Overall Treatment Strategy for Patients With Metastatic NSCLC With Activating *EGFR* Mutations

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Abstract

Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (EGFR-TKIs) are standard of care in the first-line (1L) setting for patients with metastatic non–small cell lung cancer (mNSCLC) with activating *EGFR* mutations. *EGFR*-activating mutations are a predictive factor for response to EGFR-TKIs. Meta-analyses have shown that patients with exon 21_L858R mutations exhibit reduced sensitivity to EGFR-TKIs, resulting in inferior patient outcomes compared to those with exon 19 deletion mutations, with worse overall survival, progression-free survival, objective response, and disease control rates. Clinical activity observed with 1L therapy with first-generation (1G), second-generation (2G), and third-generation (3G) EGFR-TKIs is not permanent, and resistance inevitably develops in all cases, supporting the importance of overall treatment planning. The introduction of the 3G EGFR-TKI, osimertinib, provides an opportunity to overcome T790M-mediated resistance to 1G, and 2G EGFR-TKIs. Additionally, with the use of osimertinib, fewer T790M mutations are being detected as T790M is not a reported resistance mechanism to 3G EGFR-TKIs. However, there are currently no approved targeted therapies after 3G EGFR-TKIs. In order to further improve patient outcomes, there is a need to explore additional options for the overall treatment strategy for patients, including 1L and beyond. Combination of vascular endothelial growth factor (VEGF) inhibitors and EGFR-TKIs or chemotherapy and EGFR-TKIs may be a potential therapeutic approach in the 1L setting. This review discusses current treatment options for mNSCLC with activating *EGFR* mutations based on tumor, patient, and treatment characteristics and how an overall treatment plan may be developed.

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Keywords: Non–small-cell lung cancer, epidermal growth factor receptor, tyrosine kinase inhibitor, treatment plan, mutation subtype. *Abbreviations*: first generation (1G), second generation (2G), third generation (3G), first line (1L), second line (2L), disease control rate (DCR), epidermal growth factor receptor (EGFR), EGFR–tyrosine kinase inhibitor (EGFR-TKI), exon 19 deletion mutation (ex19del), exon 21 L858R mutation (L858R), median overall survival (mOS), median progression-free survival (mPFS), non–small cell lung cancer (NSCLC), overall survival (OS), objective response rate (ORR), progression-free survival (PFS), tyrosine kinase inhibitor (TKI), vascular endothelial growth factor (VEGF)

Introduction

Lung cancer was the leading cause of cancer-related mortality worldwide in 2020 and non–small cell lung cancer (NSCLC) accounts for approximately 90% of all lung cancer cases.[1,2] In a pooled analysis across 151 global studies including 33,162 patients with NSCLC/adenocarcinoma (ADC), approximately 29% of patients had *epidermal growth factor receptor (EGFR)* mutations.[3] The prevalence of *EGFR* mutation was highest in the Asia-Pacific (47%) region and lowest in Oceania (12%). The most common EGFR-TKI-sensitive activating mutations are exon 19 deletions (ex19del) (45%) and exon 21_L858R (L858R) (44%) mutations, and the least common are exon 20 mutations (2.0%).[4] The T790M mutation is the most common resistance mutation associated with first- (1G) and second-generation (2G) EGFR tyrosine kinase inhibitors (EGFR-TKIs) treatment.[4]

There are currently a variety of treatment strategies under development for mNSCLC with activating *EGFR* mutations, see

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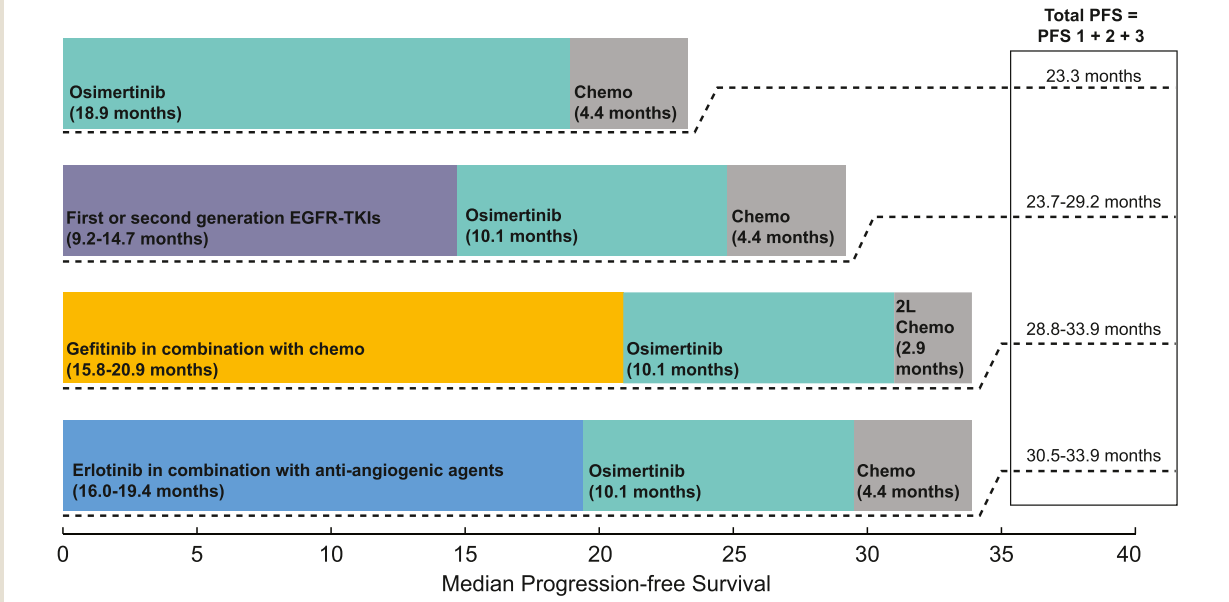
Figure 1 Indirect comparison of sequential median progression free survival estimates based on current treatment options for mNSCLC with activating *EGFR* mutations for patients who develop T790M mutation after 1L therapy with 1G or 2G EGFR-TKI.[5-24]



