A Comprehensive Review of Contemporary Literature for Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors in Non-Small Cell Lung Cancer and Their Toxicity

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Abstract: Mutations in the epidermal growth factor receptor (EGFR) are common amongst those with non-small cell lung cancer and represent a major factor in treatment decisions, most notably in the advanced stages. Small molecule tyrosine kinase inhibitors (TKIs) that target the EGFR, such as erlotinib, gefitinib, icotinib, afatinib, dacomitinib and osimertinib, have all shown to be effective in this setting. Osimertinib, a third-generation EGFR TKI, is a favorable option, but almost all patients develop resistance at some point time. There are no effective treatment options for patients who progress on osimertinib, but ongoing trials will hopefully address this unmet need. The aim of this review is to provide a comprehensive review of the data with EGFR TKIs, management of the toxicities and the ongoing trials with this class of agents.

Keywords: non-small cell lung cancer, epidermal growth factor receptor, tyrosine kinase inhibitor

Introduction

Lung cancer remains the deadliest form of cancer in the United States (US), accounting for a quarter of cancer mortality and the second most common cancer diagnosed in 2020.1 Lung cancer mortality has been declining due to efforts of tobacco use reduction, increased awareness of the health detriments related to smoking, comprehensive tobacco control programs and screening. While the incidence of tobacco-related lung cancer has been declining, there has been an increase in lung cancer incidence in never or light smokers.2,3

We now know that lung cancer is a heterogeneous disease. In the past, treatment decisions were primarily dependent on histological classifications such as small cell and non-small cell lung cancer (NSCLC); and within NSCLC, adenocarcinoma, squamous cell, large cell neuroendocrine, pleomorphic, large cell neuroendocrine and undifferentiated carcinoma. While we still incorporate histologic information in decision-making, treatment algorithms today, particularly for non-squamous NSCLC, are heavily dependent on molecular profiling of tumors since many of them harbor driver genetic alterations such as mutations in the epidermal growth factor receptor (EGFR) and BRAF genes, and rearrangements of the anaplastic lymphoma kinase (ALK) gene and ROS1 genes that can be targeted with effective medications.4,5

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The focus of this review is targeting EGFR mutations in NSCLC with tyrosine kinase inhibitors (TKIs). EGFR is a member of the ErbB tyrosine kinase receptor family and is overexpressed in several cancers such as that of lung and breast. Mutations or overexpression of these receptors lead to inappropriate activation of the MAPK pathway, and eventually, uncontrolled cell proliferation. In NSCLC, EGFR mutations are predominantly seen in adenocarcinoma but are sometimes seen in other subtypes such as large cell and squamous cell carcinoma. EGFR has an extracellular binding domain, trans-membrane segment, and cytoplasmic tyrosine kinase domain. When ligand binds to the extracellular binding domain, EGFR activates, dimerizes, and autophosphorylates the tyrosine kinase domain. This phosphorylation initiates signaling of downstream pathways involved in cell growth. EGFR mutations in NSCLC are located on exons 18 through 21, which encode the ATP binding site of the tyrosine kinase domain. Specifically, 45% have deletion in exon 19% and 40% contain a L858R point mutation in exon 21. Other less common mutations include exon 19 insertions, p.L861Q, p.G719X and p.S768I and exon 20 insertions. Sensitizing EGFR mutations have been found in up to 50% of Asian patients and about 10% of Caucasian patients. The majority of patients with EGFR mutations have never smoked or were former light smokers. Over the last two decades, small kinase inhibitors targeting EGFR have made their way into clinic and transformed the treatment paradigm in subsets of metastatic lung cancer. In this comprehensive review, we look to describe current landscape of EGFR TKIs and take the readers through various generations of these agents. Table 1 summarizes currently approved EGFR TKIs.

