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Review Article

Research progress of EGFR-TKI resistance mechanism and treatment strategy in non-small cell lung cancer

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Abstract: Epidermal growth factor receptor (EGFR) activating mutations are pivotal driver alterations in non-small cell lung cancer (NSCLC), with a markedly higher prevalence in Asian populations, female patients, and never-smokers relative to other subgroups. EGFR tyrosine kinase inhibitors (TKIs) have been established as the first-line standard-of-care therapy for EGFR-mutant NSCLC. The third-generation agent osimertinib significantly improves survival outcomes, with a confirmed median progression-free survival (PFS) of 18.9 months in the first-line setting based on the FLAURA pivotal trial. Nevertheless, acquired resistance universally develops within a finite treatment period, and primary resistance occurs in a subset of patients, collectively constituting the major clinical bottleneck limiting durable therapeutic benefits. EGFR-TKI resistance is characterized by substantial complexity and inter- and intra-tumoral heterogeneity, driven by a spectrum of genetic and non-genetic adaptive mechanisms. Notably, distinct resistance mechanisms differ substantially in clinical actionability, defined as the feasibility of clinical detection, availability of targeted therapeutic options, and potential for clinical translation. Existing review studies mainly categorize EGFR-TKI resistance based on genetic mutation types but fail to integrate clinical practicality, resulting in ambiguous hierarchical logic and limited clinical guiding value. To address this gap, the present review systematically reorganizes and classifies EGFR-TKI resistance mechanisms strictly based on clinical actionability and intervention feasibility, constructing a standardized three-tier hierarchical framework: clinically actionable core resistance mechanisms with mature clinical intervention regimens, potentially actionable auxiliary mechanisms with preclinical evidence but limited clinical validation, and refractory primary resistance mechanisms without routine effective intervention strategies. Specifically, core actionable mechanisms include EGFR on-target secondary mutations and compensatory bypass pathway activation, which are well-validated in clinical cohorts and correspond to mature targeted therapies; potentially actionable mechanisms cover tumor phenotypic transformation, metabolic reprogramming, epigenetic modification, autophagy dysregulation, and tumor microenvironment abnormalities, all of which are supported by robust preclinical data but lack large-scale prospective clinical verification; refractory primary resistance is attributed to inherent tumor genetic backgrounds and host individual factors that currently cannot be effectively targeted in routine clinical practice. On the basis of this hierarchical classification, we further correlate each tier of resistance mechanisms with corresponding targeted therapeutic strategies, including next-generation EGFR-TKIs, pathway-specific combination targeted therapy, novel translational therapeutics, metabolic intervention, and traditional Chinese medicine (TCM)-derived natural product adjuvant therapy. This study aims to clarify the hierarchical logical relationship of heterogeneous EGFR-TKI resistance mechanisms, provide evidence-based references for individualized post-resistance clinical decision-making, and offer feasible directions for subsequent translational research and therapeutic optimization.

Keywords: Non-small cell lung cancer, epidermal growth factor receptor, tyrosine kinase inhibitor, drug resistance mechanism, clinical actionability, therapeutic strategy

Introduction

Lung cancer ranks first in global cancer-related morbidity and mortality, bringing a severe economic and medical burden to the global healthcare system [1, 2]. As the dominant pathological subtype, non-small cell lung cancer (NSCLC) accounts for approximately 85% of all lung can-

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cer cases, among which lung adenocarcinoma is the most common subtype with a continuously increasing incidence year by year [3]. Activating mutations of the epidermal growth factor receptor (EGFR) gene are the core oncogenic driver of lung adenocarcinoma, with distinct population specificity. The EGFR mutation rate in Asian advanced NSCLC patients is as high as 45%, far exceeding that in European and American populations (14.1%); the mutation rates in female patients (43.7%) and non-smokers (49.3%) are also significantly higher than those in males (24.0%) and smokers (21.5%) [4, 5]. Continuous activation of EGFR signaling drives the malignant proliferation, differentiation and invasion of tumor cells, which is the key molecular basis for the occurrence and progression of lung adenocarcinoma. EGFR tyrosine kinase inhibitors (EGFR-TKIs) have revolutionized the therapeutic landscape of EGFR-mutant NSCLC. Compared with conventional platinum-based chemotherapy, EGFR-TKIs exhibit superior target specificity, favorable safety profiles, and sustained clinical efficacy, effectively prolonging patient survival and improving quality of life [6]. The phase III FLAURA trial confirmed that first-line osimertinib yields a median PFS of 18.9 months, significantly outperforming first-generation EGFR-TKIs. However, clinical cohort data demonstrate that most patients develop acquired resistance after 9-14 months of continuous TKI treatment, while approximately 10%-15% of patients present inherent primary resistance, which remains the predominant obstacle to long-term disease control in EGFR-TKI therapy [7]. Existing studies have confirmed that EGFR-TKI resistance is a multi-factor, networked regulatory process rather than a single genetic variation event, involving genetic mutation, metabolic remodeling, epigenetic modification and tumor microenvironment remodeling [8]. It is worth noting that most current reviews classify resistance mechanisms only based on genetic characteristics, lacking clinical orientation and hierarchical logic based on clinical actionability. Different resistance mechanisms differ greatly in clinical detectability, targeted intervention feasibility and therapeutic response, which is the core basis for clinical individualized treatment decision-making. Therefore, this review innovatively constructs a hierarchical classification framework of EGFR-TKI resistance mechanisms centered on clinical actionability, divides resistance mechanisms into clinically actionable core mechanisms, potentially actionable auxiliary mechanisms, and refractory primary resistance mechanisms, systematically summarizes the latest research progress of each tier of mechanisms, and matches corresponding precise treatment strategies. The study aims to standardize the clinical cognition of EGFR-TKI resistance, optimize post-resistance comprehensive intervention schemes, and provide theoretical reference for improving the long-term prognosis of EGFR-mutant NSCLC patients.