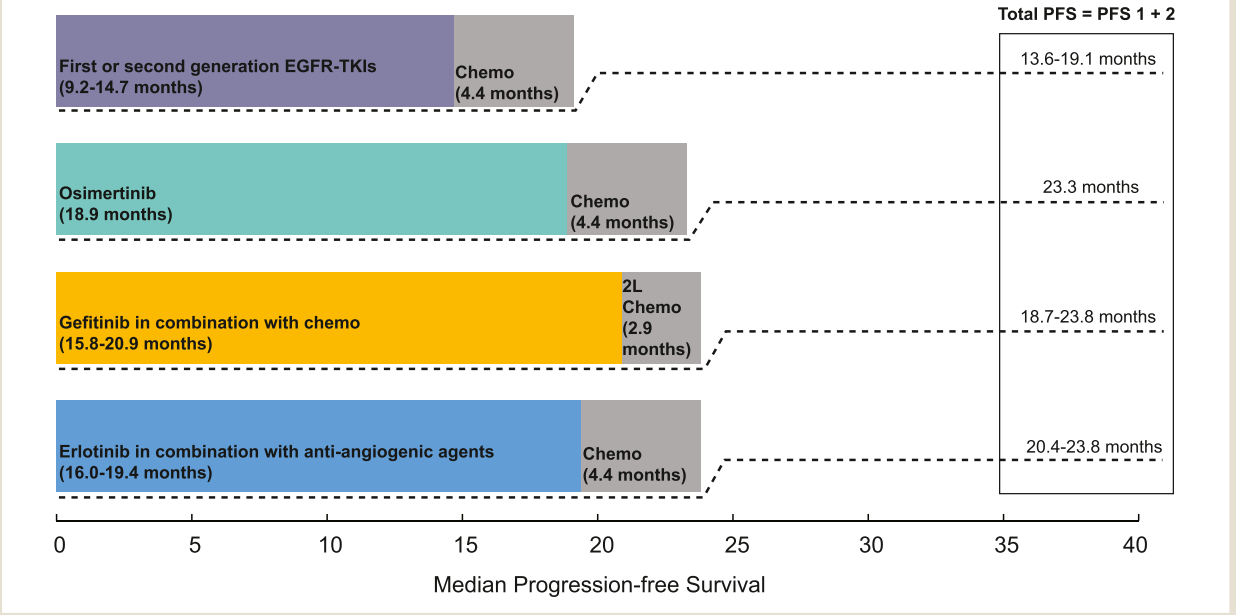
Figures 1, and 2.[5-25] Unfortunately, the majority of existing trials are not designed to specifically address the question of optimal treatment order, particularly in the context of first-line (1L) EGFR-TKI followed by second-line (2L) EGFR-TKI**.** Ongoing studies will provide valuable information about the relevance of treatment order and the initiation of 2L therapy.[26,27] It is also important to understand the relevance of testing for T790M mutations in the context of acquired resistance to 1G and 2G EGFR-TKIs to determine optimal treatment options. Mutation type affects response to EGFR-TKIs and accounting for the mutation type may help to decide which patients would most likely benefit from differing alternative 1L treatment. This review aims to identify potential treatment approaches in mNSCLC with activating *EGFR* mutations from the multiple treatment options available and how tumor, patient, and treatment factors may be considered to develop personalized treatment plans for these patients.

Randomized Clinical Trials With EGFR-TKIs in mNSCLC With Activating *EGFR* Mutations

Single-Agent EGFR-TKIs

Historically, platinum-based chemotherapy was the only choice for 1L treatment for patients with mNSCLC. The discovery of targetable mutations led to increased treatment options with 1G EGFR-TKIs demonstrating superior benefit in mNSCLC with activating *EGFR* mutations compared with chemotherapy.[10,11,13] The IPASS and NEJ002 were some of the initial trials comparing EGFR-TKI with chemotherapy, demonstrating considerably longer median progression-free survival (mPFS) for patients receiving gefitinib.[28,29] The results of the randomized, phase III trials, OPTIMAL/CTONG-0802 and EURTAC, supported erlotinib as standard 1L therapy, demonstrating considerably improved PFS in patients who received erlotinib compared with chemotherapy.[12,13] Trials comparing the 2G EGFR-TKI, afatinib, with chemotherapy further broadened the evidence base for the use of EGFR-TKIs as 1L therapy.[30] In the phase III LUX-Lung 3 and LUX-Lung 6 trials, afatinib provided PFS benefit compared with platinum-doublet chemotherapy (pemetrexed and cisplatin or gemcitabine and cisplatin).[17,19] Post-hoc analysis of LUX-Lung 2, LUX-Lung 3 and LUX-Lung 6 trials has shown that afatinib exhibits activity in uncommon EGFR point mutations or duplications in exons 18-21 but not in de novo T790M mutations or exon 20 insertions.[31] The ARCHER 1050 trial demonstrated that the 2G EGFR-TKI, dacomitinib, improved mPFS compared with the 1G gefitinib.[21] Outcomes for mNSCLC with activating *EGFR* mutations have improved significantly with the introduction of third generation (3G) EGFR-TKIs. In the FLAURA trial, 1L osimertinib provided significantly longer mPFS (18.9 months), and median overall survival (mOS) (38.6 months) compared with standard EGFR-TKIs in the overall population (gefitinib or erlotinib; 10.2 months [mPFS]; 31.8 months [mOS]).[32,33] OS improvement with 1L osimertinib was seen despite the fact that 47% of patients assigned to 1L standard EGFR-TKI, who received any 2L therapy, received osimertinib as first subsequent treatment. Although osimertinib demonstrated PFS benefit compared with EGFR-TKIs regardless of race in the FLAURA trial, OS benefit was not observed in Asian patients (HR for OS 1.0 [95% CIs: 0.75-1.32]).[33] EGFR-TKIs are now the standard of care in the 1L setting for mNSCLC with

Figure 2 Indirect comparison of sequential median progression free survival estimates based on current treatment options for mNSCLC with activating *EGFR* mutations for patients who do not develop T790M mutation after 1L therapy.[5-25]



activating *EGFR* mutations and ongoing trials are investigating if EGFR-TKI-based combination treatments could further improve patient outcomes.[1,34,35] See Table 1 for some pertinent ongoing trials in this setting.

Combination of EGFR-TKIs With Chemotherapy

The NEJ005/TCOG0902 was one of the first randomized studies to evaluate efficacy when combining EGFR-TKI with chemotherapy in patients with mNSCLC with activating *EGFR* mutations.[6] Concurrent versus sequential alternating gefitinib and chemotherapy as 1L therapy revealed similar responses between treatment arms.[6] Updated analyses have confirmed PFS was improved with the 1L combination therapy compared with gefitinib monotherapy, and the concurrent regimen provides a mOS of 41.9 months.[36] The subsequent NEJ009 study further confirmed the PFS benefit offered by 1L gefitinib combined with carboplatin and pemetrexed chemotherapy.[8] The NEJ009 trial also revealed a mOS benefit, with the chemotherapy, and gefitinib combination demonstrating longer mOS compared with gefitinib alone (50.9 months vs. 38.8 months). Another phase III trial provided further support for improved mPFS and mOS outcomes following gefitinib and chemotherapy treatment compared with gefitinib monotherapy.[5] The randomized phase II JMIT study demonstrated improved PFS with the addition of pemetrexed to gefitinib as 1L therapy in non–squamous mNSCLC with activating *EGFR* mutations.[7] All these studies have been conducted in Asian patients and there is limited evidence of the EGFR-TKI with chemotherapy approach in non–Asian patients. It should also be noted that treatment-related adverse events are increased with combination therapy compared with monotherapies.[37] Results of trials examining EGFR-TKI and chemotherapy combinations are summarized in Table 2.[5,7,8,36]

