dose range (80 mg to mg) [70]. In previous Phase 1/2 and Phase 2b studies in patients with EGFR Thr790Met mutated NSCLC, fumotinib showed encouraging efficacy and good tolerability [71,72]. Adverse events associated with drug action on wild-type EGFR, such as diarrhea and rash, were rare in these studies.

All things considered, osimertinib is a promising third-generation EGFR-TKI used to treat lung cancer today. However, the therapeutic effects of osimertinib are limited by the presence of both acquired and primary resistance. The primary resistance was caused by the EGFR exon 20 insertion and BIM deletion polymorphism. Simultaneously, EGFR reliance (miss target) and targeting are two of the diverse mechanisms of acquired drug resistance. MET amplification, HER2 amplification, EGFR_C797S mutation, and transformation of small-cell lung cancer have been recognized as common treatment resistance mechanisms. More novel mechanisms, such as carcinogenic fusion and uncommon EGFR point mutations, have been identified recently [73]. More research should be done on the combination therapy based on osimertinib in order to enhance the prognosis of patients with advanced EGFR mutations NSCLC.

4.4. Common AEs of EGFR-TKIs and their management

As EGFR-TKIs have a less hazardous profile than chemotherapy drugs, they are typically well tolerated. However, EGFR-TKIs have their own specific AEs, including rash, onychomycosis, oral mucositis, diarrhea, liver injury, and interstitial lung disease (ILD).

In terms of skin physiology, EGFR stimulates epidermal development, inhibits differentiation, and speeds up the healing of wounds. A range of unfavorable skin symptoms, including rash/acneiform rash, dry skin, itching, and inflammation of the nails/perinail tissues, can be brought on by the inhibition of EGFR activity [74]. The most frequent adverse events (AEs) linked to EGFR-TKIs are dermatologologic disorders, which include rashes such as acne, dry skin, and onychomycosis. Rashes/acne-like rashes caused by EGFR-TKIs tend to occur 1 week-2 weeks after treatment with targeted agents [75], Typical symptoms include itching, dry skin, and in severe cases, interfere with patients' daily life and sleep [76]. Before starting

treatment with EGFR-TKI, healthcare professionals should educate patients and their familie [77], instructing patients to take proper precautions, keep the skin clean and moisturized every day, and apply moisturizing creams appropriatel [74].

Drug-associated oral mucositis induced by EGFR-TKI analogs in therapy often appears on days 13–19 of drug initiation [75]. The principles and objectives of its clinical management are: to control pain and cover the ulcerated surface for early healing; to maintain oral cleanliness and reduce multiple infections; to stop the progression of oral mucositis to grade 3 or 4; and to treat the complications of bleeding ulcers, multiple oral infections, malnutrition, dehydration, and electrolyte disorders caused by oral mucositis in a multidisciplinary and collaborative manner.

After treatment with EGFR-TKI, diarrhea occurs more frequently, primarily in the form of a substantial rise in stool frequency and modifications in stool characteristics。It's critical to identify if diarrhea that develops while on EGFR-TKI therapy is caused by an infectious disease or is a result of the medication [78]. If a gastrointestinal illness is suspected, the patient has to receive the right care. Restoring the patient to baseline status or ≤ grade 1 is the aim of addressing gastrointestinal adverse events.

EGFR-TKI-associated drug-induced liver injury (DILI), the clinical manifestations of DILI are usually nonspecific. Some patients may have gastrointestinal tract symptoms like malaise, loss of appetite, anorexia, hepatic distension and epigastric discomfort, etc. In patients with obvious bile sludge, there may be yellow staining of the skin all over the body, light color of stools and itching. A few patients may have fever, rash, eosinophilia and even allergic manifestations such as arthralgia, which may also be accompanied by other extrahepatic organ damage . Basic therapeutic principles: (I) timely discontinuation of drugs suspected of liver injury; (II) consider both the possibility of the drug's worsening of liver injury from continuing use and the possibility of the underlying disease's progression from stopping it; (III) use appropriate drug therapy according to the clinical type of liver injury; (IV) acute liver failure/subacute liver failure (ALF/SALF), which is the most common type of liver injury, should be treated with the most appropriate medication, and the most effective treatment should be the most effective. failure (ALF/SALF) and other severe patients can be considered for emergency liver transplantation when necessary [79].