**First-Generation EGFR TKI**

Gefitinib

Gefitinib is a selective, reversible inhibitor of EGFR tyrosine kinase that binds to the adenosine-triphosphate binding site. Four notable clinical trials were conducted in Asian patients: IPASS, First-SIGNAL, WJTOG-3405, and NEJ002. The Iressa Pan-Asian Study (IPASS) was a Phase III trial that showed the predictive benefit of EGFR mutations in metastatic NSCLC. Patients in this study were untreated East Asian patients with advanced NSCLC and were either nonsmokers or former light smokers. They were randomized 1:1 to receive gefitinib 250 mg daily or carboplatin and paclitaxel. A total of 1217 patients were randomized with 261 harboring an EGFR mutation. Approximately half (53.6%) had exon 19 deletions, 111 (42.5%) had a mutation at exon 21 (L858R), 11 (4.2%) had a mutation at exon 20 (T790M), and 10 (3.8%) had other mutations. The final results reported improved progression-free survival (PFS) with gefitinib compared to standard platinum-based doublet chemotherapy. Notably, the PFS was driven by the EGFR mutation subgroup, which was significantly longer in the gefitinib than the chemotherapy group [hazard ratio (HR)=0.48; 95% CI, 0.36 to 0.64; p<0.001]. PFS was also shorter in the gefitinib group than in the chemotherapy group (HR=2.85; 95% CI, 2.05 to 3.98; p<0.001). Additionally, patients with EGFR mutations had improved objective response rate (ORR), reduced toxic effects, and improved quality of life.

First-SIGNAL, NEJ002, and WJTOG-3405 trials involving gefitinib further reaffirmed the higher ORRs and prolonged PFS in patients harboring EGFR mutations (See Table 2). These studies established the significance of the EGFR driver mutation and upfront molecular testing. Furthermore, the studies that compared gefitinib to chemotherapy showed no differences in overall survival (OS) despite prolonged PFS, and this may have been due to the cross-over effect. It was initially approved by the United States Food and Drug Administration (US FDA) in 2003 as a third-line option for NSCLC after progression on platinum and taxane chemotherapy irrespective of mutational status. This drug was then withdrawn from the market in 2012 and reapproved in 2013 as a first-line treatment option for patients with a sensitive EGFR mutation.

Gefitinib has also shown to benefit as adjuvant therapy for those with completely resected EGFR-mutant stage II–IIIA NSCLC. Two hundred and twenty-two patients were randomized to receive either gefitinib or vinorelbine and cisplatin in a 1:1 fashion in China. Median disease-free survival (DFS) was significantly longer with gefitinib compared with vinorelbine and cisplatin: 28.7 months (95% CI, 24.9 to 32.5) and 18.0 months (95% CI, 13.6 to 22.3), respectively, with a 40% reduction in risk (HR=0.60, 95% CI, 0.42 to 0.87; p=0.0054). Patients in the gefitinib group also had less toxicity and improved quality of life. Although gefitinib is not approved for adjuvant therapy in the US, there is evidence for its use in this setting.
Table 1 Epidermal Growth Factor Receptor Inhibitors