Anti–Angiogenic and EGFR-TKI Combination

Angiogenesis and EGFR pathways share downstream signaling targets and can function exclusive of each other during oncogenesis.[38] In mNSCLC with activating *EGFR* mutations, increased *EGFR*-signaling upregulates vascular endothelial growth factor (VEGF) pathway, contributing to resistance to EGFR-TKIs.[39] The addition of bevacizumab (anti–VEGF antibody) or ramucirumab (anti–VEGF receptor 2 antibody) to EGFR-TKIs has demonstrated considerable clinical benefit with improved PFS, supporting the rationale for dual EGFR and VEGF inhibition.[40-45] The combination of erlotinib and ramucirumab demonstrated a mPFS of 19.4 months in the RELAY trial and the combination of erlotinib and bevacizumab showed a mPFS of 18.0 months, 17.9 months, 16.9 months and 16.0 months in the CTONG1509, ACCRU RC1126, NEJ026, and JO25567 trials respectively.[40-44] Trials investigating the combination of erlotinib and bevacizumab have not shown benefit in OS and OS data for erlotinib and ramucirumab remains immature, although RELAY demonstrated PFS2 benefit for erlotinib and ramucirumab compared with erlotinib and placebo.[45-47] The CTONG1706 study (NCT02824458) is the first to investigate the efficacy and safety of apatinib (a VEGFR2-TKI) with gefitinib as 1L combination therapy, demonstrating a longer mPFS in patients receiving apatinib and gefitinib compared with placebo and gefitinib (13.7 months vs. 10.2 months).[48] Increased efficacy with combination approaches comes at a cost of increased treatment-related adverse events compared to monotherapies.[37]

Table 1 Active Clinical Trials in mNSCLC With Activating *EGFR* Mutations

Title	Trial identifier	Phase	Intervention/treatment	Line of therapy	Primary endpoint
A Biomarker-directed phase II Platform Study in Patients With Advanced Non–Small Lung Cancer Whose Disease Has Progressed on First-Line Osimertinib Therapy	NCT03944772	II	Osimertinib + savolitinib versus osimertinib + gefitinib versus osimertinib + necitumumab versus carboplatin + pemetrexed + durvalumab versus osimertinib + alectinib versus osimertinib +selpercatinib versus observational cohort	Second line	Objective response rate
Osimertinib Plus Savolitinib in EGFRm+/MET+ NSCLC Following Prior Osimertinib (SAVANNAH)	NCT03778229	II	Osimertinib+savolitinib	Second line	Objective response rate
Atezolizumab in Combination With Bevacizumab, Carboplatin, and Pemetrexed for *EGFR*-mutant Metastatic Non–small Cell Lung Cancer Patients After Failure of EGFR Tyrosine Kinase Inhibitors: a Single Arm phase II Study	NCT03647956	II	Atezolizumab + bevacizumab + carboplatin + pemetrexed	Second line	Objective response rate
Single Arm phase II Trial of Atezolizumab and Bevacizumab in Epidermal Growth Factor Receptor (*EGFR*) Mutant Non–Small Cell Lung Cancer in Patients With Progressive Disease After Receiving Osimertinib (TOP 1901)	NCT04099836	II	Atezolizumab + bevacizumab	Second line	Objective response rate
A Prospective, Multi-center, Interventional Study of Osimertinib Combined With Anlotinib in Acquired *EGFR* T790M Mutated NSCLC Patients With Gradual Progression on Osimertinib Treatment	NCT04438902	II	Osimertinib + anlotinib	Second line	Progression free survival from randomization until disease progression
A Randomized phase II Trial of Osimertinib Alone or in Combination With Bevacizumab for *EGFR*-Mutant Non–small Cell Lung Cancer With Leptomeningeal Metastasis	NCT04148898	II	Osimertinib versus osimertinib + bevacizumab	First line	Intracranial progression-free and objective response rate
Randomized phase II study of osimertinib plus ramucirumab and osimertinib for chemotherapy-naive patients with non–squamous non-small cell lung cancer harbouring *EGFR* mutations	CN-02188497	II	Osimertinib versus osimertinib + ramucirumab	First line	Progression free survival
An Open-Label Randomized phase II Study of Combining Osimertinib With and Without Ramucirumab in Tyrosine Kinase Inhibitor (TKI)-naïve Epidermal Growth Factor Receptor (*EGFR*)-Mutant Locally Advanced or Metastatic NSCLC	NCT03909334	II	Osimertinib versus osimertinib + ramucirumab	First line	Progression free survival from randomization to disease progression
A phase II Study of Osimertinib in Combination With Selumetinib in EGFR Inhibitor naïve Advanced *EGFR* Mutant Lung Cancer	NCT03392246	II	Osimertinib + selumetinib	First line	Best objective response
Open Label, Multi-center phase Ib / II Study of Glumetinib Combined With Osimertinib in the Treatment of Relapsed and Metastatic Non–small Cell Lung Cancer Patients Who Failed to Receive EGFR Inhibitors	NCT04338243	II	Osimertinib + glumetinib	Second line	Objective response rate
A phase II Trial of Osimertinib and Abemaciclib With a Focus on Non–Small Cell Lung Cancer Patients With *EGFR* Activating Mutations With Osimertinib Resistance	NCT04545710	II	Osimertinib + abemaciclib	Second line	Progression free survival at 6 mo

(*continued on next page*)

Table 1 (*continued*)

