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REVIEW

Non-small-cell lung cancer: how to manage *EGFR*-mutated disease

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Abstract

The treatment of non-small-cell lung cancer (NSCLC) harbouring *EGFR* mutations has witnessed some major breakthroughs in the last years. On the one hand, the recent advent of the third-generation tyrosine kinase inhibitor (TKI) osimertinib has reshaped the therapeutic algorithm both in the first-line and adjuvant settings for patients with common activating Ex19del and L858R *EGFR* mutations. On the other hand, the availability of new comprehensive next-generation sequencing panels, to be used on tumour tissue or on liquid biopsy, has revealed the existence of uncommon as well as compound mutations that partially explain the onset of resistance. Nevertheless, dissecting the biological mechanisms underlying primary and secondary resistance to EGFR-TKIs is crucial to developing alternative therapeutic strategies and further improving patient outcomes. Herein, we provide an updated and comprehensive summary of the latest advancements in the quest for compounds targeting *EGFR*-mutant advanced non-small-cell lung cancer, discussing the biological rationale underlying the development of a forefront combination of TKI and/or new antibody–drug conjugates. We also suggest a treatment algorithm that could be followed considering the latest published data.

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Citation

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Introduction

Epidermal growth factor receptor (EGFR) (ErbB1) is a member of a wide family of receptors, including HER2/neu (ErbB2), HER3 (ErbB3) and HER4 (ErbB4).[1] Mutations of *EGFR* are detected in about 15–20% of non-small-cell lung cancers (NSCLC), mostly of adenocarcinoma histology, and predominantly in non-smokers, women and those of Asian ethnicity.[2] The development of target therapy for *EGFR*-mutant NSCLC has revamped the course of the disease, shifting the median progression-free survival (PFS) from 5–6 months with standard chemotherapy to 18–19 months with the third-generation tyrosine kinase inhibitor (TKI) osimertinib.[3–5] This achievement has set the starting point for new challenges due to the development of acquired resistance to osimertinib as new therapeutic strategies are arising with the purpose to further improve patient outcomes. The aim of this review is to discuss and take stock of currently available therapeutic strategies for *EGFR*-mutant NSCLC with a projection of possible novelties regarding therapeutic combinations in this field.

Review

Incidence and epidemiology

The incidence of *EGFR*-mutant lung adenocarcinoma (LUAD), the most common NSCLC histology harbouring *EGFR* mutations, is around 10–20% in the white population and

40–60% in Asian populations. This subtype of lung cancer is most common in never smoker, long-time ex smokers (>10 years) or light smokers (<15 pack-years), female sex and younger patients.[6] *EGFR* mutations are usually detected in LUAD, but may also be found in cases of squamous cell lung cancer in young and never-smoker patients. In 90% of cases, the most common mutations detected are deletions in exon 19 and the L858R substitution mutation in exon 21. The germline T790M mutations in exon 20 of the *EGFR* gene predisposes to lung cancer and occurs in approximately 1% of NSCLC, predominantly LUAD, favouring the female sex.[7]

EGFR biology

EGFR mutations in LUAD are mainly located in the catalytic tyrosine kinase domain, between exon 18 and 21, which encodes the N lobe and part of the C lobe of EGFR and involves structures around the ATP-binding site of EGFR, including the phosphate-binding loop (P-loop), the αC-helix, and the activation loop (A-loop).[8] Three types of mutations have been identified: missense mutations in exons 18 and 21, deletions in exon 19, and small in-frame insertions in exon 20[1,9,10] (Figure 1). The most common *EGFR* mutations are the small in-frame deletions in exon 19 (Ex19del) and the leucine-to-arginine point mutation at codon 858 (L858R) in exon 21, located in the 5´ of the αC-helix and in the A-loop of EGFR, respectively.[8,10] Both L858R mutation and Ex19del increase the duration of ligand-dependent activation of EGFR. Taken together, Ex19del and L858R represent about 85–90% of all EGFR mutations.[1,8]

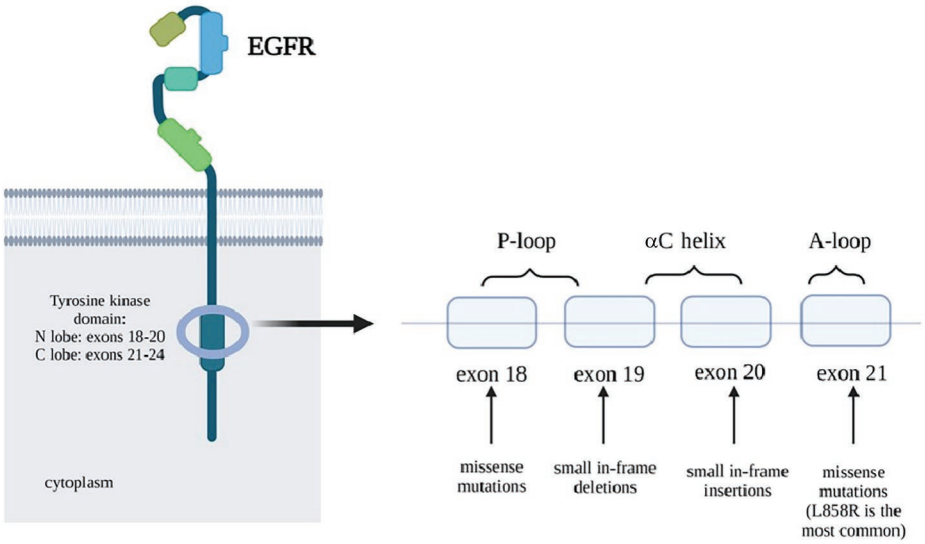
Looking at the uncommon *EGFR* mutations, they consist of a heterogeneous group of mutations with almost 600 variants identified.[11,12] Amongst them, the most frequent are the substitution mutations of G719X in exon 18 (2–4% of all EGFR mutations), L861Q in exon 21 (2% of all EGFR mutations), S768I in exon 20, and exon 20 insertions (6–10% of all EGFR mutations).[11,13] In at least 25% of NSCLC harbouring an uncommon *EGFR* mutation, other *EGFR* mutations within the same tumour can also be found ('compound' mutations).[13,14]