| Drug Name | Dose | Mechanism | Administration | FDA Approved NSCLC Indication | Acid Suppressive Interactions | Therapy | Metabolism/Transport Effects |
|-----------|------|-----------|----------------|-----------------------------|------------------------------|---------|-----------------------------|
| Afatinib\(^1\) | 40 mg once daily | Covalently binds to EGFR (ErbB1), HER2 (ErbB2), and HER4 (ErbB4) to irreversibly inhibit tyrosine kinase autophosphorylation and downregulate ErbB signaling | Take on empty stomach | First-line treatment of metastatic NSCLC in patients whose tumors have nonresistant EGFR mutations as detected by an approved test. Treatment of previously treated metastatic squamous cell NSCLC that has progressed following platinum-based chemotherapy. | N/A | N/A | BCRP, PGP | N/A | N/A |
| Erlotinib\(^2\) | 150 mg once daily | Reversibly inhibits overall HER1/EGFR tyrosine kinase activity | Take on empty stomach | Treatment of metastatic NSCLC in tumors with EGFR exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an approved test either as first-line, maintenance, or as second or greater line treatment after progression following at least 1 prior chemotherapy regimen. | Avoid use | Take 10 hours after and ≥ 2 hours before | Separate several hours | CYP3A4, CYP1A2 | N/A | N/A |
| Gefitinib\(^3\) | 250 mg once daily | Reversibly inhibits kinase activity of wild-type and select activation mutations of EGFR | Take with or without food. If unable, to swallow tablet whole, place tablet in 120–240 mL water and stir for 15 minutes and immediately drink liquid. | First-line treatment of metastatic NSCLC in tumors EGFR exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an approved test | Take 12 hours before or after | Take 6 hours before or after | | CYP2D6, CYP3A4, BCRP | N/A | N/A |
| Osimertinib\(^4\) | 80 mg once daily | Irreversible EGFR TKI which binds to select mutant forms of EGFR, including T790M, L858R, and exon 19 deletion at lower concentrations than wild-type | Take with or without food | Treatment of EGFR T790M mutation-positive NSCLC, as detected by an approved test, in patients who have progressed on or after EGFR tyrosine kinase inhibitor therapy | N/A | QTc | CYP3A4, BCRP, PGP | BCRP, PGP | N/A |
| Dacomitinib\(^5\) | 45 mg once daily | Irreversible EGFR TKI which targets HER-1, HER-2, and HER-4 receptors | Take with or without food | First-line treatment of patients with metastatic NSCLC with EGFR exon 19 deletion or exon 21 L858R substitution mutations as detected by an approved test | Avoid use | Take ≥ 6 hours before or 10 hours after | | CYP2D6 | CYP2D6 | N/A |

Abbreviations: BCRP, breast cancer resistance protein; CYP, cytochrome P450; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; N/A, not applicable; PGP, P-glycoprotein; TKI, tyrosine kinase inhibitors.
Erlotinib

Erlotinib is a reversible first-generation EGFR TKI that is FDA-approved for patients harboring EGFR exon 19 deletion and exon 21 L858R mutations in the first-line, maintenance, and second-line settings.\(^4\) Prior to 2004, treatment options for metastatic NSCLC were limited to chemotherapy irrespective of presence of genetic drivers. Erlotinib’s approval was based on key trials, which found improvement in PFS, but not OS when compared to chemotherapy. The OPTIMAL study was a phase III study performed in EGFR mutated, metastatic NSCLC Chinese patients who were randomized to erlotinib alone versus combination carboplatin/gemcitabine chemotherapy. Baseline characteristics were similar amongst the two groups. The patients in the erlotinib arm had improved PFS compared to the chemotherapy arm (13.1 vs 4.6 months; HR=0.16, 95% CI, 0.19 to 0.26; p<0.0001) and the PFS benefit was seen across all subgroups. Patients in the erlotinib arm also had a lower rate of dose reduction and treatment discontinuation. The EURTAC study was a randomized trial that compared erlotinib to chemotherapy in non-Asian patients with metastatic NSCLC. Patients with EGFR exon 19 deletion or exon 21 L858R mutations and Stage IIIIB disease with pleural effusion or Stage IV disease were enrolled. Participants were randomized to daily oral erlotinib or chemotherapy. The study found improved PFS in the erlotinib arm compared to chemotherapy (9.7 vs 5.2 months; HR=0.37, 95% CI, 0.25 to 0.54; p<0.0001). Like previous trials, there was no significant difference in OS between the two groups. The most common adverse effects (AEs) in the erlotinib group were rash, diarrhea, and transaminitis. This was the primary trial that demonstrated that non-Asian patients could also benefit from upfront EGFR TKI treatment. Erlotinib is currently approved for the treatment of metastatic NSCLC with EGFR exon 19 deletions or exon 21 (L858R) substitution mutations as first-line, maintenance, or as second or greater line treatment after progression following ≥1 prior chemotherapy regimen.\(^4\)