Hierarchical classification of EGFR-TKI resistance mechanisms

Based on Clinical Actionability Combined with clinical detectability, mature intervention means and clinical transformation potential of different resistance mechanisms [9]. This study divides EGFR-TKI resistance mechanisms into three hierarchical categories from the perspective of clinical actionability: (1) Clinically actionable core resistance mechanisms, with clear mutation targets and mature targeted treatment regimens, which are the main causes of clinical treatment failure and the key objects of routine clinical intervention; (2) Potentially actionable auxiliary resistance mechanisms, with clear regulatory pathways and emerging therapeutic targets, but most intervention schemes are in preclinical or early clinical research stage, with certain clinical transformation potential; (3) Refractory primary resistance mechanisms, inherent biological characteristics of tumors or patients, lacking mature targeted intervention measures, which are the main causes of poor clinical efficacy of initial TKI treatment [10]. The hierarchical logical framework covers all resistance types and realizes the precise docking of “mechanism classification - clinical value - intervention feasibility”.

Clinically actionable core resistance mechanisms (mature clinical intervention value)

This tier of mechanisms is the most common cause of EGFR-TKI acquired resistance in clinical practice, with clear molecular targets, mature detection technologies and standardized targeted treatment schemes, which are the core focus of current clinical resistance intervention. It is divided into EGFR-dependent

on-target mutation resistance and EGFR-independent bypass pathway activation resistance, two classic and clinically verifiable resistance modes.

EGFR-dependent on-target mutation resistance: On-target resistance is caused by secondary mutations in the EGFR kinase domain, which directly changes the drug-target binding state. It has the highest clinical detection rate and the most mature corresponding therapeutic drugs, belonging to the first-tier clinically actionable resistance mechanism. The mutation spectrum presents obvious iterative characteristics with the update of TKI generations, forming a typical "drug pressure - mutation evolution - resistance occurrence" clinical rule. T790M mutation (resistance to first/second-generation EGFR-TKIs): The EGFR exon 20 T790M secondary mutation is the dominant acquired resistance mechanism for first- and second-generation EGFR-TKIs (gefitinib, erlotinib, afatinib), accounting for approximately 60% of resistance cases in large clinical cohorts [11, 12]. The substitution of threonine with methionine at the 790 residue alters the spatial conformation of the EGFR kinase domain, elevating ATP-binding affinity and competitively displacing reversible TKIs from the ATP-binding pocket. This structural change abrogates the inhibitory effect of early-generation TKIs and sustains constitutive EGFR signaling activation, ultimately leading to drug resistance [13, 14]. As the most well-characterized clinically actionable resistance biomarker, T790M can be reliably detected via tissue biopsy or liquid biopsy (circulating tumor DNA), and osimertinib is the standardized first-line therapeutic option for T790M-positive resistant patients. C797S mutation (resistance to third-generation EGFR-TKIs): The EGFR exon 20 C797S mutation is the most prevalent on-target resistance alteration following first-line osimertinib treatment, detected in approximately 7% of osimertinib-resistant clinical cases [15]. Osimertinib exerts its anti-tumor activity via covalent binding to the cysteine residue at position 797 of the EGFR kinase domain. The C797S substitution eliminates this covalent binding site, completely abolishing osimertinib-mediated EGFR inhibition and resulting in irreversible acquired resistance [16]. Currently, multiple fourth-generation EGFR-TKIs targeting C797S mutation are under preclinical and early-phase clinical investigation, showing preliminary anti-tumor potential, yet none have been approved for routine clinical use. Rare EGFR kinase domain mutations and exon 20 insertion mutations: A spectrum of rare secondary EGFR kinase domain mutations, including G796R/D, L718Q/V, L792F/H/Y, and G724S, have been identified in osimertinib-resistant patients, with individual mutation frequencies lower than 3% [17]. These mutations impair drug binding through distinct structural mechanisms: solvent-front mutations (G796R/D, L792F/H/Y) induce steric hindrance, L718Q/V alters the electrostatic microenvironment of the drug-binding pocket, and G724S disrupts kinase domain hydrophobic stability, all of which reduce osimertinib affinity. EGFR exon 20 insertion mutations are predominantly associated with primary resistance, while a small proportion emerge as acquired resistance alterations, conferring intrinsic low sensitivity to all clinically approved EGFR-TKIs [18, 19]. Mobocertinib has been conditionally approved for EGFR exon 20 insertion-mutant NSCLC, providing a targeted option for this patient subgroup, though its efficacy is limited compared with canonical EGFR-sensitive mutations (**Table 1**; **Figure 1**).

EGFR-independent bypass pathway activation resistance: When EGFR signaling is completely inhibited by TKIs, tumor cells activate alternative survival signaling pathways to bypass EGFR dependence, resulting in drug resistance. This type of mechanism has a clinical detection rate second only to on-target mutations, and has mature targeted combination therapy schemes, which is another core clinically actionable resistance mechanism. MET amplification/overexpression: MET pathway activation is the most common EGFR-independent bypass resistance mechanism, detected in 15%-20% of EGFR-TKI-resistant clinical specimens [20, 21]. MET receptor tyrosine kinase activation triggers downstream PI3K-AKT and MAPK-ERK signaling cascades, which independently sustain tumor cell proliferation, survival, and anti-apoptotic signaling despite effective EGFR blockade. The phase III SACHI clinical trial validated that osimertinib combined with savolitinib yields significantly prolonged PFS in patients with MET amplification-mediated EGFR-TKI resistance with a manageable safety profile, establishing this combination as a standardized clinical

