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The Research Progress and Mechanism of Action of Gefitinib and Osimertinib in Non-small Cell Lung Cancer

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Abstract. Gefitinib is a first-generation tyrosine kinase inhibitor (TKI) that targets the epidermal growth factor receptor (EGFR). It works by competitively blocking adenosine triphosphate (ATP) from binding to the kinase domain of active EGFR mutants—most often exon 19 deletions and the L858R point mutation. This blockage ultimately shrinks tumors significantly and extends progression-free survival (PFS) in patients with EGFR-mutant cancer. In contrast, osimertinib is a third-generation, irreversible EGFR TKI. It is designed to form a strong bond with the cysteine-797 (Cys-797) residue in EGFR's ATP-binding pocket. Its unique structure lets osimertinib powerfully inhibit both "sensitizing" EGFR mutations (like exon 19 deletions and L858R) and the T790M mutation—which is a common cause of resistance to first-generation EGFR TKIs. Also, osimertinib is more selective for mutant EGFR than for wild - type EGFR (wtEGFR). This indicates that it has a safer profile, particularly with fewer and less severe skin and gastrointestinal side effects, which are common problems associated with first - generation EGFR TKIs. This review consolidates key research progress, different working mechanisms, clinical effectiveness, and new resistance patterns of gefitinib and osimertinib. It specifically focuses on how they are utilized to treat EGFR - mutant non - small cell lung cancer (NSCLC).

Keywords: non-small cell lung cancer, Gefitinib, Osimertinib, Epidermal Growth Factor Receptor (EGFR)

1. Introduction

Non-small cell lung carcinoma (NSCLC) stands as the predominant histological subtype of lung cancer globally, with over a million new diagnoses annually worldwide [1]. In China, lung cancer ranks first in both incidence and mortality among all malignant neoplasms, and NSCLC accounts for over 80% of all lung cancer cases. Notably, NSCLC—especially the adenocarcinoma subtype—is frequently driven by oncogenically activating mutations in the Epidermal Growth Factor Receptor (EGFR) gene, with common variants including exon 19 deletion mutations and the L858R point mutation.

Prior to the advent of targeted therapeutic strategies, clinical management options for NSCLC were relatively limited. The mainstay of treatment was conventional chemotherapy, which provided only modest clinical benefits. The identification of EGFR mutations represented a paradigm shift in

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NSCLC therapy, fundamentally changing the treatment landscape and spurring the research and development of EGFR tyrosine kinase inhibitors (TKIs) [2].

As a first-generation EGFR TKI, gefitinib has demonstrated notable clinical efficacy in the management of EGFR-mutant NSCLC. In comparison to first-line platinum-based chemotherapy (e.g., cisplatin or carboplatin combinations), gefitinib not only enhances objective response rates (ORRs) to the range of 65%–90% and prolongs progression-free survival (PFS) but also exhibits substantial activity in the central nervous system (CNS)—a property that was pivotal in establishing EGFR-targeted therapy as the standard first-line treatment for this patient population [2]. Despite this success, acquired resistance eventually emerges in nearly all cases, with the T790M "gatekeeper" mutation in exon 20 being the primary mediating mechanism; this mutation limits the durability of disease remission and poses a major clinical challenge [2]. This unmet therapeutic need has spurred the development of third-generation EGFR TKIs, which are specifically designed to inhibit EGFR harboring the T790M mutation while sparing wild-type (WT) EGFR—an attribute intended to reduce treatment-related toxicities [3].

To address T790M-mediated drug resistance, third-generation EGFR TKIs—with osimertinib as the prototype—have been timely introduced into clinical practice. Osimertinib selectively targets the T790M mutation and exerts minimal effects on WT EGFR [4]. Classified as an oral, irreversible third-generation EGFR TKI, osimertinib was initially approved for the treatment of NSCLC patients with confirmed EGFR T790M mutations; it has since evolved into a cornerstone targeted therapy for the majority of EGFR-mutant lung cancer cases [5]. Nevertheless, similar to other TKIs, osimertinib resistance has become increasingly evident as research and clinical trial data continue to accumulate. Due to the complex and diverse drug resistance mechanisms induced by EGFR mutations, all patients ultimately face disease progression [6].