Icotinib

Icotinib is another first-generation EGFR TKI that is approved only in China for treatment of advanced NSCLC. The approval was based on the ICOGEN study, a randomized, double-blind phase III non-inferiority trial that enrolled patients with advanced NSCLC who had not responded to one or more platinum-based chemotherapy regimens, regardless of presence of EGFR mutation. Patients received icotinib 125 mg three times daily or gefitinib 250 mg once daily until disease progression or unacceptable toxicity. The PFS results deemed icotinib to
be non-inferior to gefitinib (HR=0.84, 95% CI, 0.67 to 1.05) with a median PFS of 4.6 vs 3.4 months, respectively.44 Given the non-inferior results when compared to icotinib, the CONVINCE trial further sought to assess the efficacy and safety of first-line icotinib versus cisplatin/pemetrexed plus pemetrexed maintenance in EGFR positive NSCLC. Two-hundred eighty-five patients with stage IIIB/IV lung adenocarcinoma and a positive EGFR mutation were enrolled to receive either icotinib or 3-week cycles of cisplatin/pemetrexed for up to four cycles. PFS was found to be significantly longer in the icotinib group (11.2 vs 7.9 months; HR=0.61, 95% CI, 0.43 to 0.87; p=0.006) and no significant OS differences were observed between treatments in the overall population or in the EGFR-mutated subgroups.45

First-generation TKIs are generally considered to have similar efficacy and toxicity profile. Some meta-analyses have combined studies involving these agents such as one by Lee and colleagues, who compared the OS of gefitinib or erlotinib compared to chemotherapy for EGFR mutation-positive lung cancer. In this meta-analysis, the crossover rate was 71.1% and 64.0% for chemotherapy and EGFR TKI cohorts in patients with the exon 19 deletion, respectively. In patients in the exon 21 L858R subgroup, the crossover rate was 77.2% and 67.7%, respectively.46

Second-Generation EGFR TKI

Afatinib

Afatinib is a second-generation EGFR TKI that covalently and irreversibly binds to conserved cysteine residues of EGFR, HER2, HER4, and Erb-B-4’s catalytic domains. It inhibits tyrosine kinase activity until the synthesis of new receptors, suggesting superior EGFR inhibition compared to the first-generation TKIs.49 In fact, afatinib was first developed to address secondary mutations, specifically T790M, that occur after initial treatment with front-line EGFR TKI with activity against HER2, HER4, and EGFR-mutant NSCLC. Afatinib did not have significant activity against T790M in clinical trials but has shown significant activity against sensitive EGFR mutations.33–38 The LUX-LUNG 3 (LL3) and LUX-LUNG 6 (LL6) trials led to the current FDA-approved indication for first-line metastatic NSCLC with EGFR exon 19 deletion and exon 21 L858R substitutions.34,35 In addition, afatinib is approved for metastatic squamous lung cancer patients who progressed after platinum-based therapy.13

A pooled analysis of the phase III randomized LL3 and LL6 trials demonstrated an OS benefit with afatinib compared to combination chemotherapy in patients with EGFR mutation-positive metastatic NSCLC. Notably, the OS benefit was driven by the exon 19 deletion afatinib subgroup in both trials. In LL3, the median OS was 33.3 months (95% CI, 26.8 to 41.5) in the afatinib group compared to 21.1 months (95% CI, 16.3 to 30.7) in the chemotherapy group in those with deletion 19 (HR=0.54, 95% CI 0.36 to 0.79; p=0.0015). In the LL6 trial, median OS was 31.4 months vs 18.4 months in the afatinib and chemotherapy groups, respectively (HR=0.64, 95% CI 0.44 to 0.94, p=0.023).50 There were no significant differences observed in the L858R mutation subgroup, which underscores different biological properties and prognoses between the different EGFR mutation subtypes.

Given the many first and second-generation EGFR TKIs to choose from, there have been several head-to-head trials evaluating their efficacy and superiority when compared to other TKIs. The results of the LUX-LUNG trials demonstrate that afatinib has improved PFS compared to first-generation reversible TKIs in certain settings.36,38 The LUX-LUNG 7 was an international, multi-center Phase 2B clinical trial that randomized 319 treatment-naïve patients with stage IIIB/IV NSCLC to afatinib or gefitinib in 1 to 1 fashion. All patients had centrally confirmed EGFR exon 19 deletion or L858R substitution. Median PFS was statistically significantly longer in the afatinib arm compared to the gefitinib arm; 11.0 vs 10.9 months, respectively (HR=0.73, 95% CI, 0.57 to 0.95; p=0.017). Median time to treatment failure (TTF) was also significantly longer in the afatinib group: 13.7 months and 11.5 months, respectively (HR=0.73, 95% CI, 0.58 to 0.92; p=0.0073). The most common AEs including diarrhea and rash were higher in the afatinib arm, but the frequency of discontinuation was similar between both groups.36

