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Optimizing the sequencing of tyrosine kinase inhibitors (TKIs) in epidermal growth factor receptor (EGFR) mutation-positive non-small cell lung cancer (NSCLC)

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Abstract

Non-small cell lung cancer (NSCLC) is the most common type of lung cancer, accounting for 80–85% of cases. Epidermal growth factor receptor (EGFR) mutations are observed in approximately 40% and 20% of patients with NSCLC in Asian and non-Asian populations, respectively.

First-generation (gefitinib, erlotinib) and second-generation (afatinib, dacomitinib) EGFR-tyrosine kinase inhibitors (TKIs) have been standard-of-care (SoC) first-line treatment for patients with sensitizing EGFR mutation positive advanced NSCLC following Phase III trials versus platinum-based doublet chemotherapy. However, most patients treated with first-line first- or second-generation EGFR-TKIs develop resistance. Osimertinib, a third-generation, central nervous system active EGFR-TKI which potently and selectively inhibits both EGFR-TKI sensitizing (EGFRm) and the most common EGFR T790M resistance mutations, has shown superior efficacy versus first-generation EGFR-TKIs (gefitinib / erlotinib). Osimertinib is now a treatment option for patients with advanced NSCLC harboring EGFRm in the first-line setting, and treatment of choice for patients with T790M positive NSCLC following disease progression on first-line EGFR-TKIs. The second-generation EGFR-TKI dacomitinib has also recently been approved for the first-line treatment of EGFRm positive metastatic NSCLC.

There remains a need to determine appropriate sequencing of EGFR-TKIs in this setting, including EGFR-TKIs as monotherapy or in combination with other TKIs / signaling pathway inhibitors. This review considers the evolving role of sequencing treatments to maximize benefits for patients with EGFRm positive advanced NSCLC.

Keywords

non-small cell lung cancer; epidermal growth factor receptor; tyrosine kinase inhibitor; sequencing; exon 19 deletion; exon 21 mutation

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1. Introduction

Lung cancer is the leading cause of cancer-related mortality globally, with approximately 1.7 million deaths attributed to the disease each year [1]. Non-small cell lung cancer (NSCLC) is the most common type of lung cancer, accounting for approximately 80–90% of all lung cancers [2]. Historically, first-line treatment for advanced NSCLC was broadly confined to platinum-based chemotherapy. The discovery of targetable oncogenic mutations revolutionized treatment choices for NSCLC, yet refinement of NSCLC classification by biomarker target is still developing. ASCO recommends that all patients with advanced lung adenocarcinoma be screened for *EGFR*, *ALK*, *ROS1* and *BRAF* mutations irrespective of clinical characteristics. Patients with advanced lung adenocarcinoma should also be screened for *RET*, *HER2*, *KRAS, MET*, and *NTRK* by multiplex genetic sequencing (next-generation sequencing) wherever feasible, which is quickly becoming a standard approach to screening for oncogenic targets [2,3].

Epidermal growth factor receptor (EGFR) mutations are observed in approximately 40% and 20% of patients with NSCLC in Asian and non-Asian populations, respectively [4]. EGFR mutations are located in the tyrosine kinase domain and result in increased kinase activity of the EGFR, leading to sustained activation of signaling pathways and continued cell proliferation [5]. The most common EGFR mutations are deletions in exon 19 (Ex19del) or exon 21 L858R point mutation [5].

Phase III trials comparing first-generation (gefitinib, erlotinib) and second-generation (afatinib, dacomitinib) EGFR-tyrosine kinase inhibitors (TKIs) with platinum-based doublet chemotherapy established first- and second-generation EGFR-TKIs as standard-of-care (SoC) for patients with EGFR-mutated advanced NSCLC [6-14]. More recently, osimertinib, a third-generation, central nervous system (CNS)-active EGFR-TKI which potently and selectively inhibits both EGFR-TKI sensitizing (EGFRm) and EGFR T790M resistance mutations [15-19], has shown superior progression-free survival (PFS) compared with standard EGFR-TKI (gefitinib / erlotinib) [19], resulting in osimertinib becoming an additional first-line treatment option for EGFRm positive advanced NSCLC [2,3,20,21]. In the second-line setting, following disease progression on first- or second-generation EGFR-TKIs, osimertinib is treatment of choice for patients whose tumors harbor acquired EGFR resistance mutation T790M [2,16,20].

Treatment of EGFRm positive advanced NSCLC has more therapeutic options than ever before, particularly with regards to choice of first-line EGFR-TKI. Herein, we review first- and second-generation EGFR-TKIs, including acquired resistance mechanisms, and consider the evolving role of third-generation EGFR-TKIs, and other emerging therapeutic approaches in order to optimize the sequencing of EGFR-TKIs.