A recent paper published by *Nature* showed a different way to classify the uncommon *EGFR* mutations according not to exon location but to structure and function. Four subgroups were identified: (1) classical-like mutations, distant from the ATP-binding pocket, (2) T790M-like mutations, localized in the hydrophobic core, (3) insertions in the loop at the C-terminal end of the αC-helix in exon 20 and (4) mutations on the interior surface of the ATP-binding pocket or C-terminal end of the αC-helix, predicted to be P-loop and αC-helix compressing. They observed that structure–function-based groups predicted drug sensitivity and patient outcomes better than exon-based groups. Moreover, they demonstrated that structure–function-based groups identified classes of EGFR-TKIs more effectively on each whole group of mutations, suggesting that mutations in different regions of the gene may lead to similar changes in protein structure.[15]

This classification, although nowadays far from being introduced in clinical practice, provides a deeper understanding of the biology of EGFR alterations, which may be useful for the development of new therapeutic strategies and design of clinical trials.

Since the early 2000s, there has been a succession of different EGFR inhibitors:[16] first-generation reversible EGFR-TKIs (gefitinib, erlotinib), second-generation irreversible EGFR-TKIs (afatinib, dacomitinib), third-generation EGFR-TKIs able to

Figure 1. EGFR tyrosine kinase domain structure and sites of mutations in non-small-cell lung cancer.



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inhibit the T790M mutation of resistance to previous inhibitors, amongst which osimertinib has been shown great superiority, and lastly, fourth-generation EGFR-TKIs, developed to overcome acquired resistance to third-generation inhibitors.[17]

Target therapy against *EGFR*-mutant NSCLC according to stage of disease

Early stages: neoadjuvant and adjuvant setting

In recent years, the impact of immunotherapy and target therapy has been investigated also in early stages with the aim to improve the limited benefit given by chemotherapy alone. Adjuvant chemotherapy gives a limited survival benefit with an absolute increase in survival of 5.4% at 5 years that is stage related, but more than half of patients still relapse.[18] In the neoadjuvant setting, an absolute survival improvement of 5% at 5 years, improved time to distant recurrence, and improved recurrence-free survival in resectable NSCLC were observed with chemotherapy alone.[19]

The prognostic role of *EGFR* mutations in early-stage NSCLC is still controversial, and several studies showed no difference in terms of disease-free survival (DFS) between patients with *EGFR*-mutant NSCLC and those with wild-type *EGFR* NSCLC.[20] Neoadjuvant treatments aim to shrink the tumour site, facilitating surgery. Regarding EGFR-TKIs in early stages, alone or in combination, several phase II clinical trials have been performed and others are still ongoing.[21,22]

A phase II clinical trial investigated the impact of neoadjuvant erlotinib (150 mg/die for 6 weeks) in a cohort of IIIA-N2 NSCLC. Despite the response rate (RR) observed for the erlotinib arm (58.3% for the erlotinib arm with *EGFR*-mutant *versus* 25.0% for the chemotherapy arm with *EGFR* wild-type), no benefits were observed in terms of overall survival (OS) and PFS;[23] the grade of pathological response was not available in this study. Another study involved 31 Chinese patients with stage IIIA NSCLC; amongst them, patients without EGFR mutation received cisplatin-based doublet chemotherapy whilst patients with *EGFR*-mutant NSCLC received erlotinib as neoadjuvant therapy. A significant better objective response rate (ORR) (67% *versus* 19%), pathological response rate (67% *versus* 38%), and OS (51.0 *versus* 20.9 months) were obtained in patients who received erlotinib compared to those receiving chemotherapy, suggesting that erlotinib was effective as neoadjuvant strategy in patients with *EGFR*-mutant locally advanced NSCLC.[24] A recent meta-analysis tried to put together several phase II studies involving EGFR-TKIs in the neoadjuvant setting with the aim to deepen this therapeutic approach. They included five phase II prospective, clinical trials involving 124 patients with stage I–IIIA *EGFR*-mutant NSCLC treated with erlotinib or gefitinib in the neoadjuvant setting.[25] The ORRs of patients in the subgroups with stage I–IIIA and stage IIIA disease were 58.5% and 51.4%, respectively, superior to those observed in patients treated with neoadjuvant chemotherapy (28–49%) but no differences in terms of OS were observed.[25]

The small number of patients enrolled and the lack of results from phase III clinical trials in the setting of neoadjuvant EGFR-TKIs for early-stage NSCLC do not allow solid conclusions to be reached. Ongoing large phase III randomized clinical trials such as NCT03203590, which compares gefitinib with oral navelbine plus carboplatin, or NeoADAURA study (NCT04351555), which compares neoadjuvant osimertinib with or without chemotherapy with chemotherapy alone, will further clarify the role of TKIs in the neoadjuvant setting in improving both surgical resection, pathological response and patient outcomes.

The adjuvant setting of early-stage *EGFR*-mutant NSCLC has been revamped by the introduction in clinical practice of osimertinib, a third-generation EGFR-TKI. Due to the excellent results of the FLAURA trial with osimertinib in first-line for advanced *EGFR*-mutant NSCLC, researchers also investigated the impact of this TKI in early-stage NSCLC.