Table 1. Standardized summary of EGFR-dependent on-target resistance mechanisms

Resistance classification	Representative molecular event	Type of evidence	Clinical context & Incidence	Feasible clinical detection method	Candidate therapeutic strategy	Level of evidence
1st/2nd-generation EGFR-TKI acquired resistance	EGFR T790M secondary mutation	Large-scale clinical cohort sequencing, phase III clinical validation, structural functional verification	Dominant resistance mechanism of 1G/2G EGFR-TKIs; accounts for 60% of all acquired resistance cases	Tissue NGS, liquid biopsy (ctDNA-ddPCR), high-sensitivity gene detection	Osimertinib (standard second-line and first-line approved regimen)	Level I
3rd-generation EGFR-TKI (osimertinib) acquired resistance	EGFR C797S secondary mutation	Clinical cohort sequencing, protein structural biology analysis, preclinical functional verification	Most common on-target resistance alteration after first-line osimertinib treatment; detected in ~7% of osimertinib-resistant NSCLC patients	Tissue NGS, ctDNA NGS (routine clinical detection available)	Fourth-generation EGFR-TKIs (JBJ-04-125-02, TQB3804); ongoing phase I/II clinical trials	Level II
3rd-generation EGFR-TKI acquired resistance	EGFR rare mutations (L718Q/V, L792F/H/Y, G796R/D)	Clinical case series, targeted sequencing, in vitro functional resistance verification	Collective incidence of 2%-5% in osimertinib-resistant populations; individual mutation frequency <3%	Tissue NGS (gold standard); ctDNA NGS for auxiliary screening	Individualized regimens including afatinib re-challenge, dual-target combination therapy; no unified standard regimen	Level II
3rd-generation EGFR-TKI acquired resistance	EGFR G724S mutation	Protein structural modeling, preclinical functional experiments, sporadic clinical case reports	Extremely rare resistance subtype; overall incidence <1% in osimertinib-resistant patients	High-depth NGS detection	EGFR allosteric inhibitors; currently in preclinical research stage	Level III
Primary & acquired multi-generation TKI resistance	EGFR exon 20 insertion mutation	Large clinical cohort analysis, phase III prospective trials, structural biological verification	Accounts for 4%-10% of all EGFR-mutant NSCLC; mainly causes primary resistance, few cases of acquired resistance	NGS, gene fragment length analysis, RT-PCR	Mobocertinib, amivantamab (NMPA/FDA approved for primary resistance); fourth-generation TKIs under clinical exploration	Level I

1G/2G: First-generation/second-generation; ctDNA: Circulating tumor DNA; ddPCR: Droplet digital polymerase chain reaction; EGFR: Epidermal growth factor receptor; FDA: U.S. Food and Drug Administration; NGS: Next-generation sequencing; NMPA: National Medical Products Administration; NSCLC: Non-small cell lung cancer; Phase I/II/III: Phase I (safety), Phase II (efficacy exploration), Phase III (large-scale validation); RT-PCR: Reverse transcription polymerase chain reaction; TKI: Tyrosine kinase inhibitor. Note: Mutations such as T790M, C797S, L718Q, L718V, L792F, L792H, L792Y, G796R, G796D, G724S refer to specific amino acid substitutions at designated positions of the EGFR gene (e.g., T790M indicates substitution of threonine by methionine at position 790).

Drug Resistance Mechanism	Related TKI	Molecular Mechanism
T790M Mutation	First and Second-generation TKI	Enhance EGFR affinity for ATP and weaken TKI competitive inhibition
C797S Mutation	Third-generation TKI (Osimertinib)	Key cysteine is replaced by serine, blocking covalent binding
G796R/D	Third-generation TKI	Steric hindrance or electrostatic repulsion interfere with drug binding
L718Q/V	Third-generation TKI	Change local hydropture and reduce drug affiment
G724S	Third-generation TKI	Affect sugar ring structure
EGFR Exon 20 Insertion	First, Second and Third-generation TKI	Primary drug resistance or low sensitivity

Figure 1. Mechanisms of EGFR-TKI resistance and their molecular basis. ATP: Adenosine triphosphate; C797S: Cysteine-to-serine substitution at position 797 of the EGFR gene; EGFR: Epidermal growth factor receptor; Exon 20: Exon 20 of the EGFR gene; G724S: Glycine-to-serine substitution at position 724 of the EGFR gene; G796R/D: Glycine-to-arginine/aspartic acid substitution at position 796 of the EGFR gene; L718Q/V: Leucine-to-glutamine/valine substitution at position 718 of the EGFR gene; T790M: Threonine-to-methionine substitution at position 790 of the EGFR gene; TKI: Tyrosine kinase inhibitor.

first-line regimen for this specific resistance subtype [22]. Abnormal activation of HER family members: HER2 amplification and HER3 upregulation are recurrent bypass alterations in osimertinib-resistant NSCLC, with higher prevalence in third-generation TKI resistance than early-generation TKI resistance [23, 24]. Additionally, RNA sequencing analysis of erlotinib-resistant lung cancer cells revealed that the transcription factor GRHL2 is significantly upregulated, and its knockdown or knockout markedly reduces erlotinib resistance. Mechanistically, GRHL2 directly upregulates HER3 expression, and HER3 knockdown similarly decreases the IC50 for erlotinib, indicating that the GRHL2-HER3 axis represents a critical bypass mechanism sustaining EGFR-TKI resistance [25]. Dual-targeted agents against EGFR and HER2/HER3 have shown preliminary efficacy in clinical trials, yet large-scale phase III validation is still lacking. Activation of other receptor tyrosine kinases and downstream signaling pathways: Aberrant activation of non-HER receptor tyrosine kinases, including AXL, FGFR, and IGF-1R, drives compensatory survival signaling and contributes to EGFR-TKI resistance, particularly in patients with extensive tumor progression [26]. Downstream of EGFR, somatic mutations in PIK3CA, KRAS, and BRAF constitutively activate PI3K-AKT and MAPK-ERK pathways independent of upstream EGFR signaling. Moreover, dysfunction of negative regulatory factors (loss of PHLPP expression, SHP2 hyperactivation) sustains downstream oncogenic signaling, further exacerbating drug resistance [27]. Combination regimens of EGFR-TKIs with MEK, PI3K, or AKT inhibitors have demonstrated anti-resistance efficacy in preclinical models and early-phase clinical trials, but universal clinical application is limited by toxicity and inconsistent efficacy across patient cohorts (**Table 2**; **Figure 2**).

