

Overcoming EGFR-TKI Resistance in EGFR-Mutant Lung Adenocarcinoma

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Abstract

EGFR-targeted therapy has substantially improved the management of EGFR-mutant lung adenocarcinoma (LUAD), but acquired resistance remains a major limitation to durable disease control. Resistance can arise through secondary alterations within EGFR or through mechanisms that reduce tumour dependence on EGFR signalling, and these two situations require fundamentally different therapeutic approaches. This review considers the evolution of EGFR tyrosine kinase inhibitors (EGFR-TKIs) in the context of these resistance mechanisms. T790M illustrates resistance caused by altered drug-target interactions, whereas C797S compromises the covalent binding mechanism of third-generation inhibitors. In parallel, MET amplification, HER2 activation and epithelial-mesenchymal transition (EMT) provide alternative routes for maintaining tumour cell survival despite EGFR blockade. Recent therapeutic development has therefore expanded beyond successive generations of EGFR-TKIs. Fourth-generation inhibitors are being designed to address resistant EGFR genotypes, while EGFR/MET bispecific antibodies and MET-directed antibody–drug conjugates (ADCs) seek to exploit bypass signalling or receptor expression as alternative vulnerabilities. However, most of these approaches remain under clinical evaluation, and treatment selection will depend increasingly on accurate identification of the resistance state present in an individual tumour. Future progress is likely to rely on serial molecular monitoring and treatment strategies that can adapt to tumour evolution.

Key words

EGFR-TKI, Lung Adenocarcinoma, EGFR-TKI Resistance

1. Introduction

Lung cancer persists as a major contributor to the global cancer burden because of its high incidence and

mortality. Non-small cell lung cancer (NSCLC) accounts for most diagnosed cases of lung cancer, representing approximately 85%, with lung adenocarcinoma (LUAD) representing its predominant histological subtype [1].

Among the molecular alterations identified in LUAD, EGFR mutations have attracted particular attention because their prevalence differs markedly between populations. Approximately half of Asian patients with LUAD harbour EGFR mutations, whereas the reported frequency in Caucasian populations is considerably lower, at around 10-15% [2]. The majority of clinically significant EGFR mutations are concentrated in a limited number of recurrent variants, particularly the exon 19 deletion and the L858R substitution in exon 21 [2,3]. By maintaining the EGFR signalling pathway in an activated state, these alterations promote the activity of downstream cascades that support cell proliferation and survival, whilst simultaneously inhibiting apoptotic responses, thereby contributing to the onset and progression of LUAD [4]. Consequently, EGFR has become a vital target for precision therapy in LUAD.

EGFR is a receptor tyrosine kinase upregulated in various solid tumours, and its downstream signalling pathways contribute to the regulation of cell proliferation and apoptosis [4]. The identification of EGFR mutations as major drivers of LUAD provided the basis for the development of EGFR tyrosine kinase inhibitors (EGFR-TKIs), which have subsequently become the standard treatment for advanced EGFR-mutation-positive NSCLC. EGFR-TKI development has progressed through several generations, beginning with reversible first-generation agents such as *gefitinib* and *erlotinib*, followed by the irreversible pan-HER inhibitor *afatinib* and the third-generation inhibitor *osimertinib* [3]. *Osimertinib* is active against both common sensitising EGFR mutations and the T790M resistance mutation [3]. In the FLAURA Phase III clinical trial, it significantly prolonged progression-free survival (PFS) and overall survival (OS), supporting its current role as a standard treatment for advanced EGFR-mutated NSCLC [5]. Despite the favourable initial responses achieved with EGFR-TKIs, acquired resistance eventually develops in most patients and is associated with disease progression. Whether it is the emergence of secondary EGFR mutations, such as T790M and C797S, or the involvement of bypass receptors such as MET and HER2, these factors can all lead to this type of resistance [6]. Furthermore, if cells undergo epithelial-mesenchymal transition (EMT) or if downstream signalling pathways change, tumour cells may also evade the effects of targeted therapies [6].

Aiming at these different mechanisms of resistance, a variety of novel therapeutic strategies have emerged in recent years, including fourth-generation EGFR inhibitors, EGFR/MET bispecific antibodies, MET-targeted therapies and antibody-drug conjugates (ADCs) [6]. These new strategies demonstrate excellent anti-tumour activity in clinical trials, offering additional treatment options for patients whose tumours become resistant to EGFR-TKIs.