Title	Trial identifier	Phase	Intervention/treatment	Line of therapy	Primary endpoint
A phase II, Open-Label, Multicenter, Single-Arm, Prospective Clinical Study to Investigate the Efficacy, and Safety of Tislelizumab Combined With Chemotherapy in Non–squamous NSCLC With *EGFR* Sensitizing Mutation Who Failed EGFR TKI Therapy	NCT04405674	II	Tislelizumab + carboplatin/ nabpaclitaxel, followed by tislelizumab + pemetrexed	Second line	1 y progression free survival rate
A Prospective, Single-center, One-arm Clinical Study of Apatinib Combined With Chemotherapy for Patients Who Progressed After First Line EGFR-TKI Treatment Without T790M Mutation	NCT03758677	II	Apatinib + chemotherapy	Second line	Progression free survival
Open-Label, Randomized Trial of Nivolumab (BMS-936558) Plus Pemetrexed/Platinum or Nivolumab Plus Ipilimumab (BMS-734016) versus Pemetrexed Plus Platinum in stage IV or Recurrent Non–Small Cell Lung Cancer (NSCLC) Subjects With Epidermal Growth Factor Receptor (*EGFR*) Mutation Who Failed 1L or 2L EGFR Tyrosine Kinase Inhibitor Therapy	NCT02864251	III	Nivolumab + pemetrexed/ platinum or nivolumab + ipilimumab versus pemetrexed + platinum	Second or third line	Progression free survival
A phase III, Randomized, Double-blind Study to Assess the Efficacy, and Safety of Lazertinib Versus Gefitinib as the First-line Treatment in Patients With Epidermal Growth Factor Receptor Sensitizing Mutation Positive, Locally Advanced or Metastatic Non–Small Cell Lung Cancer	NCT04248829	III	Lazertinib versus gefitinib	First line	Progression free survival
Phase III Study Comparing Osimertinib Monotherapy to Combination Therapy With Osimertinib, Carboplatin and Pemetrexed for Untreated Patients With Advanced Non–squamous Non–Small Cell Lung Cancer With Concurrent *EGFR* and TP53 Mutations	NCT04695925	III	Osimertinib versus osimertinib + chemotherapy	First line	Progression free survival from randomization to disease progression
A phase III, Randomized, Double-Blind, Placebo-Controlled Study of Platinum Plus Pemetrexed Chemotherapy Plus Osimertinib Versus Platinum Plus Pemetrexed Chemotherapy Plus Placebo in Patients With *EGFR*m, Locally Advanced or Metastatic NSCLC Who Have Progressed Extracranially Following First-Line Osimertinib Therapy (COMPEL)	NCT04765059	III	Osimertinib + pemetrexed + cisplatin or carboplatin versus placebo + pemetrexed + cisplatin or carboplatin	Second line	Progression free survival from randomization to disease progression
Randomized phase III Study of Combination AZD9291 (Osimertinib) and Bevacizumab Versus AZD9291 (Osimertinib) Alone as First-Line Treatment for Patients With Metastatic *EGFR*-Mutant Non–Small Cell Lung Cancer (NSCLC)	NCT04181060	III	Osimertinib versus osimertinib + bevacizumab	First line	Progression free survival from randomization to disease progression
A phase III, Randomized Study of Amivantamab, and Lazertinib Combination Therapy Versus Osimertinib Versus Lazertinib as First-Line Treatment in Patients With *EGFR*-Mutated Locally Advanced or Metastatic Non–Small Cell Lung Cancer.	NCT04487080	III	Amivantamab + lazertinib versus osimertinib + placebo versus lazertinib + placebo	First line	Progression free survival from randomization to disease progression
A Multi-center, Randomized, Double-Blind Study of Gefitinib in Combination With Anlotinib or Placebo in Previously Untreated Patients With *EGFR* Mutation-Positive Advanced Non–Small Cell Lung Cancer.	NCT04028778	III	Gefitinib + anlotinib versus gefitinib versus placebo	First line	Progression free survival

Table 2 Randomized Controlled Trials Examining EGFR-TKIs and Chemotherapy Combinations[5,7,8,35]

Title	Phase	mPFS		mOS	
		Concurrent regimen	Alternating regimen	Concurrent regimen	Alternating regimen
Randomized phase II study of continuous gefitinib plus chemotherapy versus alternation of gefitinib and chemotherapy in previously untreated non–small cell lung cancer (NSCLC) with sensitive EGFR mutations (NEJ005/TCOG0902)	II	17.5 mo (95% CIs: 9.7-21.9 mo)	15.3 mo (95% CIs: 11.2-17.4 mo)	41.9 mo (95% CIs: 31.8-58.0 mo)	30.7 mo (95% CIs: 22.7-38.3 mo)
		HR 0.68 (95% CIs: 0.42-1.12)		HR 0.58 (95% CIs: 0.34-0.97)	
		Combination regimen	Monotherapy	Combination regimen	Monotherapy
NEJ009 trial: A randomized phase III study of gefitinib (G) in combination with carboplatin (C) plus pemetrexed (P) versus G alone in patients with advanced non–squamous non–small cell lung cancer (NSCLC) with EGFR mutation	III	20.9 mo (95% CIs: 17.94-24.20 mo)	11.9 mo (95% CIs: 8.97-13.40 mo)	50.9 mo (95% CIs: 41.77-62.50 mo)	38.8 mo (95% CIs: 31.10-47.33 mo)
		HR 0.49 (95% CIs: 0.39-0.62)		HR 0.72 (95% CIs: 0.55-0.95)	
A study of pemetrexed and gefitinib versus gefitinib in non–small cell lung cancer (NSCLC)	II	15.8 mo (95% CIs: 12.6-18.3 mo)	10.9 mo (95% CIs: 9.7-13.8 mo)	OS data are immature	
		HR 0.68 (95% CIs: 0.48-0.96)			
A randomized study to compare gefitinib versus chemotherapy with gefitinib in EGFR mutation positive Non–Small cell lung cancer in palliative setting	III	16 mo (95% CIs: 13.5-18.5 mo)(estimated)	8 mo (95% CIs: 7.0-9.0 mo)(estimated)	Not reached (estimated)	17 mo (95% CIs: 13.5-20.5 mo)(estimated)
		HR 0.51 (95% CIs: 0.39-0.66)		HR 0.45 (95% CIs: 0.31-0.65)	

Results of trials examining EGFR-TKI and anti–angiogenic combinations are summarized in Table 2 and 3.[40-49]

The real-world study BELLA (NCT04575415) using bevacizumab and EGFR-TKIs in Chinese patients with mNSCLC with activating *EGFR* mutations may provide useful information regarding the clinical efficacy and safety of this treatment regimen.[50] Randomized phase II trials of 1L bevacizumab and osimertinib or ramucirumab and osimertinib compared with osimertinib alone in the 1L setting are ongoing and they will inform about the combination of 3G EGFR TKI with an anti–angiogenic therapy.[51-53]

Osimertinib as First-Line or Second-Line Therapy

Osimertinib as First-Line Therapy

As previously mentioned, osimertinib has demonstrated longer mPFS and OS compared with 1G and 2G EGFR-TKIs.[32] The findings from the FLAURA trial have established 1L osimertinib as the standard of care in mNSCLC with activating *EGFR* mutations.[1,35] Additionally, a phase I/II single arm trial to evaluate the combination of bevacizumab and osimertinib demonstrated promising efficacy and tolerability in patients with T790M.[54]

T790M is an acquired gatekeeper mutation, a resistance mechanism to 1G and 2G EGFR-TKIs, sensitive to osimertinib, and is rarely present at diagnosis of mNSCLC with activating *EGFR* mutations. A recent simulation study investigated whether there is a T790M positivity rate at which upfront first- (1G) or second-generation (2G) EGFR-TKIs followed by osimertinib exceeds overall PFS compared with 1L osimertinib.[55] Even with a simulated 100% T790M-positive mutation rate, upfront osimertinib therapy was found to provide a better mPFS than sequential 1G or 2G EGFR-TKIs followed by osimertinib.