2. First- / second-generation EGFR-TKI therapy and resistance

2.1 Efficacy of first- and second-generation EGFR-TKIs

In patients diagnosed with EGFRm positive NSCLC, first-generation reversible EGFR-TKIs provide superior efficacy versus platinum-based doublet chemotherapy (Figure 1; Table A.1) [6-11]. Despite initial responses, most patients treated with first-generation EGFR-TKIs eventually develop resistance [22,23]. The second-generation EGFR-TKIs, afatinib and dacomitinib have shown, *in vitro*, that they bind selectively and irreversibly to the tyrosine kinase domain of EGFR (HER1), HER2, and HER4 receptors, and certain *EGFR* mutants (including, Ex19del, L858R and T790M) to inhibit proliferation and induce apoptosis in tumor cells that overexpress these receptors [24-26]. Afatinib has also demonstrated efficacy in patients with the uncommon *EGFR* mutations G719X, L861G and S768I [27,28]. As with first-generation EGFR-TKIs, afatinib treatment showed superior efficacy versus platinum-based doublet chemotherapy in patients with EGFRm positive advanced NSCLC (Figure 1; Table A.1) [13,29]. In head-to-head trials versus gefitinib, second-generation EGFR-TKIs showed improved PFS (Figure 1; Table A.1), and in the case of dacomitinib, improved overall survival (OS; median 34.1 months versus 26.8 months; hazard ratio [HR] 0.76, 95% confidence interval [CI]: 0.58–0.99; p = .044); OS was not considered to be statistically significant in this case due to the hierarchal approach to hypothesis testing in the study design, meaning that no formal testing of OS was conducted since the formal comparison of ORR between the treatment arms was not statistically significant [30,31]. However, the irreversible binding of second-generation EGFR-TKIs has led to increased toxicity, with dose reductions occurring in 39–52% and 66% of patients treated with afatinib and dacomitinib, respectively [14,32,33]. Despite exhibiting promising anti-EGFR T790M activity *in vitro*, afatinib and dacomitinib are unsuccessful in overcoming T790M-mediated resistance in the clinical setting [34-36] because the therapeutic threshold for clinical efficacy is unachievable in humans due to dose-limiting toxicity associated with non-selective inhibition of wild-type EGFR [15]. In line with resistance to first-generation EGFR-TKIs, T790M is the most common resistance mechanism, present in approximately 50% of progressive cases [32,37-44].

2.2 Mechanisms of resistance to first- and second-generation EGFR-TKIs

Acquired mutations in the EGFR tyrosine kinase domain, the activation of bypass signaling pathways, and phenotypic or histologic transformation have been identified as mechanisms of acquired resistance to first- and second-generation EGFR-TKIs [45,46]. Of the acquired EGFR mutations that can desensitize tumors to erlotinib, gefitinib, afatinib and dacomitinib, the EGFR T790M mutation is the most common, ranging from 36–69% in resistant cases [22,38,45,47-50]. T790M mutation results in the substitution of threonine to methionine at the “gatekeeper” amino acid position 790 on exon 20 of EGFR, causing conformational change, which leads to steric hindrance and reduces the binding activity of first- and second-generation EGFR-TKIs [23,51]. Furthermore, the T790M mutation of EGFR may restore the affinity of the mutant receptor for ATP, thus reducing the potency of competitive EGFR-TKIs [52].

De novo T790M mutations have been found to co-exist at a low frequency in EGFR-TKI treatment-naïve patients with EGFRm positive NSCLC [53,54]; these are rarely seen by standard genotyping methods, occurring in 3.5% of patients [55]. However, with the introduction of highly sensitive assays, the frequency of *de novo* T790M mutation in EGFR-TKI-naïve patients has been shown to range from 22% to 80% [56-60]. In a meta-analysis of 1462 patients with EGFRm positive advanced NSCLC across 22 studies, pre-treatment *de novo* T790M mutation-positive status in TKI-naïve patients, was associated with decreased PFS (HR 2.23, $p < .001$) and OS (HR 1.55, $p = .003$) with EGFR-TKI therapy (erlotinib or gefitinib) compared with pretreatment T790M mutation-negative status [61]. There is evidence that germline T790M mutations may be present in up to 50% of all patients with *de novo* T790M [62]. This has implications both around appropriate treatment sequencing and the screening of family members, but must also be considered with the caveat that false positive results may occur [63]. The prevalence of germline T790M mutations is currently being studied in the INHERIT trial (NCT01754025) [64].

Bypass resistance mechanisms utilize alternative cellular pathways and activating downstream signal transduction, thereby facilitating tumor cell growth and survival. *MET* gene amplification, *HER2* gene amplification, and *PI3KCA* gene mutations are most frequently observed [22,38,65,66]. Changes in tumor phenotype at disease progression have also been reported, with up to 14% of EGFR-TKI resistant tumors showing transformation to small-cell lung cancer (SCLC) [22]. Rarely, epithelial-to-mesenchymal transition can occur [67]. Other rare mechanisms of resistance to EGFR-TKIs include acquired receptor tyrosine kinase fusions and *BRAF* kinase fusions [68-70].

Yu and colleagues performed targeted next-generation sequencing in EGFR-TKI-naïve EGFRm positive lung cancer. Concurrent *HER2* amplification, *MET* amplification, or *TP53* mutations were associated with a shorter time to progression and OS on EGFR-TKI therapy [71]. Thus, identification of these concurrent mutations early in the treatment pathway may help tailor personalized treatment options for these patients by adopting new therapeutic strategies from the outset to overcome primary resistance.