Potentially actionable auxiliary resistance mechanisms (potential clinical transformation value)

This tier of mechanisms is a non-genetic auxiliary regulatory pathway for EGFR-TKI resistance, which cooperates with core genetic mechanisms to aggravate drug resistance and tumor malignant progression [28]. Although no mature standardized clinical intervention scheme has been formed at present, the key regulatory targets and pathways have been

Table 2. Summary of EGFR-independent resistance mechanisms

Resistance classification	Representative molecular event	Type of evidence	Clinical context & Incidence	Feasible clinical detection method	Candidate therapeutic strategy
Bypass signaling activation	MET amplification/ overexpression	Phase III prospective clinical trial (SACHI), multi-center clinical cohort data, preclinical mechanism verification	Most common EGFR-independent resistance mechanism; 15%-20% of all EGFR-TKI-resistant cases; higher incidence in osimertinib-resistant patients	FISH (gold standard), tissue NGS, ctDNA NGS	Osimertinib combined with savolitinib/capmatinib; standardized clinical first-line combination regimen
Bypass signaling activation	HER2 amplification	Retrospective clinical cohort analysis, in vitro functional verification, phase II clinical exploratory data	Incidence of 2%-5% in EGFR-TKI-resistant NSCLC; more common in third-generation TKI resistance	FISH, tissue NGS, IHC auxiliary detection	Pyrotinib targeted therapy, T-DXd antibody-drug conjugate; approved for other solid tumors, exploratory application in NSCLC
Bypass signaling activation	HER3 transcriptional upregulation	Translational medical research, phase II clinical trial data, preclinical pathway verification	GRHL2-mediated abnormal HER3 expression; frequent emerging bypass alteration in osimertinib-resistant patients	IHC protein quantification, tumor tissue RNA-seq	Patritumab deruxtecan (anti-HER3 ADC); phase II clinical trial confirmed preliminary anti-tumor efficacy
Bypass signaling activation	AXL pathway abnormal activation	Retrospective clinical cohort, preclinical mechanism research, early-phase clinical exploration	Closely correlated with EMT phenotypic transformation; drives persistent TKI resistance in progressive NSCLC	IHC, transcriptome RNA-seq detection	Bemcentinib and other AXL selective inhibitors; ongoing phase I/II clinical trials

ADC: Antibody-drug conjugate; AXL: AXL receptor tyrosine kinase (named from Greek “anexelekto”, meaning uncontrolled); ctDNA: Circulating tumor DNA; EGFR: Epidermal growth factor receptor; EMT: Epithelial-mesenchymal transition; FISH: Fluorescence in situ hybridization; GRHL2: Grainyhead-like transcription factor 2; HER2: Human epidermal growth factor receptor 2; HER3: Human epidermal growth factor receptor 3; IHC: Immunohistochemistry; MET: Mesenchymal-epithelial transition factor receptor; NGS: Next-generation sequencing; NSCLC: Non-small cell lung cancer; Phase I/II/III: Phase I (safety), Phase II (efficacy exploration), Phase III (large-scale validation); RNA-seq: RNA sequencing; T-DXd: Trastuzumab deruxtecan (also known as DS-8201); TKI: Tyrosine kinase inhibitor.