Osimertinib as Second-Line Therapy

The AURA3 trial in patients with T790M mutations provides a 2L option with osimertinib following 1G/2G EGFR-TKIs as 1L (mPFS: 10.1 months [osimertinib] vs. 4.4 months [platinum therapy and pemetrexed]).[24,56] The TREM trial confirms the efficacy of osimertinib as 2L for patients with T790M.[57] However, the randomized phase II study, WJOG8715L, did not find any benefit in PFS or OS in adding bevacizumab to osimertinib as 2L therapy for PFS and OS outcomes in patients with *EGFR* T790M+ mNSCLC.[58]

Advantages and Disadvantages of Osimertinib in 1L or 2L Setting

The FLAURA trial shows a clear rationale for using osimertinib in 1L in all patients with mNSCLC with activating *EGFR* mutations, including those with brain metastases, and the small number of cases where T790M is detected at disease onset.[59] Osimertinib causes less toxicity (because of its decreased affinity to wild-type *EGFR*) and also results in decreased central nervous system disease progression than earlier-generation EGFR-TKIs.[60]

Table 3 Randomized Controlled Trials Examining EGFR-TKIs and Anti–Angiogenics Combinations[39-48]

Title	Phase	mPFS		mOS	
		Combination regimen	Monotherapy	Combination regimen	Monotherapy
A phase II, open-label, randomized trial of RG1415 (erlotinib hydrochloride) plus bevacizumab versus RG1415 alone as a first line therapy for advanced or metastatic NSCLC patients with EGFR mutation (JO25567)	II	16.0 mo (95% CIs: 13.9-18.1 mo)	9.7 mo (95% CIs: 5.7-11.1 mo)	47.0 mo[a]	47.4 mo[a]
		HR 0.54 (95% CIs: 0.36-0.79)		HR 0.81 (95% CIs: 0.53-1.23)	
Compare bevacizumab in combination with erlotinib versus erlotinib alone in NSCLC patients activating EGFR mutations (ARTEMIS/CTONG1509)	III	18.0 mo (95% CIs: 15.2-20.7 mo)	11.3 mo (95% CIs: 9.8-13.8 mo)	OS data are immature	
		HR 0.55 (95% CIs: 0.41-0.75)			
Erlotinib hydrochloride with or without bevacizumab in treating patients with stage IV non–small cell lung cancer with epidermal growth factor receptor mutations (ACCRU RC1126)	III	17.9 mo (95% CIs 13.3-24.1 mo)	13.5 mo (95% CIs: 8.8-21.6 mo)	32.4 mo (95% CIs: 26.9-54.4 mo)	50.6 mo (95% CIs: 49.4-not reached)
		HR 0.81 (95% CIs: 0.50-1.31)		HR 1.41 (95% CIs: 0.71-2.81)	
Randomized phase III study comparing erlotinib plus bevacizumab to erlotinib alone in patients with previously untreated non–small cell lung cancer harboring EGFR mutation (NEJ026)	III	16.9 mo (95% CIs:14.2-21.0 mo)	13.3 mo (95% CIs: 11.1-15.3 mo)	50.7 mo (95% CIs: 37.3-not reached)	46.2 mo (95% CIs: 38.2-not reached)
		HR 0.61 (95% CIs: 0.42-0.88)		HR 1.00 (95% CIs: 0.69- 1.48)	
A study of gefitinib with or without apatinib in patients with advanced non–squamous non–small cell lung cancer harboring EGFR mutations (ACTIVE/CTONG1706)	III	13.7 mo[a]	10.2 mo[a]	OS data are immature	
		HR 0.71 (95% CIs: 0.53-0.95)			
		Ramucirumab plus erlotinib	Placebo plus erlotinib		
A study of ramucirumab (LY3009806) in combination with erlotinib in previously untreated participants with EGFR mutation-positive metastatic NSCLC (RELAY)	III	19.4 mo (95% CIs: 15.4-21.6 mo)	12.4 mo (95% CIs: 11.0-13.5 mo)	OS data are immature	
		HR 0.59 (95% CIs: 0.46-0.76)			

[a] 95% CIs data not available

Osimertinib is active as a 2L treatment after 1L treatment with 1G or 2G EGFR-TKIs in the setting of T790M mutation positive disease, and the AURA 3 trial has established osimertinib as the standard of care for patients who develop T790M mutation after 1L therapy with earlier-generation EGFR-TKIs.[1,35,56]

However, reserving osimertinib for 2L therapy raises some concerns that patients would potentially not be tested for or found to be negative for T790M and miss the opportunity to receive osimertinib treatment. Not all patients will develop the T790M resistance mutation, and some patients may not receive or survive until 2L therapy. It is also not possible to predict at baseline what mechanisms of resistance will develop. A large number of clinical trials report a high attrition rate for patients switching from 1L to 2L therapy.[37] Unequal access to the most sensitive methods for detecting T790M mutations may also have an impact on clinical outcomes as T790M mutations may be under-detected.[37]

A retrospective study which compared 1L afatinib with 1G EGFR-TKIs indicated a trend of improved outcomes for afatinib followed by osimertinib for T790M-positive NSCLC compared to 1G EGFR TKI followed by osimertinib.[61] The ongoing phase II APPLE study (NCT02856893) will prospectively evaluate the strategy for sequential gefitinib followed by osimertinib.[27] Performed in patients with *EGFR*-mutated and EGFR-TKI-naïve mNSCLC, the study will help elucidate the value of a sequenced strategy of gefitinib followed by osimertinib compared with upfront osimertinib.[27]

However, to definitively determine whether osimertinib is most beneficial as 1L or as 2L therapy, trials need to be designed to directly compare the survival outcomes with 1L osimertinib compared with 1L early-generation EGFR-TKI followed by 2L osimertinib in the setting of T790M mutation positive disease.[60]

Current Treatment Guidelines for Patients With mNSCLC

National Comprehensive Cancer Network (NCCN) guidelines recommend 1L osimertinib (preferred), erlotinib, afatinib, gefitinib, and dacomitinib with 2L options for consideration based on 1L treatment received and/or disease characteristics (eg histology, mutation status).[35] Recent updates to the NCCN guidelines for patients with mNSCLC with sensitizing *EGFR* mutations include the Category 2 recommendation of erlotinib and ramucirumab ("other recommended"; Category 2A) and erlotinib and bevacizumab ("useful in certain circumstances"; Category 2B).[35] Similarly, the 1L options according to ESMO guidelines for patients with sensitizing *EGFR* mutations in mNSCLC are osimertinib (preferred), erlotinib, gefitinib, afatinib, dacomitinib, and erlotinib and bevacizumab, erlotinib and ramucirumab, as well as the addition of 1L carboplatin and pemetrexed to gefitinib (Category 1B) also for consideration.[1] For 2L treatment in mNSCLC with activating *EGFR* mutations, ESMO guidelines recommend T790M mutation testing using initial liquid biopsy in case of EGFR-TKI resistance in those patients not previously treated with osimertinib.[1] Osimertinib is recommended for patients with a T790M+ mutation. In those patients who test negative for T790M, platinum-based doublet is considered standard therapy.[1] Atezolizumab and bevacizumab plus carboplatin plus paclitaxel is another potential 2L treatment option.[1,62]