3. Third-generation EGFR-TKI therapy at acquired resistance

3.1 T790M resistance mutation

Third-generation EGFR-TKIs can effectively target both EGFRm and T790M resistance mutations, while sparing activity of wild-type EGFR [15,17-19,72-80]. Osimertinib is now globally recommended for the treatment of patients with T790M NSCLC following disease progression on EGFR-TKI [20,21]. Table A.2 summarizes third-generation EGFR-TKIs that are approved and in clinical development.

In the AURA program of clinical trials, once-daily dosing of 80 mg osimertinib consistently showed clinical benefit in patients with T790M NSCLC following disease progression on first or second-generation EGFR-TKIs [47,79,81]. In the Phase III AURA3 trial, objective response rate (ORR) by investigator assessment was 71% (95% CI: 65–76) and median PFS was significantly longer with osimertinib (10.1 months) than platinum-based doublet chemotherapy (4.4 months) (HR 0.30, 95% CI: 0.23–0.41; $p < .001$) [79]. These clinical trial

data are supported by a large, global observational study of more than 3000 patients with T790M NSCLC and disease progression on prior EGFR-TKI (ASTRIS), in which osimertinib treatment showed an ORR of 57% (95% CI: 55–58) and a median PFS of 11.0 months (95% CI: 10.6–11.1). Furthermore, in AURA3, osimertinib demonstrated clinically meaningful and durable CNS responses; CNS ORR 54–70% [17,82].

3.2 T790M testing and failure rates

Current guidelines recommend T790M testing at clinical progression on a first-line EGFR-TKI, using tissue biopsy, plasma circulating tumor DNA (ctDNA) testing or both [3,21]. Because successful tissue biopsy is often not feasible, plasma testing should be considered a viable approach as the method is time effective and has little impact on patient morbidity. Unlike conventional tissue biopsies, liquid biopsies can circumvent tumor heterogeneity and quantify the proportion of mutated gene copies, which can be beneficial when monitoring disease response and in predicting early treatment failure [83,84]. However, T790M detection rates are often lower with plasma samples than with adequate tissue or cytology samples as ctDNA testing relies on DNA being shed from the tumor [85-88]. Indeed, high rates of false negative ctDNA T790M have been observed across the AURA clinical trial program: positive percentage agreement (PPA) was 51% in AURA3 [44,79,89,90]. This highlights the need for high DNA concentrations in plasma samples and for assays with greater sensitivity when analyzing plasma ctDNA samples for T790M, such as droplet digital polymerase chain reaction assay [91]. For patients with a negative plasma T790M result, it is recommended to reflex test a tissue-based specimen [92].

There is some preliminary evidence to suggest that T790M detection may be lower in the real-world setting compared with the clinical setting [93], possibly due to poor quality specimens, pre-analytical issues or limited access to liquid biopsies. Further research and development are therefore required to improve the quality and utility of liquid biopsies in clinical practice.

Tissue re-biopsy is not feasible for up to 20% of patients with progression on an EGFR-TKI, due to the risk of complications, lack of consent for the procedure, poor performance status of the patient or inaccessibility of the tumor [94-96]. In patients for whom T790M testing (plasma or tissue) is performed, not all will receive a result for reasons such as insufficient tissue, false-negative on plasma test or test limitations [97]. Recently, in a prospective Japanese study in 236 patients with EGFRm positive NSCLC and disease progression on first- or second-generation EGFR-TKI, 13% of patients (n = 31) had not been tested for T790M mutations after disease progression. Of the 199 patients who were tested for T790M, 31% of patients tested positive. Of note, 50 patients underwent second re-biopsy and eight had third re-biopsy, which led to T790M mutation detected in an additional 12 patients [93]. In line with these findings, a US study of electronic health records showed that following first- or second-generation EGFR-TKIs, only 28% of those tested for EGFR mutations had a T790M positive status [98]. In both of these studies, the majority (>90%) of patients who were T790M positive, received osimertinib as their subsequent treatment [93,98]. There remains limited evidence to guide treatment for patients who are T790M negative, or do not receive a valid result and therefore their T790M status remains unknown.

3.2 Uncommon EGFR mutations

Uncommon *EGFR* mutations in exons 18, 20 and 21, including L861X, G719X and S768I, represent approximately 10% of *EGFR* mutations [99]. In an open-label Phase II study (n = 35), osimertinib demonstrated efficacy in patients with NSCLC with uncommon *EGFR* mutations other than exon 19 deletion, L858R, T790M and insertion in exon 20; partial responses were reported in seven (78%) patients with L861Q mutation, ten (53%) patients with G719X mutation and three (38%) patients with S768I mutation [100].

3.3 Proportion of patients who receive second-line treatment after first- / second-generation EGFR-TKIs

We reviewed the rates of subsequent therapies following discontinuation reported in randomized control trials (RCTs) of EGFR-TKIs in the first-line EGFRm positive advanced NSCLC setting (Table A.1).

For first-generation EGFR-TKIs (gefitinib / erlotinib / icotinib), the second-line systemic treatment rate was 47–82% (Table A.1). For second-generation EGFR-TKIs (afatinib / dacomitinib), the rate was 58–78%. Among RCTs that reported the types of subsequent treatment received, the majority received chemotherapy after EGFR-TKI therapy [6,7,10-13,101-103]. In the NEJ002 trial, 20 of 114 patients did not receive any subsequent regimens after first-line gefitinib due to a poor performance status, interstitial lung disease, exacerbation of co-morbidities, and patient preference [7]. There were very limited reports of T790M testing rates.