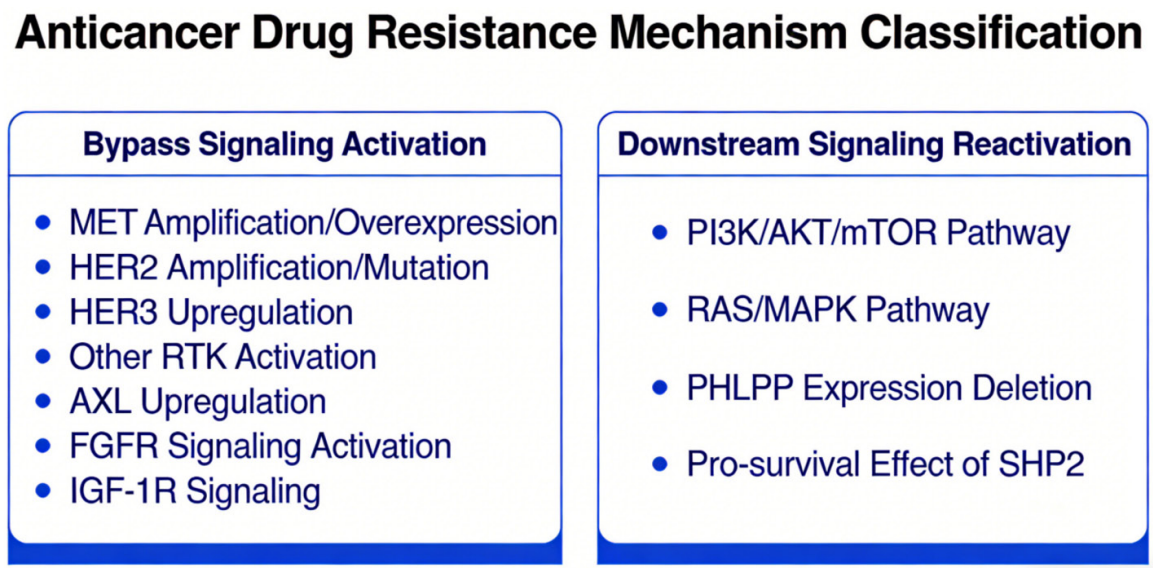

Figure 2. Mechanisms of anticancer drug resistance: bypass signaling and downstream reactivation. AKT: Protein kinase B (PKB); AXL: AXL receptor tyrosine kinase (named from Greek "anexelekto", meaning uncontrolled); FGFR: Fibroblast growth factor receptor; HER2: Human epidermal growth factor receptor 2; HER3: Human epidermal growth factor receptor 3; IGF-1R: Insulin-like growth factor 1 receptor; MAPK: Mitogen-activated protein kinase; MET: Mesenchymal-epithelial transition factor receptor; mTOR: Mammalian target of rapamycin; PHLPP: PH domain leucine-rich repeat protein phosphatase; PI3K: Phosphoinositide 3-kinase; RAS: Rat sarcoma virus oncogene; RTK: Receptor tyrosine kinase; SHP2: Src homology region 2-containing protein tyrosine phosphatase 2.

clarified, and a variety of preclinical intervention means have achieved ideal results, with great potential for clinical transformation in the future. This category includes tumor phenotypic transformation, metabolic reprogramming, epigenetic regulation, autophagy and abnormalities in the tumor microenvironment [29].

Tumor cell phenotypic transformation: Phenotypic transformation is a critical non-genetic adaptive resistance mechanism, mainly encompassing three patterns: epithelial-mesenchymal transition (EMT), histological subtype transformation, and cancer stem cell (CSC) enrichment [29]. Tumor microenvironment-derived cytokines (e.g., IL-6) induce EMT via upregulating the key transcription factor Snail, endowing tumor cells with mesenchymal characteristics, enhanced invasiveness, and TKI tolerance. Histological transformation from lung adenocarcinoma to small cell lung cancer is closely associated with concurrent biallelic inactivation of RB1 and TP53, which renders EGFR-TKIs ineffective and requires conversion to small cell lung cancer-oriented chemotherapy [30]. CSC enrichment is driven by dysregulation of IL-6/STAT3, YAP/TAZ, Hippo, and Wnt/β-catenin pathways, enhancing tumor self-renewal and drug resistance. Preclinical studies have verified that targeting these core regulatory molecules can reverse phenotypic resistance, while clinical validation remains insufficient [31].

Tumor metabolic reprogramming: Under sustained EGFR-TKI treatment pressure, tumor cells undergo adaptive metabolic reprogramming to maintain energy metabolism and redox homeostasis, thereby developing drug resistance [32]. Mechanistically, the m6A reader protein IGF2BP3 stabilizes COX6B2 mRNA to enhance mitochondrial oxidative phosphorylation (OXPHOS) and sustain tumor energy supply. AKR1B1 activates the STAT3-SLC7A11 axis to promote glutathione synthesis, enhancing cellular antioxidant capacity against TKI-induced oxidative damage [33]. Upregulated PHGDH drives serine metabolism reprogramming, and elevated GPX4 inhibits ferroptosis, both of which contribute to TKI resistance. Preclinical studies have confirmed that targeted inhibition of these metabolic pathways effectively reverses resistance, while clinical translational evidence is still limited [34].

Epigenetic regulation: Epigenetic modifications, including m6A RNA modification, non-cod-

ing RNA regulation, DNA methylation, and chromatin remodeling, modulate gene expression without altering DNA sequences, participating in the development of EGFR-TKI resistance [35]. Mechanistically, IGF2BP3-mediated m6A modification regulates the stability of resistance-related mRNA; lncRNA MALAT-1 and LINC01128 modulate downstream PI3K-AKT signaling via miRNA sponging; hypermethylation of the AXIN2 promoter silences its expression and activates the oncogenic Wnt/β-catenin pathway; ARID1A mutation alters chromatin accessibility to dysregulate drug resistance gene transcription [36]. These epigenetic regulatory networks are well-supported by preclinical data, yet no epigenetic targeted agents have been validated for clinical application in EGFR-TKI-resistant NSCLC.

Bidirectional regulation of autophagy: Autophagy exerts a context-dependent dual regulatory effect on EGFR-TKI resistance, which has been consistently validated in preclinical studies [37]. Protective autophagy is activated under TKI stress, which degrades damaged organelles and recycles metabolites to sustain tumor cell survival and aggravate drug resistance; in contrast, excessive autophagic activation triggers autophagic cell death, which can eliminate resistant tumor cells. Preclinical evidence shows that CCDC34 promotes resistance via β-catenin-mediated protective autophagy, while natural compounds (betulinic acid, magnolin) can reverse resistance by modulating autophagic signaling [38]. However, the dual role of autophagy in clinical resistance remains unclear, and targeted autophagy regulation strategies lack clinical cohort verification.

Abnormal tumor microenvironment: The tumor microenvironment (TME) constitutes a complex cellular and cytokine network that mediates EGFR-TKI resistance via multiple crosstalk mechanisms [39]. Cancer-associated fibroblasts secrete IL-6, HGF, FGF, and extracellular vesicles to induce EMT and activate bypass pro-survival pathways. Tumor-associated macrophages release exosomal bioactive substances to reactivate AKT, ERK1/2, and STAT3 signaling, promoting tumor cell drug resistance [40]. These TME-mediated resistance mechanisms are fully supported by preclinical experimental data, but clinical intervention targeting the TME for EGFR-TKI resistance is still in the exploratory stage without mature application schemes.