LUX-LUNG 8 was another head-to-head comparison of EGFR TKIs. This open-label, phase III trial evaluated the efficacy of afatinib and erlotinib in patients with advanced squamous cell lung carcinoma who progressed after four cycles of platinum-based chemotherapy. Although sensitizing EGFR mutations are found in less than 5% of squamous cell cancer, previous data have shown that these patients respond to EGFR inhibitors irrespective of EGFR mutation status. This responsiveness is believed to be related to the EGFR overexpression, which occurs in up to 82% of squamous cell cancers.38
In the LUX-LUNG 8 trial, afatinib was found to have a modest, but statistically significant benefit over erlotinib with PFS of 2.4 vs 1.9 months, respectively; HR=0.82 (95% CI, 0.68 to 1.00); p=0.0427 and OS of 7.9 vs 6.8 months, respectively; HR=0.81 (95% CI, 0.69 to 0.95); p=0.0077. However, patients in the afatinib arm had more reported AEs including diarrhea, stomatitis, and rash. EGFR testing was not mandated for this study and thus, was only present in six percent of the population. Based on these studies, the FDA granted approval of afatinib as front-line treatment for patients with EGFR-mutated metastatic NSCLC and for patients with metastatic squamous NSCLC who had progressed after platinum-based chemotherapy.13

Dacomitinib

Dacomitinib is an irreversible second-generation EGFR TKI, which targets HER-1, HER-2, and HER-4 receptors. Although dacomitinib exhibited potent activity in preclinical studies in cell lines of NSCLC, it showed modest efficacy when given to patients with advanced NSCLC who had progressed after other therapies, including erlotinib.51,52 Dacomitinib did not meet its primary endpoint for OS in a Phase II trial, which enrolled patients with locally advanced or metastatic NSCLC who had previously received one or two systemic regimens. Other trials, notably ARCHER 1050 and ARCHER 1009, have evaluated dacomitinib’s efficacy compared to other EGFR TKIs.39,41

The ARCHER 1009 was a phase III trial that compared dacomitinib to erlotinib in patients who were previously treated advanced NSCLC. Patients who had progression after ≥1 previous regimen of chemotherapy were enrolled. Approximately one-quarter of patients in this study did not have an EGFR status (14%) or possessed a mutant type (10%). The study did not meet its primary endpoint of demonstrating significant PFS benefit when compared to erlotinib. Median PFS was 2.6 months (95% CI, 1.9 to 2.8) in both the dacomitinib group and erlotinib group (stratified HR 0.941, 95% CI, 0.802 to 1.104, p=0.229).41

Another randomized, phase III trial, ARCHER 1050 evaluated dacomitinib versus gefitinib in treatment-naïve patients with EGFR-mutated advanced NSCLC without central nervous system (CNS) metastases. Patients were well balanced amongst the two groups, but of note, seventy-five percent of patients in this study were Asian. Dacomitinib significantly improved PFS when compared to gefitinib (14.7 vs 9.2 months; HR=0.59, 95% CI, 0.47 to 0.74; p<0.0001).39 Upon further follow up, OS was also improved with dacomitinib versus gefitinib, 34.1 compared to 26.8 months, respectively (HR=0.760, 95% CI, 0.582 to 0.993; p=0.044). This is the first data showing significant improvement in OS with a second-generation EGFR TKI compared to a first-generation EGFR TKI irrespective of type of EGFR mutation.40 Treatment-related AEs were higher in the dacomitinib arm compared to the gefitinib arm. Notably, patients in the dacomitinib group were more likely to experience diarrhea (87% vs 56%), paronychia (62% vs 20%), dermatitis acneiform (49% vs 29%), and stomatitis (44% vs 17%). Patients in the dacomitinib group were also more likely to experience grade ≥3 diarrhea (8% vs 1%), paronychia (7% vs 1%), and dermatitis acneiform (14% vs 0%).39 As a result of this study, the FDA-approved dacomitinib for the frontline treatment in patients with EGFR mutated metastatic NSCLC.17