RCTs provide a good indicator of the rate of subsequent treatment for patients who discontinue first-line EGFR-TKIs. However, these are not representative of the real world, as patients enrolled into RCTs are usually healthier (performance status <2 and good organ function), do not have symptomatic brain metastases and are monitored well as per protocol. As a result, in real-world practice, the proportion of patients receiving second-line treatment can be lower. In a German study investigating patients with EGFRm positive advanced NSCLC, 30% of patients did not reach second-line therapy [104]. However, in a US study only 38% of patients with NSCLC treated with a first- or second-generation EGFR-TKI received a subsequent treatment [98]. In a recent analysis of treatment patterns from the US Flatiron Electronic Health Record-derived database, 44% of patients with EGFRm positive advanced NSCLC received second-line treatment [55].

It should be noted that when many of the RCTs listed here were undertaken, T790M testing was not routine and third-generation EGFR-TKIs were unavailable as a post-first-line EGFR-TKI treatment option. In fact, among patients in the RCT chemotherapy arms, a higher proportion received subsequent treatment, mainly cross-over to second-line EGFR-TKI therapy [8-12,102,103].

In the best-case scenario, approximately 50% of patients with EGFRm positive advanced NSCLC who start with first- or second-generation EGFR-TKIs will be T790M positive at disease progression and eligible to receive second-line osimertinib. However, some of these patients would not receive valid results, which may reduce the T790M positive rate to as low as 30%, as reported by Seto and colleagues [93]. Furthermore, 18–53% of patients (based on

RCT data), may not receive any second-line treatment. A composite estimate of the proportion of patients who receive first- or second-generation EGFR-TKIs but do not receive osimertinib after progression could be as high as approximately 70%, meaning only 30% of patients with EGFRm positive advanced NSCLC may ever receive the clinical benefit of osimertinib if treated in the second line (Figure 2).

4. Third-generation EGFR-TKI therapy as first-line treatment

The selective nature of third-generation EGFR-TKIs, makes them an attractive therapeutic option in the first-line EGFRm positive NSCLC setting. The efficacy and safety of first-line osimertinib in advanced EGFRm positive NSCLC was recently assessed against the first-generation EGFR-TKIs erlotinib or gefitinib (standard EGFR-TKI) in the global Phase III FLAURA trial [19]. FLAURA achieved its primary endpoint, with osimertinib demonstrating PFS superiority over standard EGFR-TKI (median PFS, 18.9 versus 10.2 months, HR 0.46; 95% CI: 0.37–0.57, $p < .001$). The PFS benefit was consistent across all subgroups and was similar in patients with (HR 0.47) and without known CNS metastases (HR 0.46) at study entry. Response rates did not differ significantly between the treatment groups (80% with osimertinib and 76% with standard EGFR-TKI); however, the median duration of response was longer in patients treated with osimertinib (17.2 versus 8.5 months). At data cut-off, OS data were immature (25%) and were not statistically significant; however, they suggest a favorable trend for patients treated with osimertinib (HR 0.63, 0.45–0.88; $p = .0068$). PFS2 results are a good surrogate for OS and were non-calculable (NC) (95% CI: 23.7–NC) for osimertinib versus 20.0 months (95% CI: 18.2–NC), HR 0.58 (95% CI: 0.44–0.78; $p = .0004$) for standard EGFR-TKI [19]. Based on these findings, osimertinib is approved in the US, EU and Japan for the first-line treatment of patients with EGFRm (Ex19del / L858R) positive advanced NSCLC [105,106].

At present, the optimal therapeutic strategy for osimertinib and its positioning within the current sequential treatment paradigm is not definitive. When considering a first-line EGFR-TKI, several factors must be considered. Certainly, giving osimertinib in the first-line setting would provide every eligible patient with EGFRm positive NSCLC the chance to benefit from the improved efficacy (as shown in FLAURA) versus erlotinib or gefitinib, along with the known reduced risk of CNS progression associated with osimertinib treatment.

A second consideration would be that multiple exposures to systemic agents, as in the multiple EGFR-TKI sequencing strategy, can lead to increasing heterogeneity and genomic complexity in tumors, resulting in a poorer response with later lines of therapy [107]. Consequently, a patient may derive greater benefit from a more potent EGFR-TKI administered in the first-line setting rather than in the second-line or later.

A third consideration is the high risk of CNS metastases among patients with EGFRm positive NSCLC [108,109]. Thus, demonstrable efficacy and safety of EGFR-TKI therapy in patients with EGFRm positive NSCLC and CNS metastases is particularly relevant. Both AURA3 and FLAURA reported greater CNS efficacy with osimertinib versus platinum-pemetrexed and standard EGFR-TKI (gefitinib / erlotinib), respectively [17,18]. In FLAURA, CNS PFS in patients with measurable and / or non-measurable CNS lesions was

not reached with osimertinib (95% CI: 16.5 months–NC) and was 13.9 months (95% CI: 8.3 months–NC) with standard EGFR-TKI (HR 0.48; 95% CI: 0.26–0.86; p = .014 [nominally statistically significant]). Moreover, CNS ORR were significantly higher in patients with one or more measurable CNS lesions (91% versus 68%; odds ratio, 4.6; 95% CI: 0.9–34.9; p = .066) and in patients with measurable and / or non-measurable CNS lesions (66% and 43%; odds ratio, 2.5; 95% CI: 1.2–5.2; p = .011) versus standard EGFR-TKI, and the probability of experiencing a CNS progression event was consistently lower with osimertinib [18].