Real-World Evidence

A recent review showed that the proportion of patients with mNSCLC with activating *EGFR* mutations that receive subsequent 2L treatment in the clinical trial setting ranges from 41% to 82% (dacomitinib [41%], erlotinib [47%-70%,] gefitinib [49%-82%], osimertinib [59%], afatinib [71%], icotinib [73%]).[63] Analysis of treatment patterns from the US Flatiron Electronic Health Record-derived database revealed EGFR-TKIs as the most common 1L therapy (72.8%; $n = 700$), and 44% ($n = 422$) of patients with mNSCLC with activating *EGFR* mutations received 2L treatment (erlotinib [32.7%], chemotherapy [32.5%], afatinib [16.1%]).[64] The global ASTRIS real-world study, which included 3,015 patients, is currently the largest real-world treatment study using osimertinib in T790M-positive mNSCLC.[65] Findings demonstrated clinical efficacy and safety comparable with that observed in previous clinical trials (ie AURA) with osimertinib as 2L therapy for patients who had received 1L EGFR-TKIs.[65] Although biased by its retrospective design and eligibility criteria, the GioTag study investigated sequential 1L afatinib followed by 2L osimertinib in 203 patients with *EGFR* T790M-mutated mNSCLC.[66] Median time on treatment, median treatment failure, and mOS (almost 4 years) were most encouraging in patients with ex19del disease.[66,67] This supports 1L afatinib followed by osimertinib as a treatment option in ex19del disease, especially when considering the high rate of T790M-acquired mutation in this subgroup (~75%).[68] The efficacy of osimertinib after afatinib in GioTag is aligned to the results of the AURA 3 study, demonstrating the possible role of an EGFR-TKI sequencing strategy in the setting of T790M mutation. As evidenced by meta-analyses, clinical trials, and real-world evidence such as the GioTag study, ex19del and L858R-positive tumors should potentially be considered as 2 different disease entities due to differences in sensitivity to EGFR-TKIs.[32,46,66,69,70]

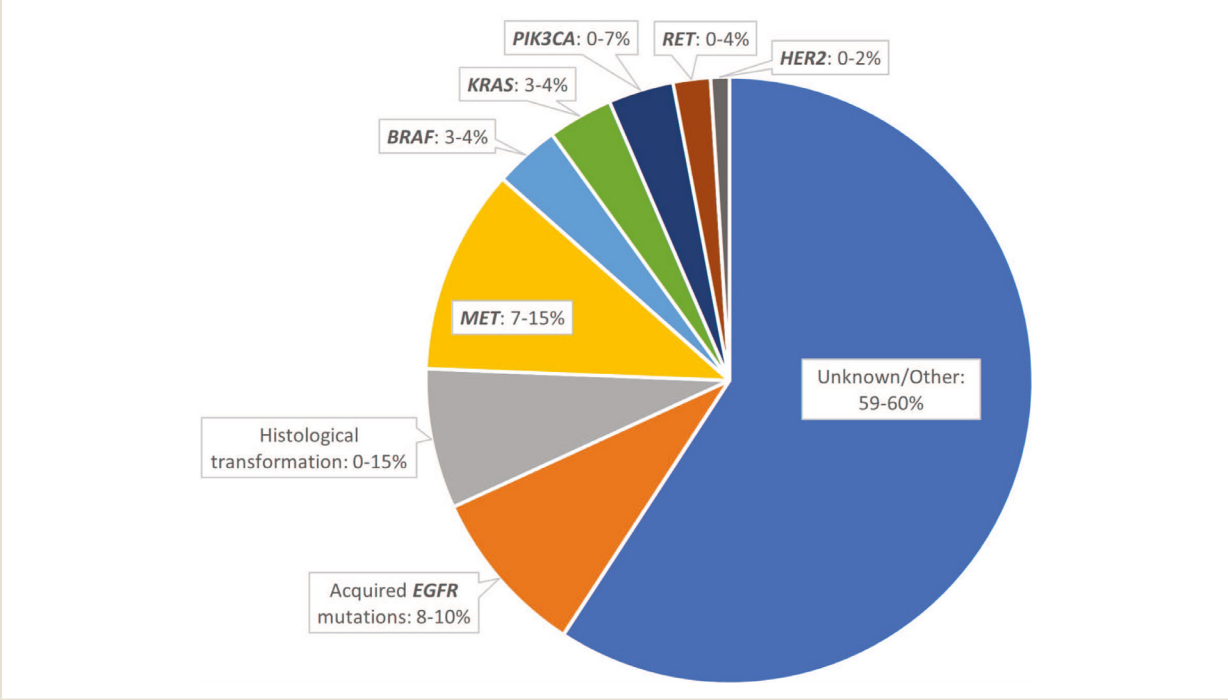
Unfortunately, all patients eventually develop resistance to osimertinib regardless if used as a 1L or 2L therapy, thereby making the treatment no longer effective.[71] Therefore, novel strategies combining EGFR-TKIs with other agents and/or the development of fourth-generation EGFR-TKIs to provide improved survival and duration of response for these patients are of utmost importance.

Considerations for Choosing Therapy for Patients With mNSCLC With Activating *EGFR* Mutations

EGFR-TKIs are the standard of care in patients with sensitizing *EGFR* mutations. Determining the optimal 2L therapy for patients following disease progression on 1L therapy depends largely on the molecular mechanisms driving resistance (eg T790M mutation, C797S mutation, mesenchymal-to-epithelial transition factor [MET] amplification, fusions, histologic transformation).[72] The most common resistance mechanism to 1G and 2G EGFR-TKIs is T790M mutation, occurring in up to two-thirds of cases and osimertinib is the treatment of choice in this case.[73] There is a paucity of 2L options for T790M-negative patients and this is an area of urgent unmet medical need. Current options include continuing with EGFR-TKIs, local therapy or systemic chemotherapy depending on patient characteristics.[74] Small clinical benefits may be obtained in this population with afatinib plus bevacizumab and bevacizumab plus platinum-based chemotherapy compared with chemotherapy and targeted therapy.[75-77] Exploratory analyses have shown atezolizumab plus bevacizumab plus chemotherapy improved survival trend compared with bevacizumab plus chemotherapy but further research is needed to determine the optimal 2L option for T790M-negative patients.[62] A phase 1 trial assessing the anti–HER3 antibody–drug conjugate, HER3-deruxtecan (DXd), in patients with T790M-negative acquired resistance to erlotinib, gefitinib, or afatinib, acquired resistance to osimertinib and other diverse mechanisms of EGFR-TKIs resistance demonstrated antitumor activity and further research is ongoing.[78-80]

The mechanisms of resistance to osimertinib are varied and continue to be investigated.[60] The most common resistance mechanisms are *MET* amplification and the emergence of the tertiary EGFR resistance mutation, C797S. Other mechanisms identified included *HER2* amplification and the emergence of *PIK3CA, BRAF* or *KRAS* mutations, and histologic transformations (Figures 3 and 4).[81-85] There may be some differences in the mechanism of resistance to osimertinib in 1L versus subsequent lines of treatment and most mechanisms of resistance to osimertinib are currently not targetable with approved treatments. Combined *MET* and *EGFR* inhibition to target osimertinib resistance driven by MET amplification is a compelling therapeutic approach. CHRYSALIS-1 evaluated the combination of lazertinib, a 3G EGFR-TKI, with amivantamab, which is a bispecific antibody that can inhibit tumor growth driven by EGFR, and MET receptors. CHRYSALIS-1 demonstrated durable responses for patients treated with amivantamab plus lazertinib who progressed on earlier osimertinib.[86] Amivantamab has also demonstrated response in patients with both *MET*

Figure 3 Resistance mechanisms reported following 1L osimertinib therapy (resistance mechanism reported may overlap with another).[81,82]