Studies have confirmed that certain specific oncogenes, after undergoing mutations, can become effective drug targets. This is primarily attributed to the phenomenon of "oncogene addiction" — where the growth and survival of certain tumors are highly dependent on a key oncogenic protein or signaling pathway [7]. Such oncogenic mutations encompass various types, with activation mutations in the KRAS and EGFR genes being the most common in non-small cell lung cancer (NSCLC) [8]. Figure 1 illustrates the specific distribution of these mutations. In recent years, multiple EGFR tyrosine kinase inhibitors have been developed, among which gefitinib and osimertinib are the most widely used in clinical practice, with the most extensive research conducted on them.

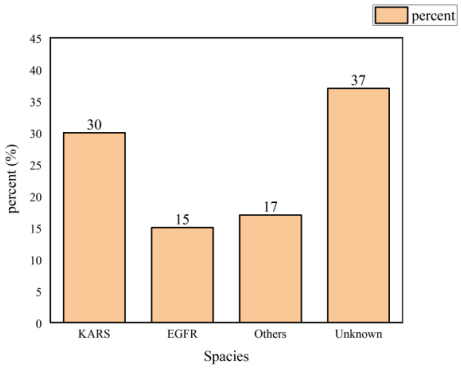

Figure 1. Driver oncogenic mutations in NSCLC [8]

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Upon ligand binding, EGFR forms dimers with other EGFR or HER family members and undergoes self-phosphorylation at key tyrosine sites, thereby initiating downstream signaling pathways. These pathways regulate various cellular life activities, including proliferation, survival, and apoptosis [9]. In epithelial-derived tumors such as non-small cell lung cancer (NSCLC), colorectal cancer, head and neck cancer, and pancreatic cancer, EGFR signaling is often abnormally activated, promoting uncontrolled tumor growth and survival. The primary mechanisms of resistance to EGFR-targeted therapy are twofold: one is termed secondary or acquired resistance, where new molecular mutations emerge after initial treatment efficacy or disease stabilization, driving resistance; the other is primary or intrinsic resistance, which is relatively rare and arises from pre-existing resistant clones that are selected and rapidly proliferate during early treatment [6,9].

In this review, we will elaborate on the mechanisms of action of these two drugs and the progress of research on drug resistance.

2. Disease

Non-small cell carcinoma accounts for about 85% of lung cancer [10]. Detailed pulmonary symptoms of non-small cell carcinoma are shown in Figure 2 and Figure 3.

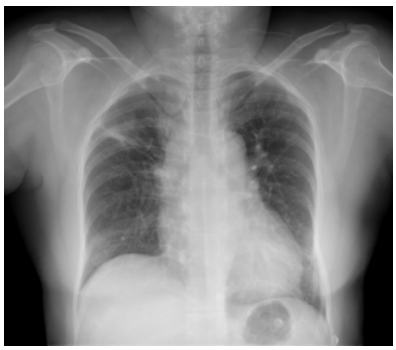

Figure 2. The patient's chest X-ray (photo courtesy of Radiopaedia, case courtesy of Ben Chan, Radiopaedia.org, rID: 161046.)

In the right upper lobe, a mediastinal shadow is seen adjacent to the small fissure of the elevation. A mass is seen in the right hilum and mediastinum, with a right diaphragmatic bulge and an enlarged heart shape.

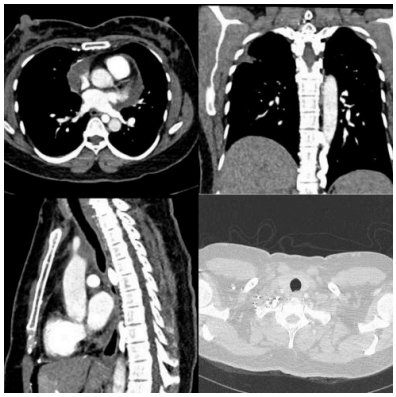

Figure 3. CTPA image of the patient (photo courtesy of Radiopaedia, case courtesy of Ben Chan, Radiopaedia.org, rID: 161046.)