Currently, no direct comparable data for second- versus third-generation EGFR-TKIs exists in the first-line setting. Moreover, OS data for both AURA3 and FLAURA are immature [19,79]. Interestingly, in the post-progression analysis of FLAURA, the PFS benefit with osimertinib versus standard EGFR-TKI was maintained throughout all time-to-event post-progression endpoints: PFS HR 0.46, time to first subsequent treatment HR 0.51, PFS2 HR 0.58, and time to second subsequent treatment 0.60 [110]. This step-wise increase of the statistically significant hazard ratios HRs provides confidence in the interim OS data. Nevertheless, the final OS results are eagerly awaited.

The position of osimertinib in the treatment pathway may also be dictated by the resistance mechanisms identified in the first-line setting and the available treatment options following progression. Very limited data are available for resistance mechanisms to osimertinib as first-line therapy but preliminary data from AURA (first-line cohort) and FLAURA suggest similar resistance mechanisms to those observed with osimertinib in the second-line T790M setting (Figure 3), and also to first- and second-generation EGFR-TKIs, with the exception of T790M mutation, of which there was no evidence [111,112]. Further research into resistance mechanisms to first-line osimertinib are ongoing with the ELIOS (NCT03239340) trial [113].

Given the dearth of post-osimertinib treatment options, there is an argument that greater survival benefit may be derived from the sequential initiation of EGFR-TKIs rather than initiating osimertinib in the first-line setting. However, the PFS benefit with osimertinib demonstrated as preserved throughout time-to-event post-progression endpoints versus standard EGFR-TKIs in the first-line setting must be noted. Furthermore, the majority of patients with progression on standard EGFR-TKIs receive chemotherapy.

5. Emerging approaches to targeting EGFR-mutant NSCLC

It is critical that we explore novel approaches to overcome acquired resistance mechanisms to EGFR-TKIs and to determine the appropriate sequencing of therapy to prolong patient survival.

The acquired C797S mutation, which blocks the covalent binding of second- and third-generation EGFR-TKIs to the ATP-binding site, has been identified as a potential resistance mechanism for irreversible third-generation EGFR-TKIs. In the post-second-line T790M setting, data have indicated that the C797S mutation is acquired while retaining both EGFRm and T790M mutations [114-116]. The emergence of this tertiary acquired mutation

that mediates resistance to all known third-generation EGFR-TKIs is driving the development of fourth-generation EGFR-TKIs. EAI001, EAI045, and JBJ-04–125-02 are allosteric EGFR inhibitors that target T790M and C797S EGFR mutants, and have demonstrated initial efficacy in the preclinical setting [117-119]. Importantly, C797S acquisition after first-line osimertinib only co-exists with EGFRm (since osimertinib prevents T790M resistance). Moreover, in-vitro modelling supports the potential use of osimertinib in combination with first-generation EGFR-TKIs to target EGFRm / C797S resistance when T790M and C797S mutations occur in *trans* allelic context [120].

As new resistance mechanisms to EGFR-TKIs come to light, it is becoming clear that the inhibition of EGFR alone may not be sufficient for sustained antitumor activity. Combined MET and EGFR inhibition to target EGFR-TKI acquired resistance driven by MET amplification is a compelling therapeutic approach, with Phase Ib studies in patients with EGFRm positive NSCLC and MET positive acquired resistance demonstrating promising safety, tolerability, and preliminary activity of osimertinib (TATTON, NCT02143466) [121] or gefitinib (NCT02374645) [122] in combination with the MET-TKI savolitinib. This approach provided the basis for the ongoing Phase II SAVANNAH (NCT03778229) trial, which will investigate the efficacy of osimertinib in combination with savolitinib in patients with EGFRm and MET positive NSCLC, following progression on osimertinib treatment. Indeed, a multi-drug, biomarker-directed Phase II platform trial (ORCHARD; NCT03944772) is evaluating resistance mechanisms and combination treatment options for patients with EGFRm positive NSCLC whose disease has progressed on first-line osimertinib therapy. Preliminary results from an ongoing Phase I trial (NCT02609776) investigating the EGFR-cMET bispecific antibody JNJ-372 demonstrated a manageable tolerability profile [123]. Recently, several case reports have shown that the administration of crizotinib (an ALK / ROS1 / MET inhibitor) in combination with osimertinib is effective and well tolerated in patients with EGFRm positive NSCLC with acquired T790M and MET amplification resistance mutations [124]. Other MET plus EGFR combinations have been investigated, but showed discordant results, so the benefit of this approach remains to be fully elucidated [125-129].