Even though EGFR-TKI-induced ILD is rare, it can be fatal when it does happen [80]. The primary clinical manifestations of ILD caused by EGFR-TKI include cough, primarily dry cough, with or without fever and dyspnea that gets worse over time [81]. The main therapeutic approaches include oxygen therapy, mechanical ventilation, glucocorticoids, and empirical anti-infective therapy as needed, with close monitoring of disease changes and timely reassessment and examination.

Most of the adverse effects caused by EGFR-TKI are preventable and controllable, and the grade of these adverse effects can be reduced after stopping the drug. Patient education, early recognition, and proactive measures to intervene and treat EGFR-TKI-induced adverse events are key.

5. Resistance mechanisms to osimertinib

Although third-generation EGFR-TKIs have demonstrated remarkable clinical success, the majority of patients ultimately develop EGFR-TKI resistance [82]. Acquired Osimertinib resistance is very variable, encompassing EGFR-dependent (on-target) and EGFR-independent (off-target) mechanisms, due to the great heterogeneity of tumors and adaptive cellular signaling pathways in NSCLC [83]. Between third-generation and early EGFR-TKIs, there are differences in the relative frequency of off-target and on-target resistance mechanisms. When treated with early EGFR-TKIs, patients primarily develop targeted resistance mechanisms, with T790M accounting for about 50% of cases [84]. Targeted resistance, however, only develops in 10%–20% of individuals receiving osimertinib; the most prevalent mechanism of targeted resistance is the C797S mutation [85]. In contrast to previous EGFR-TKIs, Osimertinib has a decreased rate of targeted resistance, which could be attributed to variations in targeted inhibition and selective pressure, as well as improved clonal evolution in EGFR-mutant NSCLC [86].

5.1. EGFR-dependent resistance mechanisms

Changes in important amino acid residues that spatially obstruct Osimertinib's ability to interact with the ATP-binding site in the structural domain of the EGFR tyrosine kinase are the main cause of targeted resistance mechanisms.

In exon 20, the most prevalent mechanism of EGFR-dependent resistance is the C797S tertiary mutation. In the ATP-binding pocket, osimertinib and residue Cys797 create a covalent connection, and the C797S mutation prevents the drug from binding to the EGFR by deleting the cysteine side chain that covalently binds to Osimertinib [87]. Since the C797 mutation has no effect on first- or second-generation TKIs, they could be a viable therapeutic option for treating the C797S resistance mutation in osimertinib [88]. Because this residue forms a narrow "hydrophobic sandwich" with L718, the G796 mutation prevents Osimertinib from binding to the EGFR kinase structural domain at the phenyl aryl ring position. In contrast, the L792F/H mutation prevents Osimertinib from binding to the methoxy group on the phenyl ring [89]. The glycine-rich ring may adopt a configuration that is incompatible with osimertinib as a result of G724S [90]. Other mutations include C797G, S768I, E709K, L692V and L798 [73,91].

Exon 20ins, which are primarily primary resistance, EGFR amplification, and T790M deletion are other mechanisms of EGFR-dependent resistance. Early resistance and several competing resistance mechanisms are linked to acquired resistance to osimertinib, which is mediated by T790M deletion [92]. In NSCLC cells, amplification of the wild-type EGFR allele results in acquired resistance to mutant-selective EGFR TKIs; however, amplification of the wild-type EGFR allele alone is insufficient to give acquired resistance. These results highlight the role that wild-type EGFR allele signaling plays in the development of resistance to EGFR-TKIs that are mutation-selective [93].

5.2. EGFR-independent resistance mechanisms

EGFR-independent resistance mechanisms are relatively more complex, involving activation of bypass signaling pathways, tumor microenvironment, phenotypic transformation, immunosuppressive tumor immune microenvironment (TIME) and others.

When EGFR binds to its ligands, it initiates downstream signaling pathways (such as PI3K/AKT, RAS/MAPK/ERK, JAK/STAT) to carry out its biological activity.Tumor cells adapt further to pharmacological selective pressures by activating growth-proliferative signaling pathways through bypass when TKIs block EGFR.

Among the mechanisms of bypass signaling pathway

activation, MET amplification is the most common, followed by HER2 amplification [94]. The RTK c-Met, which binds to the ligand HGF and phosphorylates the receptor, is encoded by the MET oncogene. This activation triggers the bypass of downstream signaling pathways associated with EGFR. The MET signaling pathway promotes tumor angiogenesis, invasion, and metastasis by having a significant impact on cell migration, proliferation, and apoptosis [95]. Osimertinib resistance is mediated by EGFR downstream signaling, which is directly activated by HER2. Osimertinib resistance was found by HSU et al. to be caused by the exon 16 skipping HER2 deletion (HER2D16), in which mutant EGFR and HER2D16 worked together to trigger the downstream signaling that results in Osimertinib resistance. Additionally, co-treatment with Src kinase inhibitors and osimertinib did not succeed in reversing resistance, indicating that the canonical route is not the source of HER2D16-driven signaling in NSCLC. It was also discovered that Osimertinib and afatinib, a pan-HER small molecule inhibitor, worked in concert to suppress H1975-HER2D16 cell proliferation and signaling [96].