Refractory primary resistance mechanisms (low clinical actionability, lack of mature intervention)

Primary resistance refers to the lack of clinical response in patients with EGFR-sensitive mutations after initial TKI treatment, which is caused by inherent biological characteristics of tumors and patients. This type of mechanism has no mature targeted detection and intervention scheme at present, with low clinical actionability, and is the main difficult point of current EGFR-TKI clinical treatment. Co-existing inherent mutations: A small subset of EGFR-mutant NSCLC patients harbor concurrent T790M or KRAS mutations prior to TKI treatment, which is a key cause of primary resistance [41]. Retrospective clinical cohort studies have confirmed that patients with baseline compound mutations exhibit significantly shorter PFS and lower objective response rates to first-line EGFR-TKIs compared with patients with isolated EGFR-sensitive mutations [42]. However, the low prevalence of baseline compound mutations limits large-scale clinical validation and standardized targeted intervention strategies. Innate bypass pathway activation: Baseline dysregulation of compensatory signaling pathways contributes substantially to primary EGFR-TKI resistance. PTEN deletion or functional mutation leads to constitutive activation of the PI3K-AKT-mTOR pathway, abrogating EGFR-TKI efficacy. In addition, pre-treatment activation of IGF-1R and NF-κB/STAT3 signaling sustains oncogenic proliferation independent of EGFR activity [43]. Preclinical studies have demonstrated that targeted inhibition of these pathways restores TKI sensitivity, but clinical application is restricted by non-specific toxicity, off-target effects, and lack of prospective clinical trial data. Host genetic polymorphism and individual differences: The BIM intron 2 deletion polymorphism is a population-specific genetic variant predominantly detected in East Asian populations, with a carrier rate of approximately 12.8% in Chinese lung cancer patients [44]. This polymorphism eliminates the pro-apoptotic BH3 isoform of BIM, impairing EGFR-TKI-induced tumor cell apoptosis. Retrospective clinical data show that

Table 3. Classification of EGFR-TKI resistance mechanisms and associated clinical/molecular characteristics

Resistance classification	Representative molecular event	Type of evidence	Clinical context & characteristics	Feasible detection method	Candidate intervention strategy	Level of evidence
Baseline compound mutation	Pretreatment EGFR T790M co-mutation	Retrospective multicenter clinical cohort analysis	Rare baseline subclonal mutation; leads to primary TKI resistance and significantly shortened PFS after first-line TKI treatment	Ultrasensitive ctDNA PCR, high-depth tissue NGS	Early osimertinib intervention; inferior efficacy in baseline compound mutation patients compared with pure sensitive mutation patients	Level II
Baseline bypass pathway dysregulation	PTEN loss/deletion	Clinical cohort correlation analysis, preclinical pathway verification	Incidence of 5%-10% in EGFR-mutant NSCLC; causes persistent PI3K-AKT pathway activation and primary TKI insensitivity	IHC protein detection, FISH, tissue NGS	PI3K/AKT targeted combination therapy; limited clinical efficacy, no standardized regimen	Level III
Baseline bypass pathway dysregulation	NF-κB/STAT3 sustained activation	Preclinical pathway modeling, in vitro cell verification, sporadic clinical correlation	Abnormal baseline activation is closely associated with de novo EGFR-TKI resistance; no large-scale clinical cohort validation	Tissue IHC, intracellular protein phosphorylation detection	Selective NF-κB/STAT3 inhibitors combined with EGFR-TKIs; only preclinical exploratory evidence	Level III
Host genetic polymorphism	BIM intron 2 deletion polymorphism	Population genetic study, meta-analysis, retrospective clinical cohort validation	Carrier rate ~12.8% in Chinese lung cancer patients, ~13% in Asian populations; accounts for 19% of primary resistance cases	Peripheral blood PCR genotyping	BH3 mimetics (navitoclax) combined with TKIs; under clinical exploration, only serves as predictive biomarker currently	Level II
Baseline oncogenic co-mutation	Concurrent KRAS mutation	Large clinical cohort correlation analysis	Present in 25% of TKI-insensitive EGFR-mutant patients; leads to dual oncogenic pathway activation and poor TKI response	Tissue/liquid biopsy NGS	MEK inhibitor combination therapy or chemotherapy conversion; mainly serves as negative prognostic biomarker	Level II
Host individual heterogeneity	Pharmacokinetic variability, systemic immune dysfunction	Clinical observational study, descriptive correlation analysis	Multifactorial host factors; indirectly affect TKI metabolism and tumor microenvironment, leading to unstable treatment efficacy	No routine clinical detection indicators	Individualized therapeutic drug monitoring and supportive care; empirical intervention only	Level III

AKT: Protein kinase B (PKB); BIM: BCL2-like 11 (BCL2-interacting mediator of cell death); ctDNA: Circulating tumor DNA; EGFR: Epidermal growth factor receptor; FISH: Fluorescence in situ hybridization; IHC: Immunohistochemistry; KRAS: Kirsten rat sarcoma viral oncogene homolog; MEK: Mitogen-activated protein kinase kinase; NF-κB: Nuclear factor kappa-light-chain-enhancer of activated B cells; NGS: Next-generation sequencing; NSCLC: Non-small cell lung cancer; PCR: Polymerase chain reaction; PI3K: Phosphoinositide 3-kinase; PTEN: Phosphatase and tensin homolog; STAT3: Signal transducer and activator of transcription 3; TKI: Tyrosine kinase inhibitor.

BIM deletion carriers have an objective response rate of only 25% and a median PFS of 4.7 months under EGFR-TKI treatment, and this variant is an independent prognostic factor for poor treatment response. Additionally, host factors including immune dysfunction and metabolic disorders may indirectly affect TKI efficacy via altering pharmacokinetic profiles or TME status, yet relevant clinical evidence remains sporadic and lacks systematic verification (**Table 3**).

Hierarchical matching treatment strategies for EGFR-TKI

Resistance Based on Clinical Actionability Corresponding to the three-tier resistance mechanism framework of "clinically actionable core - potentially actionable auxiliary - refractory primary", this study matches hierarchical and differentiated clinical intervention strategies, realizing precise docking of resistance mechanism grade and treatment scheme. For core actionable mechanisms, mature targeted precise treatment is the mainstay; for potentially actionable mechanisms, novel auxiliary intervention means are applied; for refractory primary resistance, comprehensive multi-modal combination therapy is adopted to maximize clinical efficacy (**Table 4**).