Other potential combinations that target resistance mechanisms that are currently under investigation include EGFR-TKIs in combination with MEK1 / 2 inhibition [121], antibodies against EGFR [130], antibodies against vascular endothelial growth factor (VEGF; NCT02803203) and VEGF receptor (NCT02789345), mTOR inhibition (NCT02503722) and immunotherapy. Preclinical models have demonstrated that activation of the EGFR pathway induces PD-L1 expression, enhancing susceptibility of the lung tumors to PD-1 blockade [131]. This suggested that the combination of PD-1 blockade with EGFR-TKIs might be a viable therapeutic approach to extend duration of treatment response and delay development of resistance in the EGFRm positive NSCLC setting [131]. However, the combination approach of EGFR-TKIs with immunotherapy (gefitinib + durvalumab [132], erlotinib + atezolizumab [133], pembrolizumab + gefitinib [134]) yielded an unexpectedly high incidence of grade 3 / 4 adverse events. Thus, further development of this approach is considered controversial. However, other immunotherapy approaches may provide benefit as salvage treatment strategies following progression on EGFR-TKIs. For instance, in the Phase III IMpower150 study, atezolizumab in combination with

bevacizumab and chemotherapy has shown promising activity in patients with pretreated EGFRm positive NSCLC following progression on EGFR-TKIs [135]. This suggests that immunotherapy checkpoint inhibitors in combination with chemotherapy or other treatments may be a viable therapeutic approach following resistance to EGFR-TKIs. Furthermore, the ongoing KEYNOTE-789 trial (NCT03515837) is evaluating if chemotherapy combined with pembrolizumab improves outcomes in patients with EGFRm positive NSCLC and progression on an EGFR-TKI.

In addition to immunotherapy checkpoint inhibitors, other emerging immunotherapy strategies warrant investigation for treatment of resistance to EGFR-TKIs, such as combinations with anti-CD73 agents (for example oleclumab; NCT03381274).

The combination of EGFR-TKIs with chemotherapy is also under investigation for treatment-naïve patients where the availability of third-generation EGFR-TKIs is limited. The Phase III study NEJ009 evaluated the superiority of gefitinib in combination with pemetrexed-carboplatin versus gefitinib monotherapy in patients with newly-diagnosed EGFRm positive NSCLC. Although the combination did not demonstrate superiority in PFS2, the results reported a potential increase in long survivors [136]. Another Phase III study showed the addition of pemetrexed-carboplatin to gefitinib therapy significantly prolonged PFS and OS in patients with chemotherapy-naïve EGFRm positive NSCLC, albeit with increased toxicity [137].

At the core of future research will be the need to determine the appropriate sequencing of treatments for patients with advanced EGFRm positive NSCLC along with standard EGFR-TKIs and, as the disease landscape evolves, with use of later-generation EGFR-TKIs in the first-line setting, such as osimertinib. This will ultimately require selected treatments for a given patient to be based on the results of comprehensive, sensitive molecular profiling throughout the treatment journey. In the first-line setting, this may include EGFR-TKIs administered either as monotherapy, or in combination with other mechanistic approaches, in order to improve benefit in molecularly identified high-risk patients or delaying resistance. Monitoring dynamic disease evolution using liquid biopsies is likely to play an important role in this setting, enabling clinicians to serially monitor changes in circulating tumor DNA, mutation burden, the appearance or disappearance of mutations during treatment, and as a predictor of response or progression. Finally, as our biological and translational understanding of acquired resistance continues to develop, this will inform specific treatments for subsequent lines of therapy in the second-line setting and beyond.

6. Conclusions

Advancements in the clinical development of EGFR-TKIs have led to evolving improvements in clinical outcomes for patients with EGFRm positive advanced NSCLC. In the first-line setting, osimertinib treatment provided superior efficacy to previous standard EGFR-TKI therapy with significantly longer PFS and improvements in time to treatment failure and time to second subsequent therapy or death. Furthermore, preclinical and clinical data indicate that osimertinib can cross the intact blood-brain barrier, and CNS efficacy has been demonstrated in patients with EGFRm positive advanced NSCLC. Acquired resistance

in patients receiving first-line osimertinib is currently being investigated but, encouragingly, preliminary data show that no new unexpected mechanisms of resistance have been so far identified. Due to the observed multifactorial resistance mechanisms, including EGFR mutations, activation of bypass signaling pathways, phenotypic and histologic transformation, new therapeutic strategies are needed to tailor personalized treatment options. Several clinical development programs are ongoing to investigate the role of combination approaches with osimertinib. Further understanding of these potential combinations will provide critical information to inform future treatment decisions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

CI	confidence interval
CNS	central nervous system
ctDNA	circulating tumor DNA
ddPCR	droplet digital polymerase chain reaction
EGFR	epidermal growth factor receptor
EGFRm	EGFR-TKI sensitizing mutation
Ex19del	exon 19 deletion
HR	hazard ratio
mTOR	mammalian target of rapamycin
NC	non-calculable
NSCLC	non-small-cell lung cancer
ORR	objective response rate
OS	overall survival
PFS	progression-free survival
PPA	positive percentage agreement

RCT	randomized control trial
SoC	standard of care
TKI	tyrosine kinase inhibitor
VEGF	vascular endothelial growth factor