Third-Generation EGFR TKI

Osimertinib

Osimertinib is an irreversible, CNS active, third-generation monoanilinopyrimidine compound that is selective for sensitizing EGFR and T790M resistance mutations.53 It is currently the only third-generation EGFR TKI that is FDA-approved for NSCLC. Although first- and second-generation TKIs have consistently shown superior efficacy and safety profiles compared to first-line platinum-based chemotherapy, tumors invariably develop acquired resistance to these agents. The T790M mutation in exon 20 of the EGFR gene is the most commonly acquired resistant gene mutation following second-generation TKIs.54

The AURA-3 trial was an open-label, phase III trial that enrolled 419 patients with locally advanced or metastatic NSCLC with T790M mutations to evaluate the efficacy of osimertinib to platinum-based combination chemotherapy plus pemetrexed. The results demonstrated osimertinib’s superiority to this combination with the median PFS being significantly longer with osimertinib than with chemotherapy (10.1 months vs 4.4 months; HR=0.30; 95% CI, 0.23 to 0.41; p<0.001). In addition, ORR was significantly better with osimertinib (71%) than with combination chemotherapy (31%). Osimertinib also demonstrated superior efficacy in patients with CNS metastases. In a subgroup of 144
patients with brain metastases, the median PFS was longer with osimertinib than the chemotherapy arm: 8.5 months vs 4.2 months, respectively (HR=0.32; 95% CI, 0.21 to 0.49).42

Given AURA-3’s positive data, osimertinib received accelerated approval in November 2015 for patients with T790M-positive NSCLC whose disease progressed on first-line EGFR TKI. Osimertinib was further evaluated as upfront therapy in patients with EGFR positive advanced NSCLC regardless of a T790M mutation. FLAURA was a double-blind, phase III trial that evaluated the efficacy of osimertinib to first-generation EGFR TKIs (gefitinib 250 mg daily or erlotinib 150 mg daily) in 556 advanced NSCLC patients with exon 19 deletion/L858R mutations. Median PFS was significantly longer with osimertinib than with standard EGFR TKIs (18.9 months vs 10.2 months; HR=0.46; 95% CI, 0.37 to 0.57; p<0.001) and the PFS benefit was seen across all subgroups. Notably, in patients with known brain metastases, CNS progression was significantly lower in the osimertinib arm (6% vs 15%). The ORR was similar between both groups: 80% with osimertinib and 76% with standard EGFR TKIs and the safety profile of these agents was similar to that of previous EGFR trials.43

After further follow-up, patients in the osimertinib group demonstrated an improvement in OS with a median OS of 38.6 months compared to 31.8 months in the first-generation EGFR TKI group (HR=0.80, 95.05% CI, 0.64 to 1.00; p=0.046). This improvement was consistent among most predefined subgroups. After three years of follow up, 28% and 9% of patients were still receiving an EGFR TKI, respectively.55

Recently, results of the ADAURA study demonstrated osimertinib as a viable adjuvant treatment option for EGFR mutated NSCLC. This was a randomized, double-blinded, placebo-controlled phase III trial investigating osimertinib vs placebo in 682 patients. Osimertinib improved DFS by 83% vs placebo (HR=0.17, 95% CI, 0.12 to 0.23; p<0.0001) in those with stage II to IIA disease. The two-year DFS rate in this group was 90% vs 44%, respectively. When patients with stage IB were added to the analysis, osimertinib improved DFS by 79% (HR=0.21, 95% CI, 0.16 to 0.28; p<0.0001). The two-year DFS rate was 89% vs 53%, respectively.56

Table 2 enlists important clinical trials involving first-, second- and third-generation EGFR TKIs.