Despite EGFR-TKIs significantly improving outcomes in patients with EGFR-mutated LUAD, acquired resistance remains a major obstacle to achieving sustained long-term benefit. As resistance mechanisms continue to evolve, conventional single-target therapies are no longer sufficient to meet the demands of precision medicine. Consequently, analysing the molecular mechanisms driving EGFR-TKI resistance and exploring precision treatment strategies targeting different resistance mechanisms are of great significance for optimising clinical therapies, prolonging tumour progression and improving long-term patient survival. This article will first introduce the molecular basis of EGFR-mutated LUAD, including the characteristics of EGFR mutations, EGFR signal transduction and the development history of EGFR-TKIs. It will then focus on a review of EGFR-dependent and EGFR-independent resistance mechanisms, and summarise novel therapies targeting different resistance mechanisms that have emerged in recent years, including fourth-generation EGFR inhibitors, EGFR/MET bispecific antibodies and ADCs; finally, it will discuss the future directions and challenges in the treatment of EGFR-mutated LUAD within the context of precision medicine.

2. Molecular Basis of EGFR-Targeted Therapy

2.1 EGFR Signalling Pathway

As a member of the ErbB family, EGFR is a transmembrane receptor tyrosine kinase (RTK). The ErbB family consists of four receptors: EGFR (HER1), HER2, HER3 and HER4 [4,7]. These receptors are widely expressed in normal tissues and are involved in various physiological processes, including cell proliferation,

differentiation, migration and survival [4,7]. Under normal physiological conditions, following binding to its ligands, such as transforming growth factor- α (TGF- α) or epidermal growth factor (EGF), EGFR will undergo homodimerization or heterodimerisation, inducing autophosphorylation of its intracellular tyrosine kinase domain [7]. This provides binding sites for various signal transduction proteins, thereby activating multiple downstream signal transduction networks and regulating a range of biological processes to maintain normal cell growth and homeostasis [4]. Activated EGFR recruits various adaptor proteins, which in turn activate several classic downstream cascades. The RAS-RAF-MEK-ERK cascade, commonly referred to as the MAPK pathway, primarily regulates cell proliferation and differentiation; the PI3K-AKT-mTOR cascade is associated with cell growth; JAK-STAT signalling contributes to processes related to cell survival and immune regulation; whereas the PLC γ -PKC pathway regulates cell migration and cytoskeletal reorganisation [7,8]. These cascades interconnect to collectively maintain the physiological functions of normal cells.

2.2 EGFR Mutations in Lung Adenocarcinoma

EGFR is a major driver gene in LUAD, and its activating mutations are predominantly located within the tyrosine kinase domain. Systematic reviews indicate that EGFR mutations exhibit significant population- and region-specific variations [9]. Furthermore, EGFR mutations occur more frequently among women, never-smokers and patients with LUAD [9]. Hundreds of EGFR mutations have now been identified, of which approximately 85%-90% are classified as classic sensitive mutations, most commonly exon 19 deletions and the exon 21 L858R point mutation [10]. These mutations favour the active conformation of the EGFR kinase and increase its affinity for ATP. As a result, downstream signalling remains constitutively active even in the absence of ligand stimulation, making these variants the principal molecular targets of current EGFR-TKI therapies. Other less frequent variants, including G719X, L861Q and S768I, have also been reported, and their responses to different EGFR-TKIs are variable [11]. As activating EGFR mutations play a central role in LUAD develop-

ment and progression, therapies directed against aberrant EGFR signalling have become a significant milestone in precision medicine for lung cancer. In recent years, the successive development of EGFR-TKIs has substantially improved the clinical prognosis of patients with EGFR-mutation-positive disease; however, the emergence of drug resistance continues to limit long-term efficacy.

2.3 Development of EGFR-TKIs

EGFR-TKIs target the intracellular kinase domain of EGFR by competing with ATP for receptor binding, which interferes with kinase activity and consequently suppresses downstream signalling. In EGFR-driven tumour cells, this pharmacological blockade reduces proliferative signalling and promotes the loss of tumour cell viability. Compared with conventional chemotherapy, EGFR-TKIs offer greater therapeutic selectivity and better tolerability, significantly improving the clinical prognosis of patients with EGFR-mutation-positive NSCLC [8].