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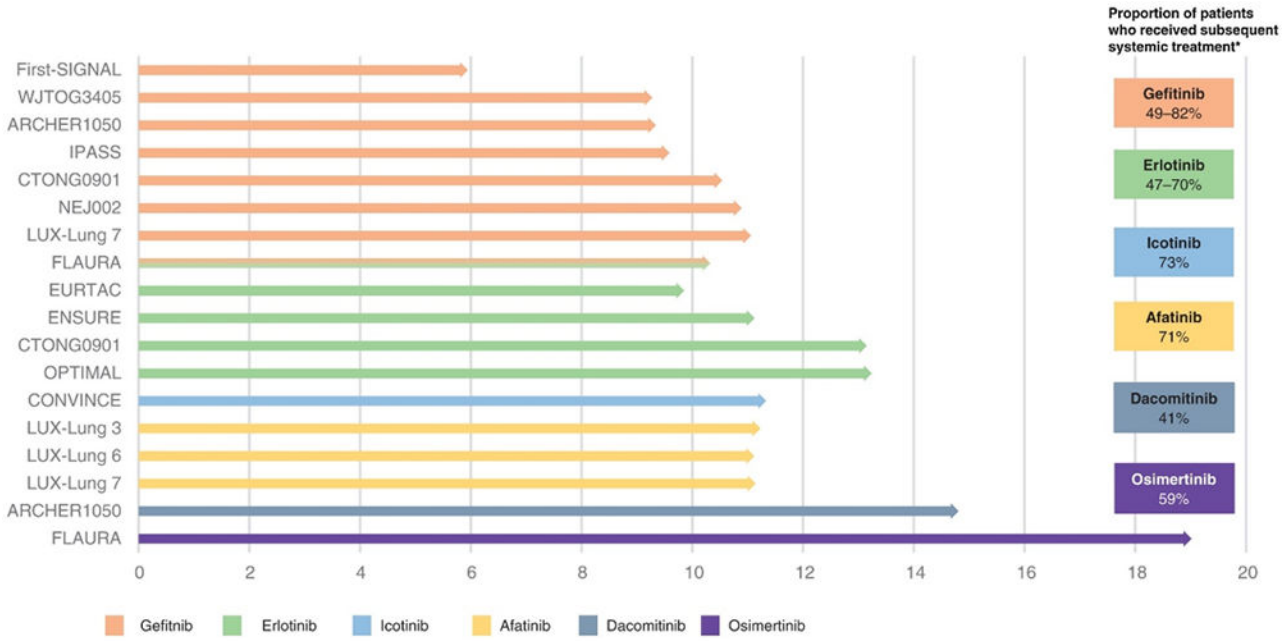

Figure 1.

Median PFS with first-line EGFR-TKI treatment in EGFR mutation-positive NSCLC and the proportion of patients who received subsequent systemic treatment [6-12,19,29,32,33,102,103,138-142]

*As a proportion of patients who discontinued EGFR-TKI at data cut-off; treatment presumed systemic when details not provided; however, some references are not clear in this respect. Note, due to the differences in trial designs and patient populations, cross-trial comparisons should be interpreted with caution.