There is growing evidence that acquired resistance to targeted therapies in NSCLC patients is associated with reciprocal domestication between the tumor and its surrounding microenvironment . Studies have confirmed that an immunosuppressive environment is found in Osimertinib resistance, characterized by decreased T-cell infiltration and activation and increased macrophage infiltration and M2 polarization. This interaction can take place through tumor-derived exosomes [97]. In addition, EGFR-mutant cancer cells can internalize exosomes by Clathrin-dependent endocytosis. The encapsulated exosomal wild type EGFR protein subsequently initiates Osimertinib resistance by activating the downstream PI3K/AKT and MAPK signaling pathways. In the future, it may be possible to block this phenotypic transmission process by targeting exosomes [98].

Spectral plasticity, the ability of cells to transition from one committed developmental pathway to another, has recently been recognized as widely involved in tumor development, invasion, and metastasis, as well as drug resistance, and has become one of the hallmark characteristics of tumors [99]. The transformation of tumor cells into different histological subtypes is associated with loss of dependence on the original oncogenic driver, leading to treatment resistance. Patients who had been resistant to Histologic phenotypic transformation, which mostly consists of SCLC phenotypic transformation, EMT, and adenocarcinoma to squamous cell carcinoma transition (SCCT), was initially seen in patients who had become resistant

to osimertinib as a first-line therapy. About 5% of EGFR-mutant lung adenocarcinomas experience histologic transformation, which is frequently associated with aberrant activation of the transcriptional regulators MYC and SOX as well as activation of the AKT pathway [100]. Furthermore, activation of the yes-associated protein (YAP) and forkhead box protein M1 (FOXM1) axes has been identified as a cause of EMT-associated EGFR TKI resistance. This histologic transformation, known as epithelial-mesenchymal transition (EMT), has also been reported as a mechanism of Osimertinib resistance [101].

Tumor expression analysis conducted after resistance revealed that EGFR-resistant NSCLC expressed higher levels of IL-6, IL-8, HGF, VEGF, CXCL16, TGF-β, NF-κB, and mitogen-activated protein kinase (MAPK) than EGFR-TKI-sensitive NSCLC. This led to the development of EGFR-TKI resistance and the induction of an immunosuppressive tumor immune microenvironment (TIME) [102–108]. One way to sum up TIME in EGFR-TKI-resistant lung cancer is as follows: (I) levels of immunosuppressive cells (e.g., M2 and myeloid-derived suppressor cells (MDSC)) increase after resistance [109,110], levels of immunoreactive cells (e.g., DCs are $CD8^+$ T cells) decrease after resistance to EGFR-TKI [111,112], and an immunosuppressive state permeates the tumor microenvironment; (II) tumor cells and immunosuppressive cells release a variety of negative immunomodulatory factors that prevent the presentation and recognition of tumor antigens by immune cells as well as their ability to suppress tumor growth, allowing immune escape; (III) tumors that are resistant to EGFR-TKI stimulate EMT. These three characteristics work together to create a regulatory signaling network that causes EGFR-TKI resistance [113].

6. Management of EGFR-TKI resistance

6.1. Development of the fourth generation of EGFR-TKIs

For some lung cancer patients undergoing targeted therapy, resistance to osimertinib, a third-generation targeted medication, presents a challenge. Targeted therapy has not yet received FDA approval for use in conjunction with osimertinib treatment. As a result, research into the creation of fourth-generation EGFR-TKI medications has lately gained momentum, with several of these medications demonstrating encouraging outcomes in clinical studies.

Targeting certain drug-resistant EGFR mutations while maintaining the wild-type receptor, EAI045 is the first fourth-generation EGFR-TKI medication. In mice with the L858R/T790M/C797S mutation, EAI045 in conjunction with cetuximab dramatically decreased tumor size; however, EAI045 by itself was ineffective in preventing cellular EGFR-driven proliferation [114]. To et al. modified EAI045 in order to increase its activity and enable the drug to be used as a single agent. This resulted in the creation of a new variant inhibitor, JBJ-04-12502, which, when compared to the parent compound, inhibited cell proliferation and EGFR L858R/T790M/C797S signaling both in vitro and in vivo. Osimertinib and JBJ-04-125-02 together improved in vitro and in vivo efficacy, boosted apoptosis, and more successfully reduced cell proliferation [115].