The ADAURA trial evaluated the impact of adjuvant osimertinib compared to placebo in radically resected stage IB to IIIA (TNM 7) *EGFR*-mutant NSCLC. The primary endpoint was DFS amongst patients with stage II to IIIA disease. With a median follow-up of 24 months, amongst patients with stage II to IIIA disease, the DFS was 90% for those in the osimertinib group whilst 44% for those in the placebo group were alive and disease-free at 24 months ($p<0.001$). The DFS benefit with osimertinib was observed across all disease stages, also in stage IB. Looking at the recurrence, locoregional-only recurrence was observed in 7% of patients in the osimertinib group and in 18% in the placebo group; 4% in the osimertinib group and 28% in the placebo group had distant recurrence. Moreover, osimertinib led to reduction of 82% in the risk of central nervous system (CNS) disease recurrence. OS data were still immature at the time of the interim analysis.[26] Interesting data are emerging by a sub-analysis of ADAURA indicating that the quality of life was maintained during osimertinib treatment. This trial came with many unanswered questions, mostly related to the impact of adjuvant osimertinib on patient OS and the duration of adjuvant therapy (3 year-treatment was employed in the trial). Moreover, the development of acquired resistance at tumour recurrence after adjuvant osimertinib could impair the opportunity to receive this treatment in the metastatic setting.[27]

The final analysis of the CTONG1104/ADJUVANT trial, a randomized phase II trial comparing adjuvant gefitinib *versus* chemotherapy for resected N1-N2 NSCLC with *EGFR* mutation, showed a significant improvement in DFS in the gefitinib arm, which did not translate into OS difference.[28] The ongoing ALCHEMIST trial (Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trial) is investigating the real role of adjuvant target therapy in early-stage driver mutant NSCLC.[29]

Advanced disease: standard of care for common point mutations in exon 21 and deletions in exon 19 of *EGFR*

First-line strategy

Based on findings from the FLAURA trial that compared osimertinib with gefitinib and erlotinib in the first-line setting,

osimertinib has been established as first-line standard of care in advanced NSCLC with common activating *EGFR* mutations. Using osimertinib upfront in all patients, including those with brain metastases and those where T790M is detected at disease onset, has emerged as the most rational choice. In fact, all predefined subgroups included in the FLAURA study showed a benefit in terms of PFS, even if the magnitude of OS benefit seems to be less pronounced amongst Asian patients and those with an *EGFR* L858R mutation.[30]

The use of osimertinib in first-line therapy should not be restricted for any of the patients with common *EGFR* mutations, and first-generation or second-generation EGFR-TKIs should be administered only in the absence of access to third-generation EGFR-TKIs.[6] Two new third-generation EGFR-TKIs presented at the European Lung Cancer Congress 2022, furmonertinib (phase III FURLONG trial) and oritinib (phase II trial), showed similar efficacy compared to osimertinib but OS data are immature and it is still too early to reach a conclusion.[31,32]

The use of osimertinib should even be prioritized for those patients with CNS metastasis due to its capacity to guarantee a better CNS control over gefitinib or erlotinib but also to delay the emergence of new brain metastases.[33,34] In these cases, the exact role of radiotherapy remains a matter of debate, with local stereotactic radiation being preferred over whole-body radiation therapy and initiating osimertinib as the first intervention before radiotherapy being the most common strategy.[6] In case of leptomeningeal involvement, osimertinib at a preferred dose of 160 mg is currently accepted in most countries as this strategy proved to be effective in the single-arm BLOOM study, which included patients with cytologically proven leptomeningeal carcinomatosis.[35]

Some frontline combination strategies, including erlotinib plus the antiangiogenic agent ramucirumab and gefitinib plus chemotherapy, have shown interesting results in clinical trials and have been encompassed by NCCN guidelines,[36] yet have rarely been adopted in clinical practice.

As osimertinib has been moved from the second-line to the first-line and adjuvant settings, the question arises on how to treat patients post osimertinib failure. In the absence of clear evidence from clinical trials, optimal subsequent management should be tailored on resistance mechanism. In case of disease recurrence after the completion of 3 years of adjuvant osimertinib, experts from a recent European Society for Medical Oncology (ESMO) consensus recommends consideration of a repeated course of osimertinib as the recurrence itself is more likely to be responsive to osimertinib rechallenge.[6,37] On the contrary, in case of disease recurrence during adjuvant treatment or in the advanced setting, cessation of osimertinib and rebiopsy should be pursued.

Treatment strategy after first-line therapy

On-target mechanisms of resistance are detected in ~15% of patients following first-line osimertinib, and whilst platinum-based chemotherapy remains the standard of care in this setting, alternative on-target therapies such as earlier generation TKIs (especially in case of p.C797S mutation, which is not cross-resistant), amivantamab (a bi-specific monoclonal antibody that targets both EGFR and MET)[38,39] and patritumab deruxtecan (an antibody–drug conjugate (ADC) consisting of a HER3 antibody attached to a topoisomerase I inhibitor payload)[40] might be considered, preferably in the context of genotype-directed clinical trials. In case of off-target resistance to osimertinib, such as *MET* amplification (which represents 10–15% of the cases), some promising results were observed in clinical trials with the combination of the MET-inhibitor savolitinib and osimertinib (RR was 30% in pretreated patients).[41] An alternative strategy could be represented by the combination of amivantamab and lazertinib (RR of 36%)[39,42,43] or the use of ADC patritumab deruxtecan (RR 36%),[40] yet chemotherapy remains the only recommended treatment outside of clinical trials. Acquired *ALK* and *RET* fusion should also not be overlooked, as evidence of radiological responses was observed with different combinations of TKIs.[42,44,45]