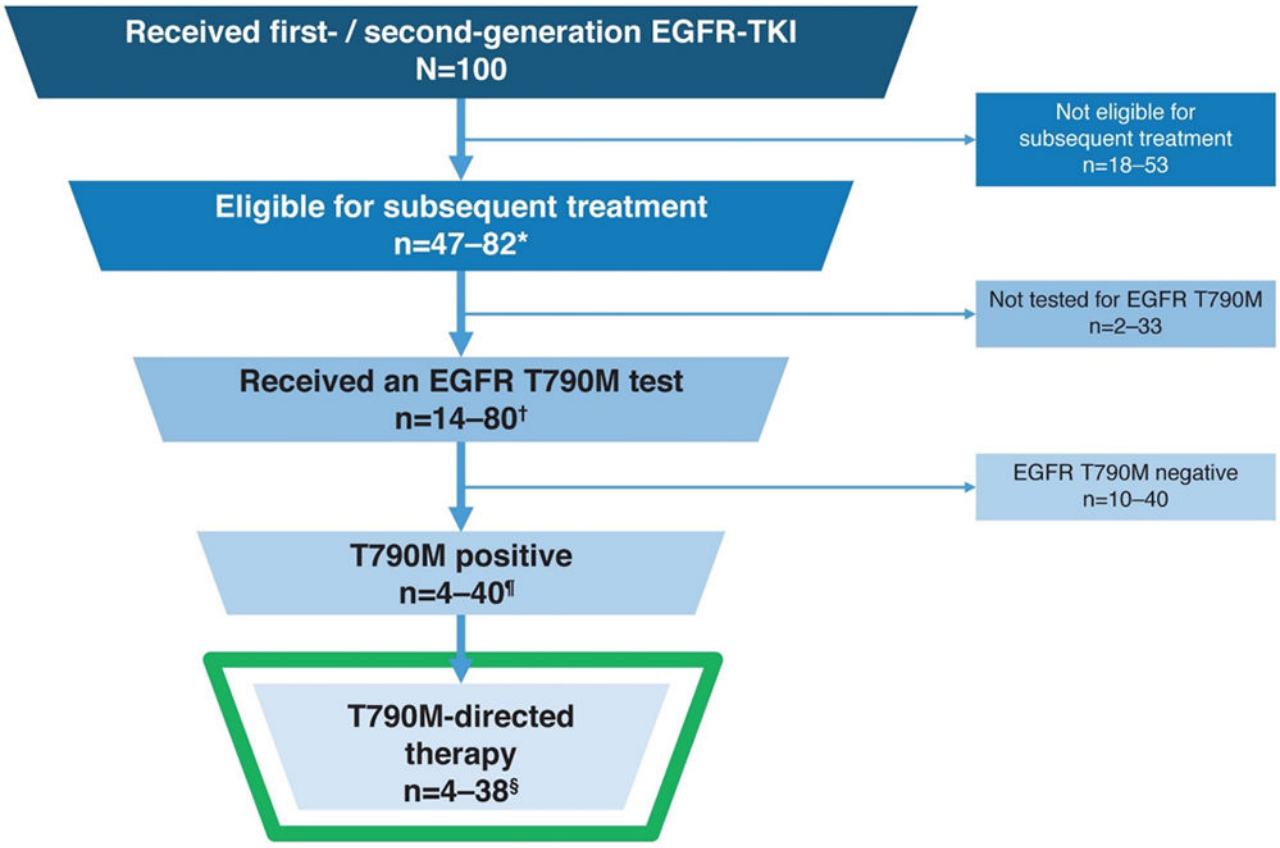

Figure 2.

Approximation of proportion of patients with EGFRm positive advanced NSCLC treated with first- / second-generation EGFR-TKIs and who go on to receive osimertinib as second-line therapy [6-12,19,93,95,98,102,103,111,138-140,143-145]

*Based on the proportion of patients who discontinued first-line EGFR-TKIs in randomized-controlled trials and who received subsequent systemic treatment: 47–82%

†Based on real-world evidence studies indicating the proportion of patients who received an EGFR T790M test: FLATIRON (30%) and REMEDY (97% of patients with samples collected)

¶Based on a meta-analysis of literature indicating a prevalence of 50% (Wang et al. BMC 2018), and real-world evidence studies indicating a lower than expected T790M positive rate: FLATIRON (28%) and REMEDY (31%)

§Based on real-world evidence studies, the vast majority of patients who test positive for T790M receive osimertinib treatment: FLATIRON (96%) and REMEDY (90%)

FLATIRON: US Flatiron Electronic Health Record-derived database study

REMEDY: A prospective study of molecular testing status in the EGFR mutation positive NSCLC patients with disease progression during EGFR-TKI treatment

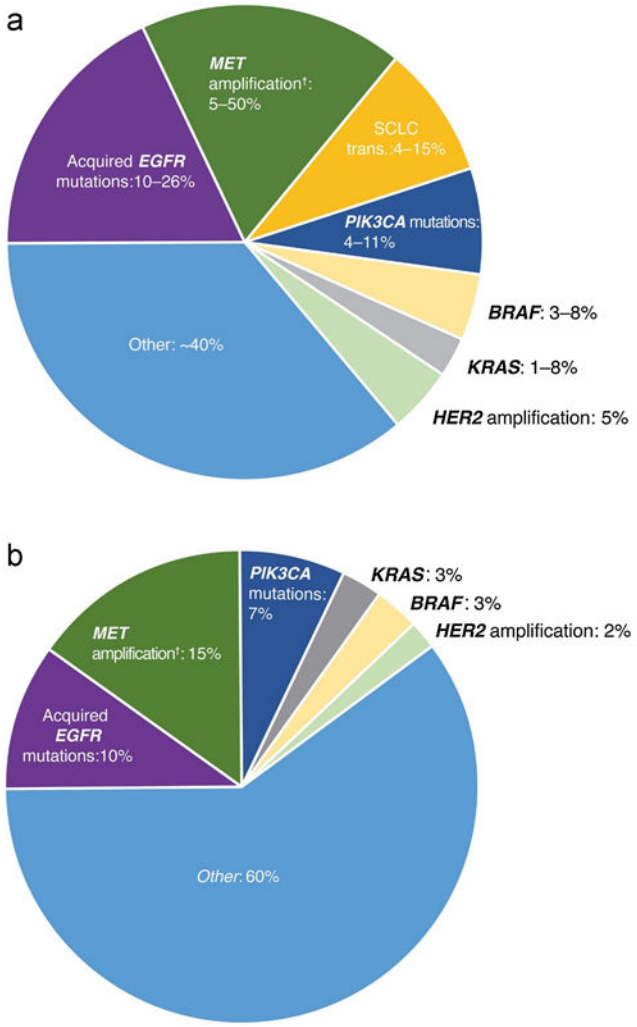

Figure 3.

A. Resistance mechanisms post ≥second-line osimertinib* [146-152]

Composite pie chart (range of data values correspond to the size of each segment)

*Resistance mechanism reported may overlap with another

†Resistance mechanisms in plasma; frequency of MET amplification is expected to be higher in tissue

B. Plasma-based resistance mechanisms post first-line osimertinib (FLAURA)* [112]

*Resistance mechanism reported may overlap with another

†Resistance mechanisms in plasma; frequency of MET amplification is expected to be higher in tissue