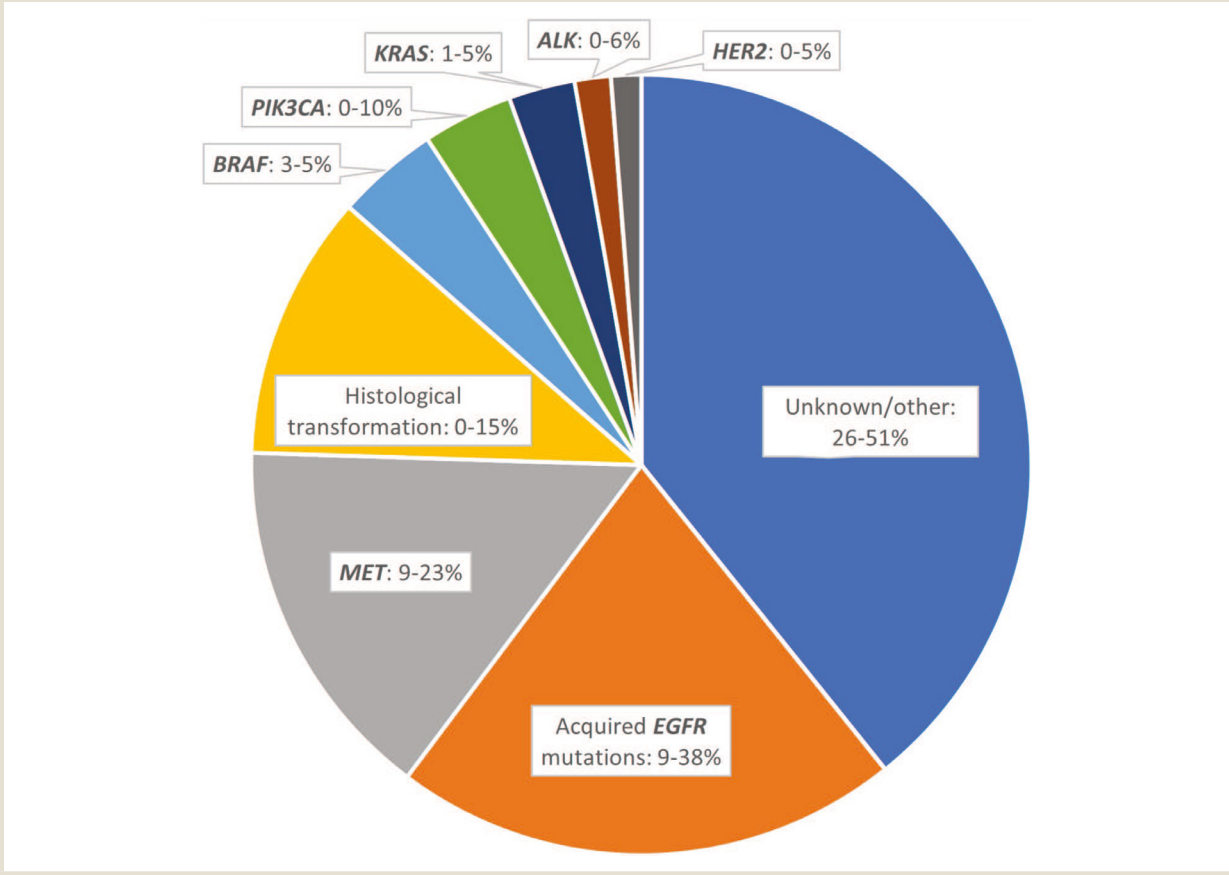


amplification and C797S mutations.[87] Brigatinib plus cetuximab may provide an effective treatment option for patients with T790M and cis-C797S mutations with resistance to osimertinib.[88] Acquired fusions in *ALK, BRAF, FGFR3, HER2, RET*, and other oncogenes have been identified on disease progression while receiving osimertinib therapy. Like the *MET* amplification, combining EGFR-TKIs with an inhibitor of the altered fusion protein is an emerging treatment strategy.[89,90] Therefore, at least some mutations within *EGFR* gene and oncogenic aberrations which allow the consequences of *EGFR* inhibition to be bypassed appear to be actionable and could be used to treat patients who have progressed on osimertinib.[37]

Longer follow-up and prospective, multi-institutional studies, such as the ongoing ELIOS trial (NCT03239340) will be required to gain a more complete picture of osimertinib resistance.[91] The ongoing biomarker-directed ORCHARD study investigates 6 different treatment combinations in patients with mNSCLC with activating *EGFR* mutations with acquired resistance following 1L osimertinib therapy.[26] Findings from this study may provide additional insights into the correlation between biomarker profiles and the treatment effect, thereby guiding future treatment planning.[26] Further research is also required to enhance our understanding of treatment options for patients with unknown mechanisms of resistance or resistance to EGFR-TKIs.

There is emerging evidence of biological difference between ex19del and L858R mutations.[92] Taking into account major studies in the setting of ex19del subgroups, the FLAURA trial demonstrated the greatest mPFS with osimertinib (21.4 months), followed by RELAY with the erlotinib and ramucirumab combination (19.6 months), and both JO25567 and NEJ026 trials with the erlotinib and bevacizumab combination (18.0 months and 16.6 months respectively) among patients with ex19del mutations.[32,40,43,46] A number of meta-analyses have shown that patients with L858R mutations derive more modest benefit to treatment with 1L EGFR-TKIs compared to patients with ex19del mutations,[69,70,92-94] although this may not be true in the setting of a dual-inhibition strategy of anti–angiogenic, and EGFR-TKI treatment.[95,96] In L858R mutations, the longest mPFS was observed with erlotinib and ramucirumab (19.4 months) followed by erlotinib and bevacizumab (17.4 months [NEJ026] and 13.9 months [JO25567]).[40,43,46,70,93] Patients with L858R in the FLAURA trial had a mPFS of 14.4 months.[32] Data from the FLAURA trial indicate no OS benefit for patients with L858R (HR 1.0 [0.71-1.40]), while OS data is still awaited from the RELAY trial.[33] It should be noted that there were differences in populations included in the RELAY, NEJ026, JO25567, and FLAURA trials which may have affected the above results. The RELAY trial did not include patients with central nervous system (CNS) metastases unlike the FLAURA (21% patients) and NEJ026 trials (32%), and the RELAY, NEJ026 and JO25567 trials included more patients with *Eastern Cooperative Oncology Group performance status* 0, compared with the FLAURA trial.[32,40,41,43] RELAY, NEJ026, and JO25567 only included patients who were eligible for antiangiogenic therapy. However based on current data,

Figure 4 Resistance mechanisms reported following 2L or 3L osimertinib therapy (resistance mechanism reported may overlap with another).[82-85]



patients with L858R mutations may be candidates for combination approaches of EGFR-TKI and antiangiogenic treatment in 1L setting, although this would need to be confirmed in prospective comparative studies. L858R mutations may have differing affinities and sensitivity to EGFR-TKIs, biological behavior of cells, and mechanisms of resistance which may contribute to poorer treatment outcomes compared to ex19del.[69] Patients with L858R also have increased chance of concomitant mutations compared with ex19del which impacts prognosis, resulting in reduced ORR, and PFS.[69,92,97]