Second-line platinum-based chemotherapy is recommended for patients with evidence of histological transformation or with no targetable alterations. In the first scenario (for which tumour tissue assessment is required), using platinum-etoposide as chemotherapy is recommended as it has been associated with an RR of 54% whilst none of the patients receiving immunotherapy experienced a response.[46] When no targetable alterations are detected, platinum-based chemotherapy with or without atezolizumab and bevacizumab could be considered as an alternative option based on a subgroup analysis of the phase III IMpower-150 showing an OS improvement (HR 0.60, 95% CI 0.31–1.14) with atezolizumab plus bevacizumab and chemotherapy also in patients with classical *EGFR* mutations.[47] Noteworthy, *EGFR*-mutated tumours tend to have negative or low PD-L1 expression, and clinical response to immune-checkpoint inhibitors (ICIs) remains scarce also in the context of high PD-L1 expression.[48–50] Relevant toxicity concerns have been raised, especially when EGFR-TKIs were used in combination with PD-1/PD-L1 inhibitors or after initial immunotherapy.[51,52]

Patients with slow progression or those who have been off osimertinib for at least 6 months might be considered for treatment beyond progression or for a rechallenge, especially in the absence of clinical trials. It could be helpful also to repeat a tumour biopsy, whenever available, or to perform a liquid biopsy to see if EGFR mutation is maintained.[53] Conversely, available data do not support the use of chemotherapy in combination with osimertinib beyond progression.

Advanced disease: standard of care for uncommon *EGFR* mutations

Whilst exon 19 deletions and the L858R point mutation (which comprise about 90% of all *EGFR* mutations) are established as strong predictors of response to EGFR-TKIs, low-frequency mutations showed different sensitivity. Those atypical/

uncommon mutations that revealed variable sensitivity include insertions in exon 19, point mutations in exon 18 at position G719X, the exon 21 p.L861Q mutant, and the p.S768I mutation in exon 20. In this patient population, use of afatinib is recommended based on a post hoc analysis from the LUX-Lung 2, LUX-Lung 3, and LUX-Lung 6 trials showing an ORR of 71% and a median PFS of 10.7 months (similar to those of patients with the two common sensitizing *EGFR* mutations).[54] Additionally, osimertinib showed signs of efficacy in this setting, though evidence is more limited and its use should be considered as a possible alternative.[55,56]

Other mutations, such as in-frame insertion mutations within exon 20 of *EGFR*, different exon 19 insertions, p.L747S, p.D761Y, p.T790M and p.T854A, are associated with primary resistance to EGFR-TKIs. In these cases (with the only exception of *EGFR* exon 20 insertions), as strength of recommendation in favour of TKI is missing, platinum-based chemotherapy should be regarded as the first-line option whilst no data supports the addition of ICIs.[6]

EGFR exon 20 insertions deserve a separate discussion. These mutations seem to account for about 12% of all *EGFR* mutations and are mutually exclusive with other driver mutations. They are resistant to standard EGFR-TKIs because of the steric conformation that impairs the affinity, rendering the inhibitory activity similar to that observed in *EGFR* wild-type cases.[57] Although platinum-based chemotherapy should still be offered as a first-line option without ICIs because of the risk of toxicity with targeted therapy in later lines[58], new approval has been granted to amivantamab and mobocertinib as rescue therapies. These approvals are based on ORRs of 36% and 43% observed in early-phase trials.[59,60]

Thus, testing by next-generation sequencing (NGS) to deeply detect the high heterogeneity of mutations in this region for *EGFR* exon 20 insertion becomes crucial. New comprehensive NGS panels have also revealed the existence of compound mutations, namely a TKI sensitizing or other mutation together with a mutation of unknown clinical significance, yet new studies are warranted to evaluate TKI efficacy in these rare cases.[61–63]

The major oncogenic driver alterations (e.g. *ALK, ROS1, RAS, MET*) are generally mutually exclusive with *EGFR* mutations yet, when they rarely co-occur, the efficacy of targeted therapies might be impaired and comprehensive NGS analyses become essential to identify the more dominant clone and better tailor treatment.

Mechanisms of resistance to EGFR-TKIs

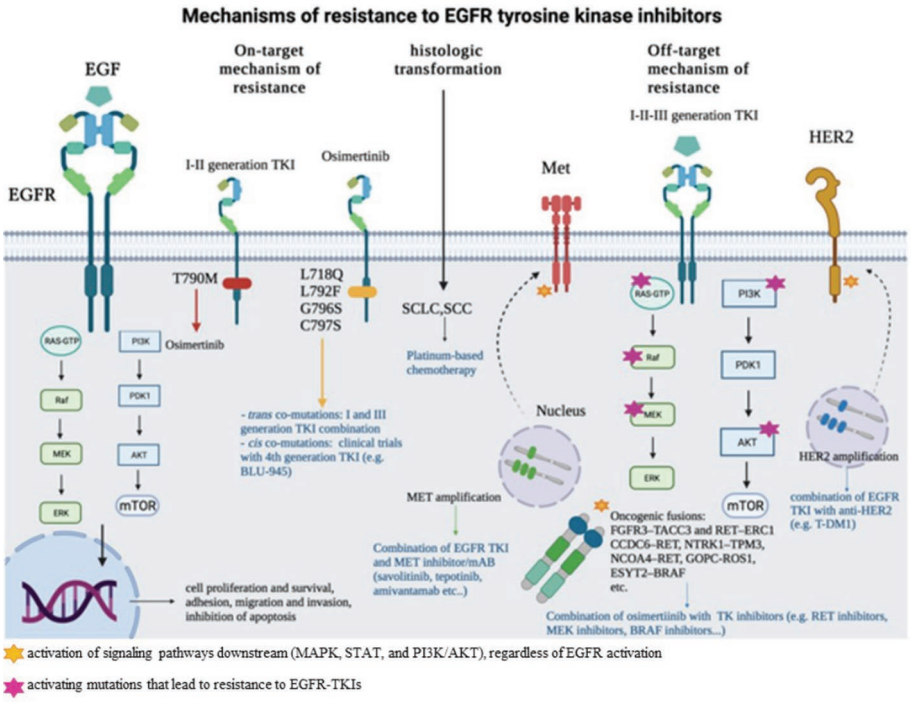
Mechanism of resistance to target therapy could be divided into primary resistance, referring to patients that do not respond to TKI immediately, and secondary resistance, referring to patients who develop progression to the ongoing treatment after a period of benefit from it. Even if, in clinical practice, the border between the two is more blurred, the use of new technologies of NGS detains a key role to better recognize both and calibrate the therapeutic choice.