There are no efficient inhibitors that target Del19/T790M/C797S, despite the identification of variant EGFR TKI (such as EAI045) that may overcome

L858R/T790M/C797S. Roche Chugoku Pharmaceuticals developed CH7233163, a fourth-generation EGFR-TKI inhibitor, specifically for patients with Del19 mutations. Using EGFR-Del19/T790M/C797S, CH7233163 demonstrated strong anticancer efficacy both in vitro and in vivo in this study [116].

Blueprint Medicines has produced two fourth-generation EGFR-TKI inhibitors: BLU-945 and BLU-701. Both are resistant to T790M and C797S resistance mutation activity, as well as EGFR activating mutations (del19, 21L858R) [117,118]. In NSCLC animal models, BLU-945 in combination with gefitinib or osimertinib results in a more substantial tumor clearance [119]. Additionally, BLU-701 had intracranial anticancer action, showing strong antitumor activity both alone and in combination with BLU-945 [120].

A fourth-generation oral EGFR-targeting medication is TQB3804. In addition to treating oxytetracycline resistance brought on by d746750 (19del)/T790M/C797S and L858R/T790M/C797S, it also effectively combats double mutations linked to first- and second-generation TKI, namely d746-750/T790M and L858R/T790M [121].

Bridge Biotherapeutics is a Korean company that created BBT-176, an inventive EGFR-TKI. In xenograft animal models with triple mutations Del19/T790M/C797S and L858R/T790M/C797S, BBT-176 shown potent anti-cancer efficacy. Furthermore, BBT-176 demonstrated noticeably increased activity when combined with cetuximab, an anti-EGFR antibody [122].

One such EGFR-TKI that is categorized as fourth generation is amivantamab (JNJ-61186372). By attaching to each receptor's extracellular structural domain, amivantamab, an EGFR-MET bispecific antibody with immune cell-targeting ability, overcomes resistance at the binding site of TKIs. It works well against C797S mutations, MET amplification following Osimertinib resistance, and EGFR exon 20 insertion mutations (primary resistance mutations) [123]. Amivantamab can be safely used in combination with lazertinib at their respective full single-agent therapeutic doses. The encouraging initial activity was observed in oxytetracycline recurrent disease [124]. All of these medications are still in various phases of research and development or clinical trials, with the exception of amivantamab, which is authorized to treat EGFR exon 20 insertional mutations in NSCLC. Consequently, it will take a few years before these medications are accessible for clinical application.

6.2. Combination of EGFR-TKI and chemotherapy to delay TKI resistance

Chemotherapy plus EGFR-TKI is the primary non-elective strategy to postpone EGFR-TKI resistance. First-generation EGFR-TKI and chemotherapy have been used in the past to treat patients with non-EGFR-mutated NSCLC. Gefitinib did not provide any additional benefit in terms of survival, TTP, or RR when compared to standard chemotherapy alone in a phase III randomized, placebo-controlled, double-blind trial evaluating gefitinib plus paclitaxel and carboplatin in patients treated with primary chemotherapy for primary advanced NSCLC [125]. For patients with unresectable stage III or IV NSCLC, a phase III randomized, double-blind, placebo-controlled multicenter trial of primary chemotherapy found that gefitinib plus gemcitabine and cisplatin was not better than gemcitabine and cisplatin alone for treating primary

patients with advanced NSCLC [126]. Erlotinib plus cisplatin and gemcitabine as first-line treatment for advanced NSCLC was the subject of another phase III randomized, double-blind, placebo-controlled, multicenter trial. The trial's findings revealed no benefit to survival for patients with advanced NSCLC who had received primitive treatment [127]. Erlotinib plus carboplatin and paclitaxel did not improve survival over carboplatin and paclitaxel by itself in patients with advanced NSCLC who had not received prior treatment [128].