Targeted intervention for clinically actionable core resistance mechanisms

Aiming at on-target mutations and bypass pathway activation with mature clinical value, we adopt iterative new-generation TKI therapy and pathway-specific combination targeted therapy to realize precise and standardized clinical intervention.

New-generation EGFR-TKI iterative therapy: Novel fourth-generation EGFR-TKIs, represented by JBJ-04-125-02 and TQB3804, are designed to target tertiary EGFR mutations (19del/T790M/C797S, L858R/T790M/C797S) that mediate third-generation TKI resistance [45]. Preclinical studies have demonstrated their potent inhibitory activity against multi-mutant EGFR, while clinical efficacy and safety verification are still ongoing. Mobocertinib is the only approved targeted agent for EGFR exon 20 insertion-mutant NSCLC, providing a dedicated treatment option for this refractory core resistance subtype, though its efficacy is inferior to conventional EGFR-TKIs for canonical sensitive mutations [46]. Collectively, next-generation TKIs fill the therapeutic gap for iterative on-target resistance mutations and represent the most promising frontier for core resistance intervention.

Pathway-specific combination targeted therapy: For bypass pathway-mediated resistance, pathway-specific combined targeted therapy is the most evidence-based clinical strategy [47, 48]. The phase III SACHI study prospectively confirmed that osimertinib plus savolitinib significantly improves PFS in patients with MET amplification-induced EGFR-TKI resistance with acceptable safety, supporting its routine clinical application [22]. For MAPK pathway hyperactivation, combined inhibition of EGFR and MEK exhibits synergistic anti-resistance effects in preclinical and early-phase clinical studies. Novel targeted formulations further expand therapeutic options: the bispecific antibody amivantamab (targeting EGFR/cMet) and ADC drug patritumab deruxtecan have shown promising anti-tumor activity in resistant patients in clinical trials, with breakthrough therapy designations, though long-term efficacy and safety require further validation [49].

Novel auxiliary intervention for potentially actionable auxiliary resistance mechanisms

Aiming at non-genetic auxiliary resistance mechanisms with clinical transformation potential, we adopt emerging therapeutic technologies, metabolic intervention and TCM natural product regulation to reverse drug resistance, which is an important supplementary means of clinical comprehensive treatment.

Novel targeted therapeutic technologies: Proteolysis-targeting chimera (PROTAC) and lysosome-targeting chimera (LYTAC) technologies represent innovative therapeutic modalities that eliminate oncogenic proteins rather than merely inhibiting their activity [50]. Preclinical studies have optimized LYTAC molecular structures to achieve efficient degradation of membrane EGFR proteins. For instance, Li et al. developed a pan-EGFR lysosome-targeting chimera (LY-dE#5) that effectively degraded both wild-type and drug-resistant EGFR mutants (including 19del, L858R/T790M, and 19del/T790M/C797S) in H1975 non-small cell lung cancer cells via IGF2R-mediated lysosomal

Table 4. Treatment strategies

Strategy tier	Specific therapeutic approach	Target/core mechanism	Development status	Key clinical/preclinical evidence	Clinical limitations & challenges	Level of evidence
Tier 1: Clinically mature & guideline-recommended strategies	Osimertinib + savolitinib combination therapy	Dual inhibition of EGFR and MET bypass pathway	Fully approved for clinical routine use (phase III trial positive)	SACHI phase III trial confirmed significant PFS benefit in MET-amplified resistant patients with controllable safety	Only applicable to MET-amplified resistance subtypes; no efficacy for non-MET bypass resistance	Level I
Tier 1: Clinically mature & guideline-recommended strategies	Amivantamab single-agent therapy	Dual-targeting EGFR/c-Met oncogenic signaling	FDA/NMPA approved for EGFR exon 20 insertion mutant NSCLC	Phase III clinical trials verified reliable objective response rate in refractory exon 20 insertion patients	High economic cost; risk of infusion-related adverse reactions; limited efficacy for common sensitive mutations	Level I
Tier 2: Prospective clinical exploratory strategies	Fourth-generation EGFR-TKIs (JBJ-04-125-02, TQB3804)	Targeting tertiary EGFR mutations (19del/T790M/C797S, L858R/T790M/C797S)	Ongoing phase I/II clinical trials	Preclinical studies confirmed potent inhibitory activity against multi-mutant EGFR; early clinical data shows preliminary anti-tumor effect	Immature clinical efficacy and safety data; no large-scale phase III validation	Level II
Tier 2: Prospective clinical exploratory strategies	Patritumab deruxtecan (HER3 ADC)	Targeting HER3 overexpression-mediated bypass resistance	Completed phase II clinical exploration, pending phase III verification	Phase II trials achieved favorable ORR in osimertinib-resistant NSCLC patients with high HER3 expression	Tumor antigen loss easily causes secondary resistance; population applicability needs further screening	Level II
Tier 3: Preclinical exploratory & immature strategies	PROTAC/LYTAC targeted protein degradation technology	Inducible degradation of abnormal EGFR oncoproteins (non-inhibitory mechanism)	Preclinical research stage (in vitro/in vivo model verification)	Preclinical data confirmed over 90% membrane EGFR protein degradation efficiency, effectively reversing TKI resistance	Unresolved in vivo delivery difficulty; potential off-target toxicity; no clinical trial initiation	Level III
Tier 3: Preclinical exploratory & immature strategies	Tumor metabolic targeted therapy (OXPHOS/GPX4 inhibitors)	Blocking tumor adaptive metabolic reprogramming, restoring TKI drug sensitivity	Preclinical mechanism verification stage	Metabolic intervention significantly reverses non-genetic TKI resistance in cell and animal models	Potential normal tissue metabolic toxicity; lack of safe and effective clinical dosage regimens	Level III
Tier 3: Preclinical exploratory & immature strategies	EGFR-TKI combined with PD-1/PD-L1 immunotherapy	Dual regulation of oncogenic signaling and tumor immune microenvironment	Phase I/II trials terminated; not recommended for routine clinical use	Multiple clinical studies confirmed limited survival benefit	Significantly increased risk of severe immune pneumonitis and overlapping organ toxicity	Level III
Tier 3: Preclinical exploratory & immature strategies	TCM natural products & compound adjuvant therapy	Multi-pathway regulation of tumor autophagy, metabolism and immune microenvironment	Pure preclinical research (in vitro cell + in vivo animal experiments)	Active ingredients (liensinine, artesunate) show synergistic anti-resistance effects with TKIs in preclinical models	Low bioavailability, unclear functional components; no high-level clinical evidence support	Level III