Primary resistance to EGFR-TKIs is not fully understood but several mechanisms have been recognized, to be considered for the therapeutic choice. About 20–30% of patients do not respond or respond for a very short time (less than 3 months) to TKIs due to intrinsic resistance.[64] One of the most common primary resistance mechanisms is the presence of non-sensitive EGFR mutations such as exon 20 insertions (1–10% of *EGFR*-mutated LUAD), which have a dramatic steric effect on the drug-binding pocket. In fact, patients with *EGFR* exon 20 insertion mutations showed a median PFS of only 2 months when treated with erlotinib, gefitinib or afatinib.[65] Rarely, EGFR exon 20 T790M, one of the most common mechanisms of resistance to first-generation EGFR-TKIs, can be found even before treatment commencement, conferring intrinsic resistance to gefitinib and erlotinib.[64,66–68]

A wide percentage of patients develop progressive disease due to the onset of mechanisms of resistance within 9–14 months of treatment with TKIs. Acquired resistance is observed when patients with *EGFR*-mutant NSCLC achieve a response or stable disease lasting longer than 6 months and then develop progression under the same treatment.[69] However, in clinical practice, there are several progression clinical-radiological patterns that should be approached in different ways. Gandara et al. divided disease progression patterns to EGFR-TKIs into three subtypes, namely oligoprogression, systemic progression (multisite progression) and CNS progression, excluding leptomeningeal carcinomatosis. Both for CNS and oligoprogression patterns, local therapy such as surgery, radiotherapy, or both, should be considered without discontinuing the current TKI. Moreover, in case of slow progression or progression without worsening of clinical conditions, continuation of the present EGFR-TKI may be considered.[70] Yang et al. proposed another classification of progression to TKIs according to the duration of disease control, evolution of tumour burden and clinical symptoms, leading to the elaboration of three subgroups of progression disease: dramatic progression, gradual progression and local progression.[71] A key role in disease progression under EGFR-TKIs that might impact on the following treatment choice is detained by the detection of potential molecular mechanisms of resistance on tumour tissue, when available in case of rebiopsy, or on circulating tumour DNA by liquid biopsy.

The comprehensive analysis of resistance mechanisms in patients at progression on EGFR-TKIs has led to the development of their classification into three categories: on-target mechanisms that involve the onset of other mutations in the *EGFR* gene, off-target mutations, regarding the onset of alterations in alternative molecular pathways, and histological transformation (Figure 2). Looking at on-target mechanisms of acquired resistance to first-generation and second-generation EGFR-TKIs, the *EGFR* T790M mutation, which involves the substitution of methionine for threonine at amino acid position 790 at exon 20 of *EGFR*, is the most common, present in 50–60% of the cases.[72,73] The 790 residue is located within the ATP-binding pocket of the EGFR protein and leads to

Figure 2. Mechanisms of resistance to first-generation, second-generation and third-generation EGFR tyrosine kinase inhibitors (TKIs) and relative treatment strategies to overcome them.



On-target mechanisms: related to intrinsic additional mutations of EGFR.
Off-target mechanisms: related to additional mutations in alternative intracellular pathways (MAPK, PI3K–mTOR). In this case, the use of combination of EGFR-TKIs with other types of TKI (such as MEK inhibitors and BRAF inhibitors), antibody–drug conjugates such as Ado-trastuzumab emtansine (T-DM1), and monoclonal antibodies (mAB) such as amivantamab.
Histological transformation: transformation from adenocarcinoma histology to small-cell-lung cancer (SCLC) or squamous cell carcinoma (SCC).
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conformational change that causes steric hindrance for TKIs, increasing protein affinity for ATP and decreasing the efficacy of first-generation and second-generation EGFR-TKIs.[72] *EGFR* T790M should be searched on tumour biopsy, when available, or in liquid biopsy in case of progression to first-generation and second-generation EGFR-TKIs. As a negative liquid biopsy for T790M alone without testing tumour tissue might lose a group of patients that could benefit from osimertinib due to false-negative results,[74] the ESMO guidelines allow the performance of plasma genotyping as an option at disease progression when tissue-based testing is not feasible; however, if plasma testing results negative for T790M, tissue biopsy should be strongly recommended to determine T790M status because of the risk of false-negative plasma results.[75]

EGFR amplification is detected in about 10% of cases that are positive for T790M and contributes to the acquisition of resistance to gefitinib, erlotinib and afatinib.[76] Rare *EGFR* point mutations detected in less than 10% of patients that lead to first-generation and second-generation EGFR-TKI resistance include D761Y, T854A and L747S but specific molecular mechanisms of resistance are still unclear.[73,77–79]