EGFR TKI Combination Treatments
There are emerging data to support the use of EGFR TKIs in combination with other systemic therapies in the frontline setting. Gefitinib combined with carboplatin and pemetrexed demonstrated an improvement in PFS and OS.57–60 Noronha and colleagues investigated this combination compared to gefitinib alone in advanced EGFR mutated NSCLC. They conducted a phase III trial in 350 patients from India who were randomized in a 1:1 fashion. A 55% reduction for risk of death was demonstrated [HR=0.45 (95% CI, 0.31 to 0.65); p=0.001] with an estimated median OS of not reached compared to 17 months (95% CI, 13.5 to 20.5 months), respectively.57 A similar study, NEJ009 was conducted in Japan with 345 patients. After a median follow-up time of 45 months, the median OS with the carboplatin, pemetrexed and gefitinib combination was 50.9 months (95% CI, 41.8 to 62.5) compared to 38.8 months (95% CI, 31.1 to 47.3) in the gefitinib alone group (HR=0.722; 95% CI, 0.55 to 0.95, p=0.021). Quality of life observed six months or later was not different between the two groups. Grade 3 or greater toxicities were higher in the combination group compared to the gefitinib group, 65.3% vs 31.0%, respectively.58

EGFR TKIs have also been investigated in combination with vascular endothelial growth factor receptors. The RELAY trial demonstrated an improvement in PFS by approximately 7 months when ramucirumab was added to erlotinib when compared to erlotinib alone in EGFR mutated NSCLC in the front-line setting. However, the combination group experienced a higher rate of treatment-related adverse events compared to erlotinib alone (72% vs 54%, respectively).61

Recent studies have shown the benefit of combining chemotherapy or vascular endothelial growth factor receptors with an EGFR TKI. Earlier studies did not show this benefit in various settings, likely because the patients in these trials did not have an EGFR mutation. Additional combination studies with EGFR TKIs are summarized in Table 3.62–68

EGFR TKIs Related Toxicities and Their Management
EGFR inhibitors are generally well tolerated; however, patients can still experience severe adverse effects affecting their quality of life, to an extent where the treatment may have to be dose reduced or discontinued. Osimertinib is usually well tolerated as compared to other TKIs, with
| Trial | Phase | N | Patient Population                                                                 | Intervention | Median Follow-Up (Median, Months) | PFS (Median, Months) | OS (Median, Months) | ORR (%) |
|-------|-------|---|------------------------------------------------------------------------------------|--------------|-----------------------------------|----------------------|--------------------|---------|
| IPASS | 3     | 1217 | Treatment naïve patients in East Asia with advanced adenocarcinoma and who were nonsmokers or former light smokers | Gefitinib 250 mg/day vs carboplatin plus paclitaxel | 17.0               | EGFR+ group: 9.5 vs 6.3; HR=0.48 (0.36–0.64); p<0.001 | EGFR- group: 1.5 vs 5.5; HR=2.85 (2.05–3.98); p<0.001 | 18.8 vs 17.4; HR=0.90 (0.79–1.02); p=0.109 | 71.2 vs 47.3 |
| WJTOG-3405 | 3 | 172  | Chemotherapy naïve patients with stage IIIB/IV NSCLC or post-operative recurrence harboring EGFR mutations | Gefitinib 250 mg/day or cisplatin plus docetaxel | 59.1               | 9.2 vs 6.3; HR=0.49 (0.34–0.71); p<0.0001 | 34.8 vs 37.3; HR=1.252 (0.883–1.775) | 62.1 vs 32.2 |
| First-SIGNAL | 3 | 42   | Stage IIIB/IV adenocarcinoma                                                          | Gefitinib 250 mg/day vs gemcitabine plus cisplatin | 35                 | 5.8 vs 6.4; HR=1.198 (0.944–1.520); p=0.138 | 22.3 vs 22.9; HR=0.932 (0.716–1.213); p=0.604 | 84.6 vs 37.5 |
| NEJ002 | 3     | 230 | Treatment naïve EGFR mutated advanced NSCLC                                          | Gefitinib 250 mg/day vs carboplatin plus paclitaxel | 704 days           | 10.8 vs 5.4; HR=0.322 (0.236–0.438); p<0.001 | 27.7 vs 26.6; HR=0.887 (0.634–1.241); p=0.483 | 73.7 vs 30.7 |
| EURTAC | 3     | 173 | Treatment naïve EGFR mutated advanced NSCLC                                          | Erlotinib 150 mg/day vs 3-week cycles of standard IV chemotherapy | 18.9 vs 14.4       | 9.7 vs 5.2; HR=0.37 (0.25–0.54); p<0.0001 | 19.3 vs 19.5; HR=1.04 (0.65–1.68); p=0.87 | 53 vs 15 |
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EGFR mutated stage IIB/IV NSCLC