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The patient initially received antibiotic treatment for cough but showed no improvement. Chest X-ray indicated potential malignancy, while CT scans revealed extensive lesions. The right upper lung showed atelectasis with reduced perfusion, along with lymphatic obstruction and/or infiltration. The right diaphragm was elevated due to lung collapse in the upper lobe. The final diagnosis was non-small cell lung cancer (NSCLC), with these symptoms being characteristic manifestations of the disease.

Lung cancer had the highest mortality rate in 2022, with nearly 2.5 million new cases—accounting for one in eight of all new cancer cases worldwide (12.4% of all cancer cases worldwide). Lung cancer is also a major cause of cancer-related deaths, with an estimated 1.8 million people succumbing to it annually (18.7%) [11]. In addition, according to the World Health Organization, lung cancer is far more common and deadly than any other cancer.

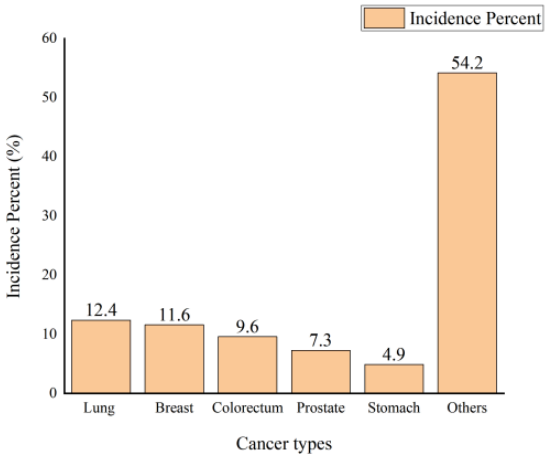

Figure 4. Incidence of different types of cancer worldwide

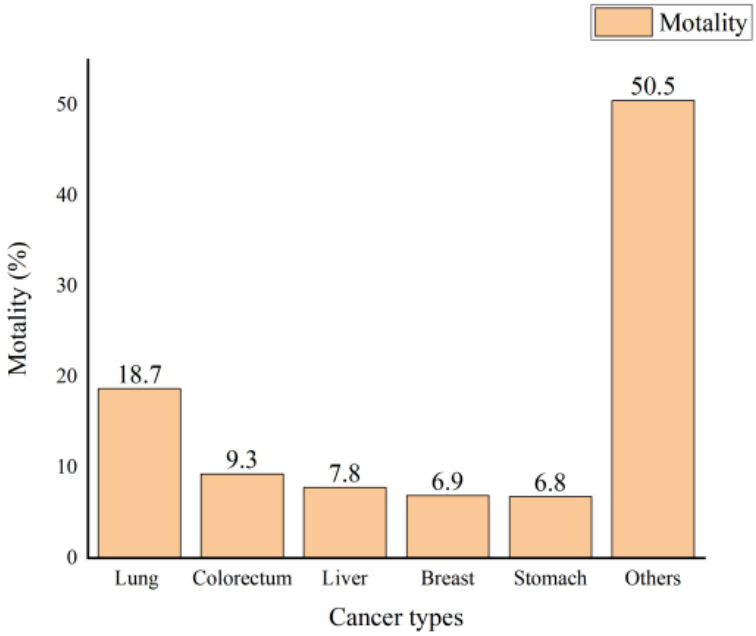

Figure 5. Global mortality rates for different types of cancer

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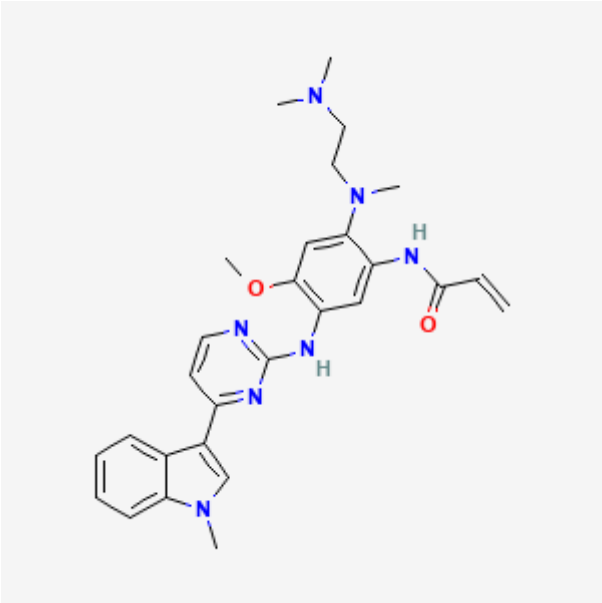
NSCLC leads global lung cancer mortality with 1.8 million annual deaths, posing significant challenges to health and safety worldwide. For China, this presents challenges in medical resource allocation and treatment technology development. Globally, the research on drug resistance mechanisms and therapeutic approaches remains a critical challenge. Simultaneously, these developments may foster international collaboration opportunities in non-small cell carcinoma research.