Looking at on-target resistance mechanisms to the third-generation EGFR-TKI osimertinib, the most common one (27%) is represented by the *EGFR* C797S point mutation that occurs in *EGFR* exon 20, causing the substitution of a cysteine with a serine in the position 797. The cysteine located at position 797 is used by third-generation EGFR-TKIs for the covalent binding to the receptor, which is necessary to contrast the increased affinity for ATP determined by T790M mutation, and this amino acid substitution leads to inability to block EGFR activity by third-generation TKIs.[80] Preclinical findings suggest that T790M-negative cells harbouring C797S could maintain sensitivity to gefitinib or afatinib. Moreover, it has been observed that, in case of *cis* position of both point mutations T790M and C797S, cells are resistant to any EGFR-TKIs, and the enrolment in clinical trials with fourth-generation EGFR-TKIs

could be a therapeutic option.[81] Conversely, if these alterations are in *trans*, cells could retain sensitivity to a combined therapy with first-generation and third-generation EGFR-TKIs. Another mechanism of resistance to third-generation EGFR-TKIs is due to loss/maintenance of EGFR T790.

Oxnard et al. demonstrated that, in a cohort of patients treated with osimertinib, patients with T790M loss had a median time to treatment discontinuation of 6.1 months, shorter compared to the median time to treatment discontinuation of 15.2 months in patients with maintained T790M.[82] Another study showed that high baseline plasmatic T790M levels are correlated with better tumour shrinkage and could predict benefit from rociletinib, another third-generation TKI.[83,84] *EGFR* amplification is known to be a mechanism of acquired resistance of first-generation TKI, but emerging clinical evidence demonstrated that it could also be involved in the development of acquired resistance to third-generation TKI treatment.[84]

Looking at off-target mechanisms, the activation of alternative pathways that overcome *EGFR* inhibition, such as the Ras–Raf–MEK–ERK pathway, represents another common resistance mechanism to all three generations of EGFR-TKIs. Oxnard et al. detected four *MET* amplifications, two *PIK3CA* mutations, two *BRAF* mutations, *RET*, *FGFR* and *BRAF* fusions (one each), and a *KRAS* Q61K mutation amongst patients who developed acquired resistance to osimertinib by tumour tissue NGS.[85]

The most common off-target mechanism of resistance bypassing the *EGFR* inhibition pathway is represented by *MET* amplification (10–15%),[86] leading to the activation of the downstream AKT pathway, which is the key signalling pathway for cell proliferation and antiapoptosis.[87] The amplification of the *ErbB2* gene has been found in 12% of cases of resistance to first-generation and second-generation EGFR-TKIs and in about 2% of cases of resistance to osimertinib. Moreover, *FGFR*, *BRAF*, *KRAS* and *PIK3CA* mutations could lead to resistance to EGFR-TKIs from first, second and third generations, conferring survival advantages to cancer cells.[86,88,89]

About 2–15% of patients treated with EGFR-TKIs develop transformation from adenocarcinoma to small-cell lung cancer (SCLC), acquiring resistance to EGFR-TKIs.[90,91] Different hypotheses have been suggested regarding the molecular basis of SCLC transformation as a mechanism of resistance to EGFR-TKIs such as inactivation of tumour suppression via RB1 and TP53.[92,93] Offin et al. demonstrated that patients with co-occurring *EGFR*/*RB1*/*TP53* alterations, who represent about 5% of all *EGFR*-mutant lung cancers, have a high risk of SCLC transformation during their disease course.[94] Moreover, it could be possible that SCLC and NSCLC histologies are both present within the same initial tumour, and then, under TKI treatment, the SCLC subtype becomes the dominant cell clone after an initial response to treatment.[73] Squamous histological transformation has been observed as another mechanism of resistance to third-generation EGFR-TKIs.[95]

Both primary and secondary mechanisms of resistance to EGFR-TKIs suggest the key role of an appropriate molecular analysis of tumour samples or liquid biopsy both at diagnosis and at time of progression due to the dynamics of cancer cells and the presence of tumour cell subclones, fundamental to guide clinicians through different treatment choices.

New therapeutic perspectives

Considering the increasingly personalized approach to cancer therapy and the impactful role of in-depth knowledge of tumour biology in NSCLC, combination therapy strategies to improve the efficacy of EGFR-TKIs and overcome the mechanism of resistance have been studied both in preclinical and clinical settings, and several clinical trials are ongoing both in first and further treatment lines.

Looking at new developing strategies in first-line settings, researchers are trying to overcome the most common on-target mechanism of resistance to osimertinib, the *EGFR* C797S, and considering that gefitinib is functionally active against it, a phase I/II study with osimertinib plus gefitinib enrolling patients with stage IV *EGFR*-mutated (L858R or del19) NSCLC who are treatment naive has been designed with the aim of early prevention of this type of resistance.[96] The resulting ORR was 85.2%, consistent with previously reported first-line response rates to osimertinib (80%). Median PFS was not reached. The most common treatment-related adverse effects were rash, diarrhoea and dry skin, defining this combination as tolerable for first-line treatment of *EGFR*-mutated NSCLC. Survival outcome data are still immature.