The development of EGFR-TKIs was initially aimed at selectively inhibiting activating EGFR mutations while reducing the systemic toxicity associated with conventional chemotherapy. *Gefitinib* and *erlotinib* were among the earliest EGFR-targeted agents to enter clinical practice [3]. These drugs reversibly compete with ATP at the EGFR kinase domain and show activity against the canonical sensitising mutations [3]. Evidence from phase III studies established the clinical advantage of first-generation TKIs over conventional treatment, particularly with respect to the objective response rate (ORR) and progression-free survival (PFS). These findings provided the clinical basis for incorporating EGFR inhibition into the first-line management of advanced EGFR-mutated NSCLC. However, acquired resistance develops in most patients after approximately 9-14 months of treatment, and the secondary EGFR T790M mutation accounts for approximately 50%-60% of these resistant cases [12].

The limited duration of efficacy of first-generation therapies has prompted the development of drugs with different pharmacological properties. Indeed, the frequent emergence of T790M resistance highlighted the need for stronger and more durable inhibition of ErbB signalling, which contributed to the development of second-generation tyrosine kinase inhibitors (TKIs).

Afatinib and *dacomitinib* represent the second generation of EGFR-TKIs. Unlike the reversible inhibitors that preceded them, these compounds form irreversible interactions with the kinase domain and additionally suppress other ErbB receptors, including HER2 and HER4 [3,13]. Second-generation drugs further extended progression-free survival in some patients; however, as they also inhibit wild-type EGFR, adverse reactions were more pronounced, including rash and diarrhoea. Furthermore, their inhibitory effect on the T790M resistance mutation is limited, and they are therefore gradually being replaced in clinical practice by next-generation EGFR-TKIs [12].

The clinical limitations of second-generation inhibitors exposed two important problems: inadequate control of T790M and dose-limiting toxicity resulting from wild-type EGFR inhibition. These limitations shaped the design principle of third-generation agents, which aimed to retain activity against sensitising mutations and T790M while reducing pharmacological effects on wild-type EGFR. *Osimertinib* became the representative agent of this strategy, combining activity against the common sensitising variants with inhibition of T790M and comparatively limited activity against wild-type EGFR [3]. This molecular selectivity provided a more favourable balance between antitumour efficacy and tolerability [3]. In the FLAURA Phase III clinical trial, first-line *osimertinib* treatment significantly prolonged the median progression-free survival and overall survival in patients with advanced EGFR-mutant NSCLC [3,13,14]. It has now become the standard treatment recommended by international guidelines. Although third-generation EGFR-TKIs have become the standard of care, their efficacy remains limited against new resistance mutations such as C797S [3,13,14]. Consequently, novel targeted therapies, such as fourth-generation EGFR inhibitors and bispecific antibodies, are currently under active development, offering new therapeutic approaches to address resistance to EGFR-TKIs.

EGFR-TKIs have substantially improved the treatment of EGFR-mutated LUAD, but acquired resistance is almost inevitable. As treatment duration increases, tumour cells can reactivate oncogenic signalling pathways through several mechanisms, including secondary EGFR mutations, bypass pathway activation and cellular phenotypic remodelling, leading to disease progression.

Although successive generations of EGFR-TKIs have progressively improved efficacy and selectivity, new resistance mechanisms, particularly C797S, continue to motivate the development of fourth-generation EGFR inhibitors and other therapeutic approaches.

3. Mechanisms of EGFR-TKI Resistance

3.1 EGFR-dependent Resistance

Although EGFR-TKIs can substantially improve outcomes in patients with EGFR-mutated LUAD, acquired resistance eventually develops in most patients. Depending on whether the mechanism of resistance occurs directly within the EGFR gene itself, resistance mechanisms can broadly be divided into EGFR-dependent and EGFR-independent forms [3,15]. In EGFR-dependent resistance, tumour cells remain reliant on the EGFR pathway, but structural alterations within the receptor reduce the effectiveness of kinase inhibition. Secondary EGFR mutations may modify the kinase conformation, alter its interaction with ATP, or interfere directly with inhibitor binding, thereby allowing oncogenic signalling to persist despite continued drug exposure [15]. Among these, T790M and C797S are the two main types of secondary mutations that have been most extensively studied and are of the greatest clinical significance [3,13]. These resistance mutations have also provided an important basis for the development of third- and fourth-generation EGFR-TKIs.

3.1.1 T790M Mutation

After treatment with first two generations of EGFR-TKIs, the secondary EGFR T790M mutation is detected in approximately 70% of acquired-resistance cases [6,8]. Consequently, T790M has long been regarded as the primary molecular mechanism underlying EGFR-dependent resistance. T790M is an exon 20 alteration involving substitution of threonine with methionine at codon 790. Because residue 790 occupies a critical position within the kinase domain, this variant is commonly referred to as the EGFR “gatekeeper” mutation [6,8,12].