ADC: Antibody-drug conjugate; c-Met: Mesenchymal-epithelial transition factor receptor (also known as MET); EGFR: Epidermal growth factor receptor; FDA: U.S. Food and Drug Administration; GPX4: Glutathione peroxidase 4; HER3: Human epidermal growth factor receptor 3; MET: Mesenchymal-epithelial transition factor receptor; NMPA: National Medical Products Administration; NSCLC: Non-small cell lung cancer; ORR: Objective response rate; OXPHOS: Oxidative phosphorylation; PD-1: Programmed cell death protein 1; PD-L1: Programmed death-ligand 1; PFS: Progression-free survival; PROTAC: Proteolysis-targeting chimera; LYTAC: Lysosome-targeting chimera; TCM: Traditional Chinese medicine; TKI: Tyrosine kinase inhibitor.

pathway, demonstrating potent antitumor activity superior to osimertinib [51]. For immunotherapy combination strategies, concurrent administration of EGFR-TKIs and immune checkpoint inhibitors carries overlapping pulmonary and hepatic toxicity risks. Current clinical consensus recommends rigorous patient screening and sequential administration strategies to balance efficacy and safety, while universal combination regimens lack unified clinical validation [52].

Tumor metabolic intervention therapy: Metabolic intervention therapy targets tumor-specific metabolic vulnerabilities induced by resistance reprogramming [53]. Preclinical studies have verified that inhibiting OXPHOS energy metabolism and blocking glutathione synthesis can elevate intracellular oxidative stress, specifically sensitizing resistant tumor cells to EGFR-TKIs. Metabolic intervention exhibits high specificity for non-genetic resistance mechanisms, but most relevant research remains in the preclinical stage, and clinical transformation requires further exploration of safe and effective intervention doses and regimens.

Natural products and TCM compound intervention: TCM-derived natural products and compound formulations exert anti-resistance effects via multi-target and multi-pathway regulation [54]. Natural active ingredients including liensinine and artesunate can restore TKI sensitivity by modulating EGFR downstream signaling, inducing tumor apoptosis and suppressing protective autophagy in preclinical models. TCM compounds improve the immunosuppressive TME and balance tumor metabolic disorders, exerting synergistic anti-tumor effects with targeted therapy. Nevertheless, the low bioavailability and unclear functional components of TCM agents limit clinical application, and high-level clinical evidence supporting their efficacy is currently insufficient.

Multi-modal comprehensive intervention for refractory primary resistance mechanisms

For refractory primary resistance with low clinical actionability and no standardized targeted intervention regimens, single-agent targeted therapy yields limited clinical efficacy. Current clinical management mainly relies on multi-modal comprehensive strategies, including multi-drug combination therapy, chemotherapy conversion, and individualized immunotherapy [55]. Dynamic monitoring of tumor clonal evolution via liquid biopsy guides sequential and alternating treatment regimens to delay disease progression. However, these strategies are empirical and palliative rather than curative, and unified standardized treatment guidelines for refractory primary resistance are still lacking.

Conclusion and future prospects

This review innovatively constructs a three-tier hierarchical framework of EGFR-TKI resistance mechanisms based on clinical actionability, solving the problem of disorganized framework and unclear hierarchical logic in previous studies. We systematically classify resistance mechanisms into clinically actionable core mechanisms (on-target mutations, bypass pathway activation), potentially actionable auxiliary mechanisms (non-genetic regulatory pathways) and refractory primary resistance mechanisms (inherent tumor and host factors), and realize the precise matching of hierarchical mechanisms and clinical intervention strategies, forming a standardized clinical cognition system of “mechanism classification - clinical value - treatment decision-making”. Despite accumulating progress in resistance mechanism research and therapeutic exploration, multiple key challenges remain to be addressed: tumor clonal evolution and spatial-temporal heterogeneity lead to dynamic changes in resistance mechanisms during treatment; combination therapy regimens are prone to overlapping toxicities, making it difficult to balance efficacy and safety; non-genetic auxiliary resistance mechanisms lack mature clinical transformation pathways; refractory primary resistance has no validated targeted intervention strategies; and a substantial translational gap persists between preclinical findings and clinical application. Future research directions will focus on solving the above bottlenecks: first, utilizing liquid biopsy and multi-omics technologies to realize real-time dynamic monitoring of hierarchical resistance mechanisms and tumor clonal evolution; second, constructing artificial intelligence-assisted intelligent decision-making systems based on multi-dimensional biomarkers to guide individualized hierarchical treatment; third, promoting clinical transformation of innovative technologies including target-

ed protein degradation and tumor metabolic intervention; fourth, exploring effective intervention strategies for undruggable targets and non-genetic refractory resistance mechanisms, so as to fundamentally optimize the post-resistance treatment system and improve the long-term survival prognosis of EGFR-mutant NSCLC patients. Conflict of interest statement All authors declare no conflicts of interest.

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Disclosure of conflict of interest

None.

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