When on-target *EGFR* mutations occur in *cis* with T790M, first-generation TKIs are ineffective and new EGFR-TKIs and treatment combination strategies are under investigation.[6,97] A phase I clinical trial (NCT03810807) is evaluating the safety and tolerability of the association of osimertinib with dacomitinib, a pan-HER inhibitor also active against *EGFR* C797S, with the aim to prevent the early onset of acquired *EGFR* mutations of resistance.[98]

The phase III FLAURA2 study (NCT04035486) is investigating the combination of osimertinib plus platinum-pemetrexed compared to osimertinib alone as first-line in *EGFR*-mutant NSCLC. The number of patients developing serious adverse events was similar amongst both treatment groups, suggesting a manageable toxicity profile for this combination.[99] Preclinical findings suggested that MEK inhibitors are also able to prevent resistance to EGFR-TKIs.[100] Based on these assumptions, a phase II clinical trial (NCT03392246) is evaluating the combination of osimertinib with selumetinib, an MEK1/2 inhibitor, for patients with EGFR inhibitor-naive advanced *EGFR*-mutant NSCLC.[101]

The deeper knowledge of mechanisms of resistance to EGFR inhibitors is driving towards an ever more personalized treatment approach after progression to first-line osimertinib tailored on tumour biology evolution. Based on this strategy, the ongoing biomarker-directed ORCHARD study

Table 1. Selected clinical trials investigating new treatment options for *EGFR*-mutant NSCLC.

ClinicalTrial.gov identifier	Drug or intervention combination	Phase	Design	Setting	Primary endpoints	Expected completion date
EGFR kinase inhibitors alone or in combination with other classes of TKI						
NCT03810807	Dacomitinib plus osimertinib	Phase I	Single group assignment	Patients with advanced *EGFR*-mutant lung cancer and no prior EGFR inhibitor treatment (gefitinib, afatinib, erlotinib, dacomitinib, osimertinib); prior treatment with other chemotherapies is allowed	MTD, BOR	01/31/2023
NCT03392246	Osimertinib in combination with selumetinib	Phase II	Single group assignment	Patients with no prior history of any EGFR inhibitors, including TKIs or antibodies, chemotherapy and immunotherapy naive for advanced NSCLC; patients with NSCLC who have completed adjuvant or neo-adjuvant chemotherapy >6 months ago are considered treatment naive	BOR	06/30/25
NCT03940703	Tepotinib plus osimertinib	Phase II	Non-randomized parallel assignment, two arms	Patients with *MET*-amplified advanced or metastatic NSCLC also harbouring activating *EGFR* mutations and having acquired resistance to osimertinib	Safety run-in, BOR	03/30/23
NCT02438722	S1403, afatinib dimaleate with or without cetuximab	Phase II/III	Randomized, parallel assignment, open label	Treatment-naive patients with advanced *EGFR*-mutant NSCLC	OS, PFS	03/12/22
NCT02335944	EGFR-TKI EGF816 in combination with cMET inhibitor INC280	Phase Ib/I	Single group assignment	Participants must have progressed on one prior line of therapy with first/second-generation EGFR-TKIs, osimertinib or other third-generation EGFR-TKIs for advanced/metastatic NSCLC	Safety and tolerability, ORR	07/21/25
NCT02954523	Dasatinib and osimertinib	Phase I/II	Single group assignment, open label	Patients with advanced NSCLC, no prior treatment with an EGFR-TKI, presence of sensitizing EGFR mutations (deletion in exon 19, L858R in exon 21, G719X, and L861Q); patients with the T790M mutation will also be eligible	Safety, tolerability, DCR	06/01/23

(Continued)

Table 1. (*Continued*)

ClinicalTrial.gov identifier	Drug or intervention combination	Phase	Design	Setting	Primary endpoints	Expected completion date
EGFR kinase inhibitors alone or in combination with other classes of TKI						
NCT02143466	Osimertinib in combination with savolitinib, osimertinib in combination with selumetinib	Phase Ib	Non-randomized, parallel assignment, open label, multi-arm	Patients with *EGFR*-mutant advanced NSCLC progressed after therapy with an EGFR-TKI	Safety and tolerability of drug combination	12/31/21
NCT05099172	BAY2927088	Phase I	Non-randomized, sequential assignment, open label	Advanced NSCLC harbouring an *EGFR* and/or *HER2* mutation with disease progression after treatment with at least one prior systemic therapy for advanced disease	Safety, tolerability, MTD	12/31/25
Other classes of drugs (chemotherapy, immunotherapy, ADC, monoclonal antibody) alone or in combination with EGFR kinase inhibitors						
NCT04035486	Osimertinib with or without platinum plus pemetrexed chemotherapy	Phase III	Open-label, randomized study	First-line treatment in patients with *EGFR*-mutant locally advanced or metastatic NSCLC	PFS	06/03/26
NCT02143466	Osimertinib in combination with durvalumab	Phase Ib	Non-randomized, parallel assignment, open label, multi-arm	Patients with EGFR-mutant advanced NSCLC who have progressed following therapy with an EGFR-TKI	Safety and tolerability of drug combination	12/31/21
NCT04965090	Amivantamab and lazertinib	Phase II	Non-randomized, parallel assignment, open label, single arm	Patients with metastatic *EGFR*-mutant NSCLC with progressive or new CNS metastases on previous treatment or patients with *EGFR* exon 20 insertions progressed on platinum-based chemotherapy or patients with *EGFR* alterations sensitizing to TKIs progressed on osimertinib	CNS ORR, measure CNS ORR	07/01/23
NCT04136535	Pemetrexed and carboplatin with or without anlotinib hydrochloride	Phase II	Randomized, parallel assignment, open label	Patients with advanced or locally advanced osimertinib-resistant non-squamous NSCLC	PFS	12/31/21

(Continued)

Table 1. (*Continued*)