3. Drugs

With the deepening of research on non-small cell carcinoma, compared with standardized chemotherapy, targeted therapy has been gradually applied in first-line treatment due to its high response rate and specificity. For NSCLC with EGFR activating mutation, EGFR-TKI therapy can be used, and clinical response usually lasts for several months [7]. This article focuses on gefitinib (first-generation TKI) and osimertinib (third-generation TKI), and explains their mechanisms of action and research progress.

3.1. Structure

Both drugs share a quinoline ring core structure, mimicking the purine architecture of ATP to competitively bind to the ATP site in the EGFR kinase domain, thereby establishing selective inhibition of EGFR kinase activity. Unlike gefitinib, osimertinib achieves high-selective irreversible inhibition of the T790M mutation through structural innovations: acrylamide linkage with a mutated adaptive cyanoindole ring, while optimizing pharmacokinetics (enhancing CNS penetration and reducing off-target effects in wild-type EGFR). This breakthrough makes it a paradigmatic third-generation TKI. The structure diagram of the two is as follows.



(a) Gefitinib

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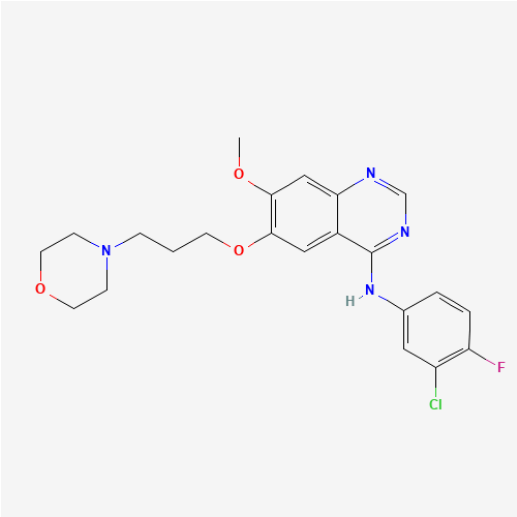

(b) Osimertinib

Figure 6. Structures of gefitinib and osimertinib

3.2. Chemical properties

The difference in chemical properties between the two is shown in Table 1. Based on the aspects outlined in Table 1, we can compare their distinct chemical properties and understand the scientific significance they bring.