Initial explanations attributed T790M-mediated resistance mainly to steric interference within the

ATP-binding site [15]. Subsequent biochemical and structural analyses provided a more complete explanation, showing that the mutation increases the kinase's preference for ATP [6,8,12]. As a result, ATP-competitive inhibitors face greater competition from the endogenous substrate and are less effective at maintaining EGFR inhibition [6,8,12]. This restores the sustained activation of downstream EGFR cascades, such as MAPK and PI3K/AKT, ultimately leading to tumour cells regaining a proliferative advantage [6,8,12].

The discovery of the T790M resistance subsequently drove the development of third-generation EGFR-TKIs. *Osimertinib*, as the representative agent of this class, selectively targets EGFR-sensitive mutations and T790M while exhibiting weaker inhibitory effects on wild-type EGFR, offering improved efficacy and safety [3]. The AURA series of studies first demonstrated that *osimertinib* is significantly effective in T790M-positive resistance patients, whilst the FLAURA Phase III clinical trial further established its role as the standard treatment for advanced EGFR-mutated NSCLC [3]. However, with the widespread use of *osimertinib*, new acquired resistance mechanisms have gradually emerged, the most representative of which is the EGFR C797S mutation [3,8].

3.1.2 C797S Mutation

C797S represents a relatively frequent EGFR-dependent resistance alteration following treatment with third-generation EGFR-TKIs, accounting for approximately 10% to 20% of cases of acquired resistance to *osimertinib* [13]. The alteration occurs in EGFR exon 20, where the cysteine residue at position 797 is replaced by serine [3]. The effectiveness of third-generation TKIs depends on covalent engagement of cysteine 797 within the EGFR kinase domain. Conversion of this residue to serine removes the chemical group required for that interaction, thereby preventing efficient covalent binding and compromising the activity of drugs such as *osimertinib*.

Significantly, the C797S mutation may exist simultaneously with the T790M mutation, and its *cis* or *trans* configuration influences subsequent treatment strategies [13]. The therapeutic implications of C797S are further influenced by its allelic relationship with T790M. When the two mutations occur on different alleles (*trans*), combining inhibitors from different generations may

retain some inhibitory activity. In contrast, the *cis* arrangement places both resistance alterations within the same EGFR molecule and is considerably more difficult to target with currently available TKIs [3]. These findings have therefore increased interest in next-generation EGFR inhibitors designed to address C797S, including BLU-945, BBT-176 and other fourth-generation EGFR-TKIs.

3.2 EGFR-independent Resistance

Resistance does not always arise from alterations within EGFR itself. In some tumours, effective EGFR inhibition is maintained, yet downstream survival can be restored through alternative receptors, bypass pathways, or changes in cellular state. Such mechanisms collectively represent EGFR-independent resistance [3,4,7]. Unlike EGFR-dependent resistance, these mechanisms typically no longer rely on EGFR itself, but instead bypass EGFR signalling through means such as bypass activation or lineage plasticity; therefore, conventional EGFR-TKI therapy has limited efficacy [3,7,13]. Among the mechanisms currently recognised in this category, MET amplification, aberrant HER2 signalling and epithelial-mesenchymal transition (EMT) are particularly important because they allow tumour cells to maintain growth despite continued suppression of the original oncogenic driver [3,7,13].

3.2.1 MET Amplification

MET amplification is a frequent bypass activation mechanisms observed after resistance to third-generation EGFR-TKIs and has been reported in approximately 15%-30% of cases of acquired resistance to *osimertinib* [3,13]. Increased MET gene dosage can strengthen HGF/MET signalling and reactivate downstream effectors that overlap with those normally controlled by EGFR, including PI3K/AKT and RAS/MAPK [4,7]. Consequently, tumour cells can maintain proliferative and survival signalling even when EGFR activity is effectively suppressed [4,7]. Thus, pharmacological suppression of EGFR with *osimertinib* does not necessarily eliminate the oncogenic signal if amplified MET has become an alternative driver of tumour cell survival. Several clinical studies are currently evaluating combinations of EGFR-TKIs with MET inhibitors, including *savolitinib* and *tepotinib* [16].

3.2.2 HER2 Alterations

HER2 amplification or activating mutations in HER2 represent additional important bypass mechanisms of EGFR-TKI resistance [3,7,13]. As another member of the ErbB receptor family, HER2 can interact with EGFR through receptor heterodimerisation and stimulate downstream signalling networks including PI3K/AKT and MAPK [4,7]. Abnormal HER2 activity therefore provides an alternative signalling route through which malignant cells may preserve growth and survival after EGFR blockade has been established [3,7]. Currently, HER2-targeted therapies, including HER2-TKIs and HER2 ADCs (ADCs), are emerging as a key area of research for overcoming resistance to EGFR-TKIs [8].