ClinicalTrial.gov identifier	Drug or intervention combination	Phase	Design	Setting	Primary endpoints	Expected completion date
Other classes of drugs (chemotherapy, immunotherapy, ADC, monoclonal antibody) alone or in combination with EGFR kinase inhibitors						
NCT04619004	Patritumab deruxtecan	Phase II	Randomized, parallel assignment, open label	Patients with previously treated metastatic or locally advanced *EGFR*-mutated NSCLC; participants must have received both prior osimertinib and systemic therapy with at least one platinum-based chemotherapy	ORR	07/01/24
NCT04923906	Aumolertinib plus chemotherapy *versus* aumolertinib alone	Phase III	Randomized, controlled, open label	First-line treatment in patients with locally advanced or metastatic NSCLC with sensitizing *EGFR* mutations	PFS	01/31/26
NCT03054038	Afatinib plus necitumumab	Phase I	Single group assignment, open label	Patients with *EGFR*-mutant NSCLC with acquired resistance to first/third-generation EGFR-TKIs	MTD	07/01/23
NCT04285671	Trastuzumab, necitumumab together with osimertinib	Phase Ib/II	Single group assignment, open label	Patients with refractory *EGFR*-mutant NSCLC, progressed on osimertinib	MTD, safety, ORR	12/02/23
NCT04487080	Amivantamab and lazertinib combination therapy *versus* osimertinib	Phase III	Randomized, parallel assignment, double blind	First-line treatment in patients with *EGFR*-mutant locally advanced or metastatic NSCLC	PFS	03/30/26
NCT04500704	Almonertinib alone *versus* almonertinib plus chemotherapy	Phase III	Randomized, parallel assignment, open label	First-line treatment in patients with *EGFR*-mutant advanced NSCLC with concomitant non-*EGFR* driver gene mutations	PFS	10/31/2023
NCT04988295	Amivantamab and lazertinib in combination with platinum-based chemotherapy compared with platinum-based chemotherapy	Phase III	Randomized, parallel assignment, open label	Patients with *EGFR*-mutant locally advanced or metastatic NSCLC after osimertinib failure	PFS	11/17/25

ADC, antibody–drug conjugate; BOR, best overall response; CNS, central nervous system; DCR, disease control rate; MTD, maximum tolerated dose; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.

(NCT03944772) is investigating six different combinations of treatment in patients with advanced *EGFR*-mutant NSCLC with acquired resistance following first-line osimertinib, with patient enrolment to a specific subgroup being based on the tumour molecular profile.[102]

Looking at the most common off-target mechanism of resistance to EGFR inhibitors, *MET* amplification, several trials have been designed to overcome it. The combination of osimertinib and savolitinib, a MET inhibitor, was investigated in a phase Ib study with advanced, *MET*-amplified, *EGFR*-mutant NSCLC who progressed on EGFR-TKIs, and an acceptable risk–benefit profile with encouraging antitumour activity was observed. The multiarm phase Ib TATTON study (NCT02143466) evaluated the safety and tolerability of osimertinib in combination with selumetinib (MEK1/2 inhibitor), savolitinib (MET-TKI), or durvalumab in patients with advanced EGFR-mutant NSCLC after progression on a prior EGFR-TKI.[52] The feasibility of the combination of osimertinib with selumetinib or savolitinib was demonstrated, suggesting that osimertinib-based combination therapeutic strategies could represent a new weapon to overcome mechanisms of resistance to EGFR-TKIs after progression. The INSIGHT 2 study is investigating the combination of osimertinib and tepotinib for *EGFR*-mutant NSCLC with acquired resistance to first-line osimertinib due to *MET* amplification (NCT03940703).[103] The SAVANNAH phase II trial (NCT03778229) is evaluating the efficacy of osimertinib in combination with savolitinib in patients with *EGFR*-mutant and concurrent *MET*-mutant (amplified/overexpressed) NSCLC that progressed to osimertinib.[104]

The TRAEMOS phase II trial (NCT03784599) was designed to investigate the efficacy and toxicity of trastuzumab-emtansine (T-DM1) and osimertinib in patients with HER2 overexpression and/or amplification after progression on one EGFR-TKI. Results showed an ORR of 11% and a DCR of 48% after 12 weeks. The PFS was 2.7 months, concluding that this treatment strategy leads to very limited efficacy in this setting.[105]

EGFR-mutated NSCLC harbours higher expression of HER3 compared with *EGFR* wild-type NSCLC; therefore, it has been suggested that HER3 could become a potential target for the treatment of advanced *EGFR*-mutated NSCLC. The safety and clinical activity of patritumab deruxtecan (HER3-DXd), a novel, HER3-directed ADC, has been investigated in a cohort of metastatic *EGFR*-mutated NSCLC after disease progression on EGFR-TKIs.[40]

HER3-DXd demonstrated clinical activity in this setting with a confirmed ORR in 39% of patients and a median PFS of 8.2 months. Moreover, HER3-DXd was manageable, with a low rate of discontinuation for adverse events, observed in 9% of cases.

A list of ongoing trials in the setting of *EGFR*-mutant NSCLC is shown in Table 1.

Conclusions

Targeted therapy against *EGFR*-mutant NSCLC has dramatically changed the course of the disease, significantly improving patient outcome, replacing chemotherapy in first-line treatment, and becoming the front-line therapeutic choice. The onset of mechanisms of resistance during treatment with EGFR-TKIs has reinforced the need to study the underlying molecular mechanisms to develop drug combinations that can overcome resistance, both in the first line and subsequent lines. The key points that arise from all these considerations are the importance of tailoring treatment to the tumour biology at the time of resistance or to prevent the onset of these mechanisms using target therapy combinations during the first-line treatment. This approach is only possible by performing tumour genomic assessment by NGS and retesting the tumour at the time of progression, looking for resistance mutations and tumour cell subclones no longer sensitive to the drug in use. The aim is to find mutations that can be potentially targeted with forefront combinations of TKIs and/or new ADCs. Therefore, the availability of clinical trials has become a key issue for patients who progressed to osimertinib. Liquid biopsy and, when available, rebiopsy of primary or metastatic tumour tissue are becoming unavoidable in daily clinical practice as it offers to the clinician a unique tool for guiding treatment choice.

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