In the phase II NEJ005 trial, however, the combination of gefitinib plus carboplatin and pemetrexed initially demonstrated extended PFS and OS in comparison to consecutive options in a subset of patients with EGFR mutations [129,130]. The same combination of gefitinib plus chemotherapy was then compared to gefitinib alone in a phase NEJ009 study. The combination group outperformed the gefitinib group in terms of ORR and PFS (ORR, 84% vs 67% [$P < 0.001$]; PFS, 20.9 vs 11.9 months; risk ratio for death or disease progression, 0.490 [$P < 0.001$]), while PFS2 (20.9 vs 18.0 months; $P = 0.092$) did not vary significantly. Additionally, the combination group's median OS was considerably longer than the gefitinib group's (50.9 vs. 38.8 months; risk ratio for death, 0.722; $P = 0.021$) [131]. The phase III FLAURA2 (NCT04035486) trial's findings demonstrated that osimertinib therapy in combination with platinum pemetrexed showed better CNS efficacy, including delayed CNS progression, compared with Osimertinib monotherapy in EGFR-mutated advanced NSCLC [132].

6.3. Combination of EGFR-TKI and anti-angiogenic agents

Combining EGFR TKIs with anti-angiogenic drugs has been investigated in the first-line context to postpone resistance. It has been established that the VEGF pathway is a crucial angiogenesis-promoting mediator of cancer. For usage in NSCLC, a number of therapeutic drugs that target VEGF and VEGF receptors have been discovered and approved [133]. The mechanism by which VEGF receptors enhance the effects of EGFR inhibitors is unclear, but in preclinical models, erlotinib resistance may be linked to elevated tumor cell and host stromal VEGF. Combined blockade of the VEGFR and EGFR pathways may eliminate primary or acquired resistance to EGFR TKI [134]. Patients with NSCLC who had an activating EGFR mutation were found to benefit from the combination of erlotinib and bevacizumab, an anti-vascular endothelial growth factor monoclonal antibody, in the single-arm phase II trial BELIEVE [135]. The median PFS in the erlotinib plus bevacizumab arm of the randomized phase II study (JO25567) was 16.0 months (95% CI 13.9–18.1), while the median PFS in the erlotinib alone arm was 9.7 months (5.7–11.1) (risk ratio 0.54, 95% CI 0.36–0.79; log-rank test $p = 0.0015$) [136]. The NEJ026 phase III trial demonstrated the benefit of PFS; however, additional research with longer follow-up, overall survival, and quality of life data is required to fully evaluate the efficacy of this combination in this context [57]. Similarly, Ramucirumab (a human IgG1 VEGFR2 antagonist) plus erlotinib demonstrated superior PFS compared to placebo plus erlotinib in untreated patients with EGFR-mutated metastatic NSCLC [137]. The role of Osimertinib in combination with anti-vascular endothelial growth factor agents in first-line and EGFR TKI treatment settings is currently being explored in Phase II and

Phase III trials. Data from a recently published Phase II trial (UMIN000023761) indicates that patients with advanced lung adenocarcinoma with EGFR T790M mutations treated with T790M-positive therapy did not show prolonged PFS in the Osimertinib plus bevacizumab arm [138].

6.4. Combination with different generations of EGFR-TKI

EGFR-dependent osimertinib resistance mechanisms typically retain their sensitivity to prior-generation EGFR-TKIs when T790M mutations are absent. As a result, osimertinib plus first- or second-line EGFR-TKI combined in first-line therapy may be a tactic to avoid targeted resistance. Osimertinib plus Gefitinib phase I/II trial preliminary results demonstrated good activity, with an ORR (ORR = 85.2%; 95% CI = 67.5–94.1) consistent with previously reported first-line remission rates[139].

6.5. Combination of EGFR-TKI and inhibitor against other pathway

Similarly, preclinical research has shown that targeting EGFR in conjunction with other pathways can stop the emergence of EGFR-independent resistance mechanisms; as a result, several clinical trials including EGFR-TKI with MET, MEK, Src, PARP, or CDK4–6 inhibitors are now being conducted. Notably, in the phase I CHRYSALIS study, amivantamab, a bispecific antibody that targets both EGFR and MET, combined with lazertinib, a third-generation EGFR TKI, produced an ORR of 100% (95% CI = 83–100) in 20 patients receiving this combination [140].

6.6. Combination of EGFR-TKI and radiation therapy

Radiation treatment is an attractive alternative for treating drug-resistant illnesses in the first-line context. According to reports, 41.25% of NSCLC patients receiving EGFR-TKI treatment experience in situ failure [141]. Furthermore, EGFR mutant NSCLC exhibits greater aggressiveness and a propensity for brain metastases in contrast to wild-type NSCLC [142]. Thus, the two primary strategies to treat EGFR-TKI resistance at this point are the combination of EGFR-TKIs with thoracic and brain radiation, with considerations for timing, method, dosage, and side effects.