3.2.3 Epithelial-Mesenchymal Transition (EMT)

EMT represents a major form of cellular phenotypic remodelling and is recognised as an important non-genetic mechanism of acquired resistance to EGFR-TKIs [3,7,13]. EMT represents a phenotypic transition in which epithelial features become progressively reduced while mesenchymal properties increase [3,4,7,13]. Typically, such molecular alterations feature the downregulation of E-cadherin, accompanied by the elevated expression of mesenchymal markers, including N-cadherin and vimentin. This transition can enhance motility and invasive behaviour and may also increase resistance to apoptotic stress [3,4,7,13]. EMT not only reduces the sensitivity of tumour cells to EGFR-TKIs but is also frequently accompanied by the aberrant activation of bypass signalling pathways such as AXL and TGF- β , further complicating the mechanisms of resistance [7,13]. Consequently, the combined targeting of EMT-related signalling pathways has become a key area of research for enhancing the efficacy of EGFR-TKIs [8,13].

4. Treatment Strategies to Overcome Resistance

The widespread use of third-generation EGFR-TKIs, particularly *osimertinib*, both progression-free and overall survival have improved significantly in patients with EGFR-mutated NSCLC, making EGFR-TKIs the current standard first-line therapy for patients with

EGFR-sensitive mutations [3,6,11]. However, acquired resistance eventually develops in most patients, and as treatment regimens continue to evolve, the mechanisms of resistance have become highly heterogeneous and complex, so relying solely on existing EGFR-TKIs is no longer sufficient to achieve long-term disease control [3,7,13]. The increasing heterogeneity of acquired resistance has shifted therapeutic development away from a single strategy toward mechanism-targeted intervention. Current approaches include next-generation EGFR inhibitors for resistant EGFR variants, dual EGFR/MET targeting to counter MET-mediated bypass signalling, and MET-directed ADCs designed to exploit elevated surface expression of the receptor [3,8,14]. Although these therapeutic strategies are still at various stages of clinical research or clinical application, existing studies have shown that they demonstrate good antitumour activity and promise in certain treatment-resistant patients and are expected to further advance the development of precision therapy for EGFR-mutated LUAD [3,8,14].

4.1 Fourth-Generation EGFR-TKIs

The emergence of *osimertinib* substantially improved the management of T790M-positive disease, but resistance did not disappear. Instead, subsequent treatment experience identified C797S as an important mechanism of failure after third-generation EGFR inhibition [3]. As third-generation EGFR-TKIs require the formation of an irreversible covalent interaction with the cysteine residue at EGFR position 797, the C797S mutation directly disrupts the drug-binding site, rendering existing EGFR-TKIs ineffective. Against this backdrop, fourth-generation EGFR-TKIs have emerged [14].

Fourth-generation compounds are being designed around alternative modes of EGFR inhibition, including reversible non-covalent interactions and allosteric binding, rather than relying exclusively on the covalent mechanism used by third-generation drugs. An important design objective is to retain activity across the mutant EGFR spectrum, including sensitising alterations and resistance-associated T790M/C797S, while maintaining limited activity against wild-type EGFR [11,14]. Achieving this balance could broaden the therapeutic window and reduce toxicity caused by non-selective EGFR inhibition [11,14]. Representative fourth-generation EGFR inhibitors currently include BLU-945, BBT-

176, CH7233163 and JBJ-09-063, amongst others [17]. Among these, BLU-945 is the most extensively studied next-generation EGFR inhibitor to date; it exhibits highly selectivity for EGFR inhibition to triple mutations (Ex19del/L858R+T790M+C797S) and has demonstrated good antitumour activity in preclinical studies and the SYMPHONY clinical trial [14,17,18]. Current several fourth-generation EGFR-TKIs remain in the Phase I/II clinical trial stage. Although their long-term efficacy and safety require further validation, existing studies suggest that fourth-generation EGFR inhibitors hold promise as a key therapeutic strategy for overcoming EGFR-dependent resistance and may be paired with *osimertinib* to forestall resistance development.