Table 1. Chemical properties of gefitinib and osimertinib

Characteristic	Gefitinib (first generation TKI)	Osimertinib (third generation TKI)	Scientific significance
Molecular formula	$C_{22}H_{24}ClFN_4O_3$	$C_{28}H_{33}N_7O_2$	The molecular weight of osimertinib is larger (499.6 vs 446.9 g/mol) and the structural complexity is higher.
logP	4.3	3.8	Gefitinib has higher lipophilicity and wide tissue distribution, but weak brain penetration; osimertinib optimizes logP to balance CNS penetration.
pKa	Alkaline group: morpholine ring (pKa=7.2).	Basic group: pyrimidine nitrogen (pKa=5.6) Acidic group: acrylamide (pKa=9.5).	Oxatinib's ionic properties reduce binding to wild-type EGFR and reduce skin toxicity.
Solubility	Water solubility is extremely low (<0.01 mg/mL) and depends on organic solvent solubility.	Low water solubility (0.1-0.2 mg/mL) but still requires preparation optimization.	Both were classified as BCS II (low solubility and high osmolarity), with osimertinib slightly superior → higher oral bioavailability (70% vs 60%).
Bonding mechanism	Reversible hydrogen bonds/hydrophobic interactions.	Irreversible covalent binding (acrylamide-Cys797).	Oxitinib covalent bond → persistent target occupancy, overcoming T790M drug-resistant mutation.
Metabolic pathway	Primarily oxidized by CYP3A4 (to produce O-demethylation metabolites).	CYP3A4/CYP3A5 oxidation + non-enzymatic covalent binding.	The high proportion of non-enzymatic pathway in osimertinib is associated with lower risk of drug interaction.
Blood plasma half-life ($t_{1/2}$)	48 hours	72 hours	Osimertinibhas a longer half-life → Once daily administration can maintain an effective concentration..
Stability	Photo-sensitive (benzene ether bond is easily degradable).	It is thermally stable, but the acrylamide group is easy to polymerize.	Gefitinib should be stored in the dark; osimertinib preparations should be protected from polymerization.

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Gifitinib was approved in 2015 as first-line treatment for EGFR-mutant metastatic NSCLC patients. In the course of historical research and clinical trials, patients treated with gefitinib have shown certain side effects, including rash, diarrhea, and abnormal liver function [7]. The core binding target of gefitinib is the mutant EGFR. Gefitinib is a reversible TKI that reversibly binds to the ATP-binding pocket of epidermal growth factor receptor [12].When resistance is developed, the targets of gefitinib will undergo mutations that lead to its failure, such as T790M mutation and MET amplification.