Significantly, patients receiving concurrent osimertinib and chest radiation therapy had an especially high incidence of radiation pneumonia [143]. Furthermore, osimertinib hindered proliferation and clonal survival after irradiation, decreased G2/M phase block in irradiated cells, and delayed DNA damage repair in a concentration- and time-dependent manner. EGFR mutant NSCLC also shown greater radiosensitivity [144]. Additionally, the phosphorylation of extracellular signal-regulated kinases, protein kinase B, and EGFR (Tyr1068/Tyr1173) was inhibited by osimertinib either by itself or in conjunction with ionizing radiation. Moreover, osimertinib improved IR's anticancer efficacy in tumor-bearing nude mice [145]. Consequently, due to uncertain guidelines and the occurrence of serious side effects, the dose of radiotherapy must be strictly limited when used in combination with a third-generation EGFR-TKI.

Brain metastases are a frequent, potentially fatal NSCLC consequence that can impair patient survival and cause neurological symptoms. Compared to wild type 1, EGFR mutant NSCLC results in higher fatalities associated with CNS progression

(44.8% vs. 8.3%, $p < 0.001$) [146]. It is therefore difficult to stop and treat CNS development in EGFR-mutant NSCLC. The BBB can be disrupted and medication penetration into the brain increased by chemotherapy or radiation therapy, although first- and second-generation EGFR-TKI have weak BBB crossing capacities. Third-generation EGFR-TKIs, however, are much more effective against brain metastases due to their increased diffusion within the brain, as previously indicated. Investigating the combined anticancer effects of RT and third-generation EGFR-TKIs has gained more attention in recent years. According to a retrospective analysis, patients who received osimertinib plus brain radiation had a longer overall survival (OS) than patients who did not get brain radiation (53 months vs. 40 months, $P = 0.014$) [147]. In patients with progressing brain metastases, radiation administered before starting osimertinib did not extend TTF, PFS, or OS, according to another retrospective analysis. For certain patients with brain metastases from EGFR-mutant NSCLC who react well to osimertinib as second-line therapy, delayed irradiation may be explored as a way to reduce the risk of radiation-related damage. [148].

6.7. Combination of EGFR-TKI with immune checkpoint inhibitors (ICIs)

Immunocheckpoint inhibitor (ICI) monotherapy often has poor clinical activity in the first-line treatment of EGFR mutant NSCLC, despite the fact that different ICIs have varying therapeutic benefits [149,150]. As a result, there has been increased focus on the use of ICIs as second-line therapy in patients with EGFR-TKI-resistant NSCLC. Furthermore, a prominent area of discussion these days is whether or not ICIs can help EGFR-TKIs overcome resistance to third-generation EGFR-TKIs. It has been demonstrated that patients with a variety of malignancies who have higher levels of intra-tumor T cells and tumor antigenicity had better survival rates [151]. Therefore, these immunomodulatory effects provide a rationale for combining these targeted therapies with immunotherapy. Recently, several molecularly targeted therapeutics, including EGFR-TKI, have demonstrated their ability to promote intra-tumor T-cell infiltration, tumor antigen presentation, and PD-1/PD-L1 expression [152–154]. Osimertinib has been shown to affect important EGFR signaling pathways and promote immune cell infiltration, among other effects [155]. Additionally, in osimertinib-resistant lung adenocarcinoma cells, Qi et al. discovered an overall decrease in the HLA class I-presenting immunopeptidome and downregulation of antigen-presenting core complexes (e.g., TAP1 and ERAP1/2) and immunoproteasome. These findings highlight the significance of immunomodulation in patients with osimertinib-resistant NSCLC [156]. Nevertheless, early termination of CAURAL recruitment was necessary because of a higher frequency of events resembling interstitial lung disease in the osimertinib plus durvalumab group in the Ib TATTON study alone (NCT02143466) [157]. In addition, Compared to treatment with either drug alone, a greater percentage of interstitial pneumonitis (IP) was observed with nivolumab in conjunction with EGFR-TKI [158]. In addition to interstitial pneumonia, a case of recurrent immune-associated colitis (initially caused by nivolumab) after osimertinib treatment for lung adenocarcinoma was reported in 2017 [159]. Osimertinib used right after nivolumab has been shown to significantly enhance