4.2 EGFR/MET Bispecific Antibodies

MET amplification is a frequent EGFR-independent resistance mechanism observed after treatment with *osimertinib* [3,13,15]. As MET signalling can bypass EGFR to reactivate downstream cascades including MARK and PI3K/AKT, continued use of EGFR-TKIs alone typically fails to achieve sustained efficacy [4,7]. Dual-target antibodies provide a different solution to MET-driven resistance by engaging EGFR and MET within the same therapeutic strategy. This approach is intended to suppress the original EGFR-dependent signal while simultaneously limiting the compensatory MET pathway that can sustain tumour growth after EGFR inhibition [8,15,16]. Among these, *amivantamab* is currently the first EGFR/MET bispecific antibody for EGFR-mutated NSCLC [19]. Beyond direct interference with signalling through EGFR and MET, *amivantamab* can recruit immune activity through antibody-dependent cell-mediated cytotoxicity (ADCC), providing an additional component to its antitumour activity [8,15]. In the MARIPOSA study, *amivantamab* combined with *lazertinib* further prolong progression-free survival in patients with advanced EGFR-mutated NSCLC, and it has now become one of the key treatment options for EGFR-mutated lung cancer [19].

4.3 MET-Targeted ADCs

Combining MET inhibitors with EGFR-TKIs may benefit some patients with MET amplification, issues such as secondary resistance and toxicity remain import-

ant limitations [15]. In recent years, ADCs have consequently attracted increasing interest in precision therapy for lung cancer, owing to their combination of targeted delivery and cytotoxic effects [16,20]. MET-directed ADCs exploit elevated MET expression as a means of selectively delivering a cytotoxic agent to tumour cells [20]. Following antibody binding and internalisation, the conjugate undergoes intracellular processing and releases its payload, thereby converting receptor recognition into a cytotoxic response [20]. Telisotuzumab vedotin (Teliso-V) is currently among the leading MET-directed ADCs under clinical investigation [20]. Studies in MET-overexpressing NSCLC have reported antitumour responses together with a safety profile considered manageable in the investigated populations [20]. Furthermore, ongoing studies are evaluating whether combining MET ADCs with EGFR-TKIs can improve treatment outcomes in patients with acquired EGFR-TKI resistance.

5. Conclusion

The development of EGFR-targeted therapy has substantially changed the treatment of EGFR-mutant lung adenocarcinoma. First-generation EGFR-TKIs established the clinical value of inhibiting oncogenic EGFR signalling, while subsequent generations of drugs were designed in response to the limitations encountered during treatment. *Osimertinib*, in particular, improved the management of T790M-mediated resistance and has become a standard treatment for advanced EGFR-mutant NSCLC. However, the clinical success of successive EGFR-TKIs has not eliminated resistance. Instead, prolonged treatment creates selective pressure under which tumour cells can acquire or exploit alternative mechanisms to maintain their survival.

The resistance mechanisms discussed in this review can be broadly classified by their relationship to EGFR dependence. T790M and C797S illustrate resistance that remains closely linked to the EGFR kinase itself. T790M increases the competitive advantage of ATP over earlier ATP-competitive inhibitors, whereas C797S interferes with the covalent interaction required by third-generation EGFR-TKIs. By contrast, MET amplification, HER2 alterations and EMT allow tumour cells to preserve downstream signalling without relying

exclusively on the inhibited EGFR pathway. This distinction is clinically important because the presence of a particular resistance mechanism determines whether further EGFR inhibition, pathway combination therapy or an alternative therapeutic approach is more appropriate.

Taken together, these approaches do not represent interchangeable options for EGFR-TKI-resistant disease. Their potential value depends largely on what has changed in the tumour after EGFR inhibition. Fourth-generation EGFR inhibitors are being investigated for resistant variants such as T790M/C797S, using binding strategies that differ from those of third-generation agents. For tumours in which MET becomes an alternative signalling driver, EGFR/MET bispecific antibodies can interfere with both receptors within the same treatment strategy. MET-directed ADCs address the problem differently by using MET expression on tumour cells to deliver a cytotoxic payload rather than relying solely on inhibition of MET signalling. These distinctions are important when considering patient selection and treatment sequence. The clinical role of each approach will ultimately depend on whether the relevant resistance mechanism can be identified reliably and whether the resulting response can be maintained during further tumour evolution.

Future management of EGFR-mutant LUAD will therefore require closer integration of molecular characterisation and treatment selection. Serial assessment of tumour evolution may help identify newly emerging resistance mechanisms and determine when a change in therapy is justified. Rather than relying on a fixed sequence of EGFR-TKIs, treatment may increasingly need to be adjusted according to the molecular state of the tumour at each stage of disease progression.

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