The presence of co-occurring putative resistance mechanisms may correlate with a negative prognosis.[85,98,99] Prior therapy is associated with increased numbers of co-mutations.[99] Co-mutations in the tumor suppressor gene *TP53* have been the most frequently detected mutation by next-generation sequencing analyses in patients with mNSCLC with activating *EGFR* mutations (55%-65%).[99-101] Mutations in *TP53* are typically observed during advanced stages of tumorigenesis, suggesting a role in tumor progression rather than initiation.[101] Several publications have implicated *TP53* mutant's critical role in primary TKI-resistance, interfering with the cell-cycle arrest mediated by EGFR-TKIs.[102-105] TP53 data have been consistent across trials, indicating that *TP53* mutations are an indicator of poorer prognosis, and a consistent predictor of worse clinical outcomes following EGFR-TKI treatment.[99,102,104] The predictive role of *TP53* mutations appears to be especially relevant in patients with ex19del, perhaps because patients with ex19del mutations are usually more responsive to EGFR-TKIs.[99,102] Patients with *TP53* mutations may potentially benefit from EGFR-TKI and anti–angiogenic agent combination therapy, as evidenced by the RELAY data.[46] Mutations in the C797S residue of EGFR have been found to interfere with drug binding of osimertinib and afatinib, indicating other treatment options may be more suitable in this situation.[106-108] Co-mutations in *PIK3CA* (9%-12%) and *CTNNB1* (5%-10%) are common in mNSCLC with activating *EGFR* mutations and may have a role in progression of disease. *RB1* co-mutations are also commonly detected co-mutations (10%). The majority of *RB1* mutant tumors also harbor *TP53* mutations and might define a subset of *EGFR* mutant NSCLC at risk for transformation to small cell carcinoma following exposure to an EGFR-TKI.[99]

As previously mentioned, osimertinib is the most effective, and also the only regulatory approved treatment for T790M mutations. However, the sensitivity of the mutation detection methods used, and frequency of testing may significantly affect

treatment decisions. Liquid-biopsy based assessment (using droplet digital-based polymerase chain reaction testing [ddPCR]) of T790M mutation and its association with afatinib resistance and response to osimertinib identified the T790M mutation in 73% of patients after afatinib failure using ddPCR.[68] In the AURA phase II trial, 82% of the patients were eligible for screening, revealing 64% positivity for T790M mutation with the cobas *EGFR* Mutation Test.[73] Furthermore, the detection rate appeared unaffected by the prior EGFR-TKI treatment (gefitinib [69%], erlotinib [68%], and afatinib [68%]).[73] T790M mutations associated with EGFR-TKI acquired resistance when assessed by locked nucleic acid-based assay (LNA) improved detection (standard sequencing [51%]; LNA PCR [68%]).[109] Liang et al identified an incidence of 32% T790M mutations in their population.[110] The SNaPshot multiplex platform detected T790M mutations in 49% of patients assessed.[111] Similarly, other researchers reported that T790M mutations were detected in 48% of patients that had a partial response to afatinib using a variety of sequencing methodologies (Cobas *EGFR* Mutation Test, ddPCR, etc.).[112]

Future studies may help to elucidate whether radiologic progression or plasmatic progression (detectable T790M mutation cDNA by liquid biopsy or reappearance of sensitizing *EGFR* mutations after initial clearance) occurs first, potentially improving treatment outcomes, and avoiding a delay in switching to 2L treatment.[113] Detection methods are not equally available everywhere, posing a caveat in cases requiring sensitive detection, such as in the context of T790M or *TP53* mutations.[37] More frequent identification of concurrent mutations early in the treatment process, using next-generation sequencing, may help to develop more personalized treatment strategies for patients to overcome previously unidentified primary resistance mechanisms.[63]

Conclusion and Future Developments

In summary, we have discussed the potential treatment approaches in mNSCLC with activating *EGFR* mutations. We have reviewed the clinical evidence supporting the use of EGFR-TKIs and which patients might potentially benefit most so that physicians may make the most appropriate therapy decision for the overall treatment plan for patients.[1,35] It is critical to optimize therapy by improving the assessment of molecular changes in tumors when analyzing mechanisms of resistance. Utilizing novel treatment options to understand and overcome potential resistance will help guide "precision medicine" for the best choice of therapies. Furthermore, 1L EGFR-TKIs in combination with anti–angiogenic agents (eg ramucirumab and bevacizumab) may provide an alternative treatment option to patients in some circumstances, such as patients with L858R mutations and/or co-mutations.[40-43,45,69]

The ongoing randomized phase II studies, RAMOSE and TORG1833, using osimertinib with or without ramucirumab are investigating the combination's efficacy in treatment-naïve mNSCLC with activating *EGFR* mutations.[114,115] Additionally, a phase III study to evaluate the clinical efficacy of the combination of erlotinib and ramucirumab compared with osimertinib monotherapy for previously untreated patients with mNSCLC with L858R mutation is now ongoing in Japan (WJOG14420L/REVOL858R trial).[116] The combination of osimertinib and chemotherapy as a 1L therapy is also being investigated in the FLAURA2 trial.[117]

The MARIPOSA trial is currently assessing the efficacy of the combination of amivantamab and lazertinib, compared with osimertinib monotherapy. This study will provide further insight into potential treatments targeting co-mutations in mNSCLC.[118] The mutation landscape that emerges following the long-term use of EGFR-TKIs with chemotherapy and EGFR-TKIs with anti–angiogenics must be monitored closely in the future to assess potential new treatment requirements.

The phase III ADAURA trial investigated the efficacy and safety of adjuvant osimertinib compared with placebo in patients with stage 1B-IIIA *EGFR*-mutated (ex19del or L858R) mNSCLC.[119] At 24 months, disease-free survival was demonstrated to be significantly longer in the osimertinib arm in comparison with the placebo arm (overall hazard ratio for disease recurrence or death – 0.20; 99.12% CI – 0.14 to 0.30), suggesting adjuvant osimertinib may have a role in delaying disease recurrence. The results of this trial may affect future treatment options and substantially change the treatment landscape if osimertinib is used more often in early-stage NSCLC and other therapies will be needed on disease recurrence.

Osimertinib is accepted as the standard of care in the 1L setting but more data needs to be generated regarding the efficacy of osimertinib either in comparison with or in combination with earlier generation EGFR-TKIs, chemotherapy, and anti–VEGF monoclonal antibodies. Table 1 lists pertinent ongoing trials in mNSCLC with activating *EGFR* mutations. The results of these trials may enhance the understanding of the mNSCLC with activating *EGFR* mutations as well as inform future treatment practice. In conclusion, as increasing information is available with regard to treatment options with EGFR-TKIs, it is critical to adapt EGFR-TKI use in order to optimally maximize patient outcomes.

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Conflicts of Interest

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