the probability of grade 3 or higher hepatotoxicity with acquired T790M resistance in patients with advanced NSCLC having EGFR mutations [160]. Recently, osimertinib and pembrolizumab were sequentially induced in a patient with advanced NSCLC, resulting in significant hepatotoxicity and Stevens-Johnson syndrome (SJS) [161]. Interestingly, significant immune-related adverse events (irAEs) were linked to osimertinib following PD-(L)1 blockage, most frequently in patients who had just undergone PD-(L)1 blocking. When osimertinib was taken before PD-(L)1 blockage or when PD-(L)1 was taken after other EGFR-TKIs, no irAEs were noted. Given that no serious adverse events (irAEs) happened when other EGFR-TKIs were given, it seems that this connection is unique to osimertinib [162]. This effect may result in the delayed onset of adverse events (AEs) even after the drug is stopped, as it appears to be connected to the extended half-life of ICIs [163]. Reminding clinicians to carefully consider sequential treatment plans is crucial when it comes to patients with NSCLC who can benefit from TKI or ICI therapy. Osimertinib and nivolumab were found to be effective in treating lung cancer with EGFR kinase domain duplication (EGFR-KDD) in one case study [164]. Compared to other EGFR mutant subtypes, which are linked to a number of possible predictors (such as TMB and concurrent PD-L1 plus CD8 TIL expression), ICIs may be more effective against L858R mutations [165]. A increasing body of retrospective research, however, has revealed that certain ICI-treated individuals exhibit aberrant reactions, such as fast disease development and accelerated proliferation of tumor cells, with unfavorable results. Hyper-progressive disease (HPD) is the term for these unanticipated adverse events (AEs), and their prevalence indicates that ICIs may be detrimental to a subset of cancer patients. The prevalence of HPD in NSCLC patients is 8%–21% and the mechanism is unclear [166]. EGFR amplification, KRAS mutations, MYC amplification, and EGFR exon 20 insertions have been reported to be involved in HPD in NSCLC [167,168]. In conclusion, Since HPD is a new phenomenon, its underlying mechanisms are still unknown. Additional research should be done on the clinical significance and predictors of HPD. In addition to offering chances and challenges for the creation of cutting-edge cancer biotherapies, HPD will promote studies aimed at enhancing the effectiveness and safety of ICI. Thorough research on this matter is necessary to shield cancer patients from the potentially dangerous side effects of immune checkpoint inhibitor therapy.

7. Summary and prospect

7.1. Summary

For many years, NSCLC patients have been able to get treatment with small molecule inhibitors of EGFR kinase. EGFR-TKI is considered to be the prior therapy strategy in advanced NSCLC with EGFR mutation, which significantly prolongs the survival time and improves the outcome. Currently, NSCLC patients with EGFR mutations in various clinical stages can be treated with one of three generations of EGFR-TKIs that have been approved. In patients with advanced NSCLC who had Ex19del and L858R mutations, the first-generation EGFR-TKIs (gefitinib, erlotinib) and the second-generation (afatinib, dacomitinib) demonstrated notable therapeutic improvements. Despite the fact that both first- and second-generation EGFR-TKIs

provide initial, successful responses, many patients acquire drug resistance during or within 9–14 months of starting EGFR-TKI treatment. Osimertinib is a novel irreversible third-generation EGFR-TKI selective medication that exhibits selectivity against T790M resistant mutations as well as EGFR-sensitized mutations. Because the penetrating power of BBB is higher than that of other EGFR-TKI, it shows significant clinical activity against central nervous system metastasis. Osimertinib's high efficacy, excellent safety profile, and decent tolerability make it the drug of choice for patients with EGFR mutant NSCLC at the moment.

But like with early EGFR-TKI, Osimertinib resistance is unavoidable. The resistance mechanisms are complex processes that can be divided into two main categories: EGFR-dependent and EGFR-independent pathways, the most prevalent of which is the tertiary EGFR-C797S mutation. The coexistence of many drug resistance mechanisms and their ongoing evolution make it more challenging to develop successful treatment plans and result in subpar response, so it is urgent and indispensable to develop drugs to overcome this thorny challenge. To address the issue of resistance mechanisms in NSCLC, a number of combination therapies combining third-generation EGFR-TKIs have been presented. Potential treatments include immunotherapy, platinum chemotherapy, and targeted therapy based on recognized mechanisms of drug resistance. Furthermore, to address the challenge of double or triple mutations (Ex19del/L858R ± C797ST790M), several fourth-generation EGFR-TKIs (EAI045/BLU-945/TQB3804/BBT-176/JNJ-61186372) have been developed as a potential solution.