3.3. Mechanism

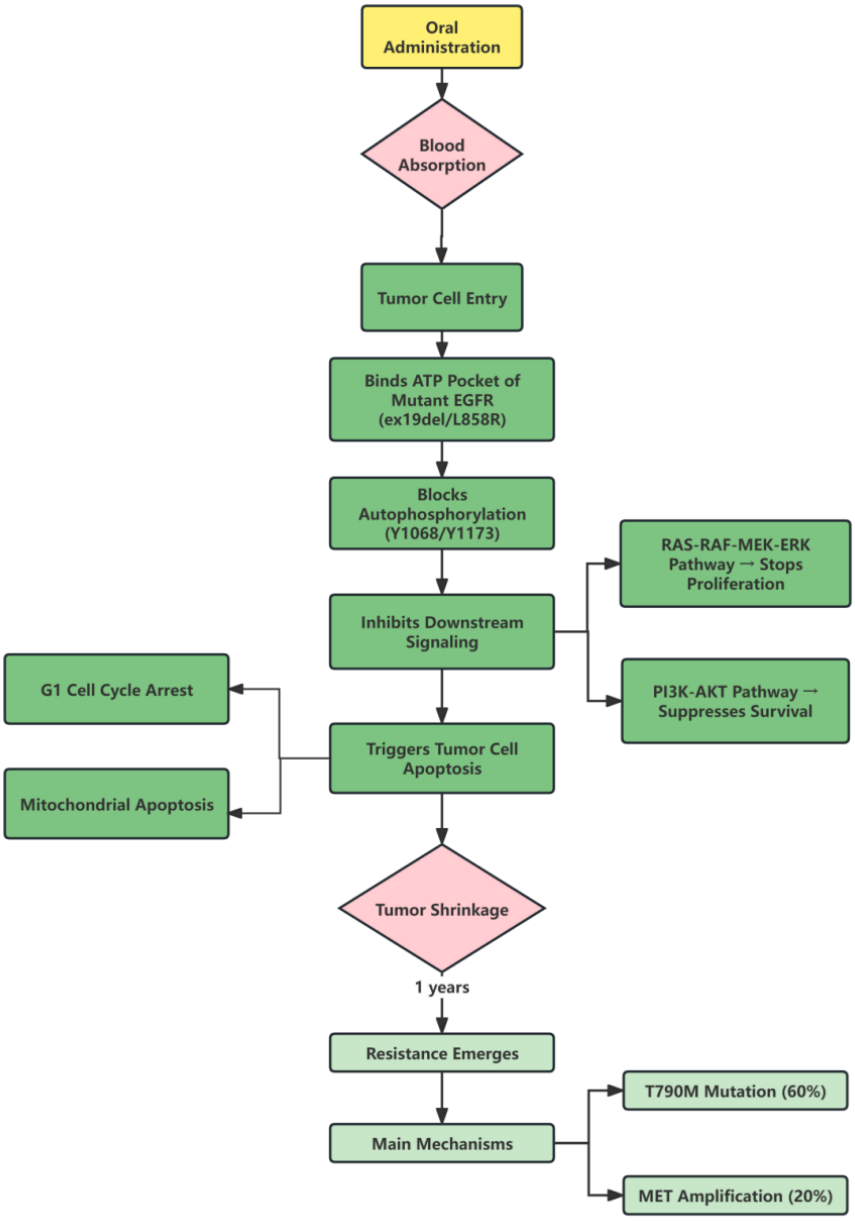

Figure 7. The action pathway of gefitinib

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Compared with gefitinib, osimertinib overcomes T790M-mediated drug resistance by targeting the T790M mutation, while having little effect on the wild-type epidermal growth factor receptor (WT EGFR) [4]. The treatment has definite efficacy for advanced NSCLC patients with first-line epidermal growth factor receptor-TKI resistance, and the incidence of adverse reactions is low and tolerable [13].