7.2. Possibility of the application of DNA repair inhibitors in NSCLC

In cancer treatment, DNA double-strand breaks (DSBs) are the most damaging type of damage; an unrepaired DSB is sufficient to cause cell death. When replication stress and endogenous DNA damage increase, malignant cells typically have a decreased capacity for DNA repair. As a result, cancer cells that proliferate too quickly depend on effective DSB repair to survive. Furthermore, increased DSB repair capacity is a significant contributor to radiation and chemical resistance, as well as the eventual recurrence of cancer. A paradigm of DNA repair targeted therapy has emerged for cancers exhibiting mutations in the BRCA1 or BRCA2 tumor suppressor genes. This approach selectively targets tumor cells that are unable to repair double-strand breaks (DSB), thereby inhibiting poly(ADP-ribose) polymerase (PARP) activity and inducing synthetic lethality of mutant BRCA1/2 cancers. Four distinct PARP inhibitors (PARPi; olaparib, rucaparib, niraparib, and talazoparib) have been approved as monotherapies for BRCA-mutant or platinum-sensitive recurrent ovarian cancer and/or BRCA-mutated HER2-negative metastatic breast cancer. Clinical studies have shown the efficacy of synthetic lethal approaches [169]. Targeted drugs are known to cause genomic instability of tumor cells, but at the same time, they also promote DNA repair of tumor cells after DSB, introducing new mutations to produce drug-resistant mutation sites, providing new options for tumor resistance and drug resistance. We hypothesize that if targeted drugs are used along with inhibitors of DNA repair, it can reduce repair after DNA breakage, promote greater tumor death

and reduce new mutations due to repair. This is an area full of opportunities, and the use of DNA repair inhibitors in NSCLC should be better explored in the coming years.

7.3. Prospect

In clinical molecular testing, effective and accurate detection of EGFR mutations, thus enabling patients to receive targeted therapy organically, is critical. Extensive testing of exon 18–21 of the EGFR tyrosine kinase region is recommended, preferably using second-generation sequencing technology, to detect all mutations of defined or potential clinical significance. For patients with NSCLC treated with EGFR-TKI, tissue biopsy (if feasible) is recommended to assess possible histopathologic changes toward resistance mechanisms. If tissue samples are not available, blood testing for circulating tumor DNA (cfDNA) is also valuable to identify EGFR mutations and some mechanisms of resistance after initial diagnosis and resistance. Concurrent PD-L1 and other biomarker testing is recommended for rapid typing in the absence of targetable mutations. Next-generation sequencing (NGS) of tissue or plasma/blood (e.g., no tissue samples) is recommended over EGFR gene testing alone to detect mutations in EGFR and other targetable genes. Rare EGFR mutations common in NSCLC have unclear biological clinical relevance in clinical practice, and therefore NGS is often used.

Liquid biopsy, as a minimally invasive tool, can provide insights into the molecular heterogeneity of tumor clonal evolution and effective drug resistance mechanisms, which may be very helpful in developing more appropriate therapeutic strategies. Longitudinal surveillance of NSCLC patients by ctDNA or CTC analysis can provide valuable information on clinical outcomes during Osimertinib treatment. Therefore, some guidelines recommend liquid biopsy as part of standard treatment in addition to tissue biopsy in the case of advanced NSCLC.

It’s interesting to note that distinct response rates to EGFR TKI were reported by mutations located at the same position in the genomic DNA. In the structural domain of the EGFR tyrosine kinase, compound mutations were characterized as double or multiple independent mutations containing EGFR TKI-sensitive mutations or other recognized mutations together with uncertain clinical significance. The possibility of finding atypical and compound mutations in the structural domains of EGFR tyrosine kinases in about 20% of the same tumor samples has increased due to advancements in tumor genotyping techniques. The biology and clinical relevance of these uncommon compound mutations require further investigation and cooperation.

In conclusion, a great deal of research has shown how well EGFR-TKIs work in combination with other treatment agents. However, the limited amount of data available on these combination strategies is currently insufficient to support their inclusion in clinical practice guidelines. Despite this, the use of combination therapies remains a promising avenue for improving treatment outcomes in patients with NSCLC and addressing the challenges posed by resistance mechanisms.

To thoroughly investigate the possibilities of these treatments and demonstrate their effectiveness in clinical settings, more investigation is required. The efficacy and safety of several therapy combinations have been investigated in an exciting number of clinical trials, and we anticipate interesting outcomes from these trials.

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