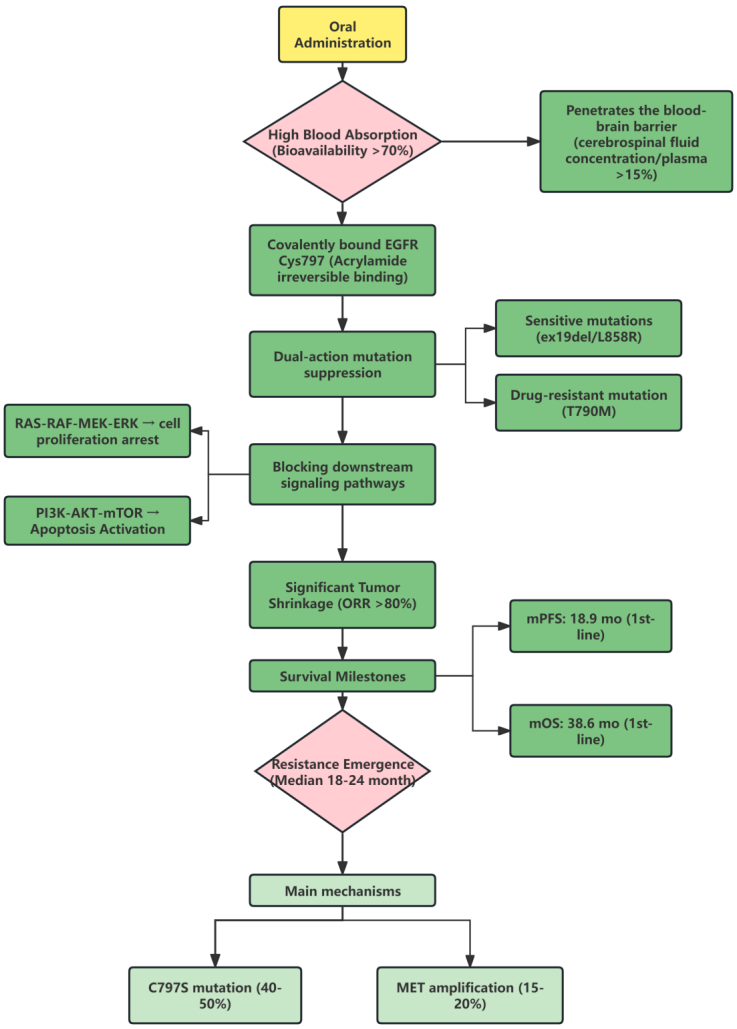

Figure 8. The path of action of osimertinib

As shown in Figures 7, the target of gefitinib is EGFR. The mechanism of gefitinib's action on this target involves competitive inhibition and signal blockage. Its quinoline ring in the molecular structure specifically binds to the ATP-binding pocket of the EGFR cell's tyrosine kinase domain, competing with ATP to inhibit the enzyme's activity [14]. This blocks its self-phosphorylation and downstream signaling pathways. The inhibitory effect is particularly pronounced in EGFR variants carrying sensitive mutations such as exon 19 deletion or L858R point mutation — Mutated EGFR can persistently activate downstream pathways without ligand binding, leading to tumor cell proliferation. Gefitinib effectively blocks this abnormal signaling pathway, thereby suppressing tumor growth, inducing apoptosis, and reducing angiogenesis to exert its antitumor effects. However, gefitinib also weakly inhibits wild-type EGFR, which may explain its potential to cause

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adverse reactions like skin rashes and diarrhea (as wild-type EGFR maintains normal physiological functions in skin and gastrointestinal mucosa).

And in Figure 8, Osimertinib (third-generation EGFR-TKI) targets mutated subtypes of the EGFR, primarily including two categories:

EGFR-sensitive mutations (e.g. exon 19 deletion, L858R point mutation) and T790M drug-resistant mutations (common resistance mechanisms after first/second-generation TKI treatment).

EGFR acts as a tyrosine kinase receptor whose mutant forms trigger sustained activation of downstream signaling pathways abnormal signaling via the RAS-RAF-MEK-ERK axis enhances cellular proliferation and the PI3K-AKT-mTOR pathway inhibits apoptosis the combined effect drives uncontrolled tumor growth osimertinib exerts antagonistic effects on this oncogenic signaling through structurally selective irreversible inhibition its acrylamide moiety forms a covalent bond with the C797 cysteine residue in the EGFR kinase domain to achieve permanent suppression of tyrosine kinase activity the drug's polycyclic framework containing indole and pyrimidine rings confers distinct steric selectivity this structural characteristic allows osimertinib to evade interference from the T790M mutation and realize specific inhibition of T790M-mutant EGFR its inhibitory potency against sensitive mutant EGFR is several hundred-fold higher than that against the wild-type receptor [15]. Osimertinib's selective action effectively blocks downstream signaling of mutant EGFR to inhibit tumor proliferation and induce apoptosis and greatly reduces the impact on wild-type EGFR which undertakes essential physiological functions in normal tissues such as the skin and gastrointestinal tract this results in a significant reduction in adverse reactions including rash and diarrhea in addition the lipophilicity of the compound enables efficient blood-brain barrier penetration and effective suppression of mutant EGFR in brain metastases thus expanding its potential clinical applications.

4. Conclusion

As treatment modalities mature, targeted therapy has become a crucial option in the management of non-small cell lung cancer. The third-generation drug osimertinib has gained widespread clinical recognition for its efficacy and safety advantages. However, nearly all patients eventually develop resistance to these drugs, a phenomenon that has hindered treatment progress for EGFR-mutated NSCLC. Consequently, developing novel therapies capable of overcoming drug resistance has become an urgent priority in both clinical practice and research.

Researchers have reported tangible progress in the development of fourth-generation inhibitors aimed at the triple-mutated EGFR, where early clinical data already signal therapeutic promise. Moving forward, continued advances in this area are likely to yield expanded regimens and meaningful clinical gains for patients with osimertinib-resistant lung cancer — ultimately paving the way toward better survival and quality of life.

Current third-generation EGFR-TKIs rarely sustain patients beyond two years without progression, nor do they meaningfully extend overall survival compared to earlier treatments [16]. That reality has spurred growing interest in combination approaches—researchers are testing novel drug partners in hopes of forestalling resistance, deepening responses, and stretching the window of clinical benefit.

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