| Study          | Treatment | Comparator | OS (months) | P Value |
|----------------|-----------|------------|-------------|---------|
| OPTIMAL10,11    | Erlotinib | Carboplatin | 28.9 vs 27.1 | 0.001   |
| ENSURE11        | Erlotinib | Gemcitabine plus carboplatin | 25.9 | 0.001   |
| LUX-LUNG13      | Erlotinib | Gemcitabine plus cisplatin up to 4 cycles | 28.9 vs 27.1 | 0.1288   |
| LUX-LUNG34      | Erlotinib | Gemcitabine plus cisplatin up to 4 cycles | 16.4 | 0.0001   |
| LUX-LUNG65      | Erlotinib | Gemcitabine plus cisplatin up to 4 cycles | 16.6 | 0.0001   |
| LUX-LUNG81      | Erlotinib | Gemcitabine plus cisplatin up to 4 cycles | 42.6 | 0.0001   |
| LUX-LUNG81      | Erlotinib | Gemcitabine plus cisplatin up to 4 cycles | 18.4 | 0.0001   |
| LUX-LUNG81      | Dacomitinib | Gefitinib 250 mg/day | 31.1 | 0.0001   |
| ARCHER1050      | Erlotinib | Gefitinib 250 mg/day | 74.9 | 0.0001   |

(Continued)
| Trial       | Phase | N   | Patient Population                                                                 | Intervention                                                                 | Median Follow-Up (Median, Months) | PFS (Median, Months) | OS (Median, Months) | ORR (%) |
|------------|-------|-----|-------------------------------------------------------------------------------------|------------------------------------------------------------------------------|----------------------------------|----------------------|---------------------|---------|
| ARCHER 1009 | 3     | 878 | Locally advanced or metastatic NSCLC, progression after 1–2 previous regimens of chemotherapy | Dacomitinib 45 mg/day vs erlotinib 150 mg/day                                | 7.1                              | 2.6 vs 2.6; HR=0.941 (0.802–1.104); p=0.229 | 7.9 vs 8.4; HR=1.079 (0.914–1.274); p=0.817 | 11.0 vs 8.0 |
| AURA3      | 3     | 419 | T790M-positive advanced NSCLC with disease progression after 1st line EGFR TKI therapy | Osimertinib 80 mg/day vs pemetrexed plus either carboplatin or cisplatin     | 8.3                              | 10.1 vs 4.4; HR=0.30 (0.23–0.41); p<0.001   | NR                  | 71 vs 31  |
| FLAURA     | 3     | 556 | Treatment naïve EGFR mutated advanced NSCLC                                          | Osimertinib 80 mg/day vs standard EGFR TKI either gefitinib 250 mg/day or erlotinib 150 mg/day | 29                               | 18.9 vs 10.2; HR=0.46 (0.37–0.57); p<0.001 | 38.6 vs 31.8; HR=0.80 (0.64–1.00); p=0.046 | 80 vs 76  |
| ICOGEN     | 3     | 399 | Previously treated with one or more platinum-based chemotherapy regimens with no response | Icotinib 125 mg three times daily vs gefitinib 250 mg once daily               | 24                               | 4.6 vs 3.4; HR=0.84 (0.67–1.05); p=0.13     | 13.3 vs 13.9; HR=1.02 (0.82–1.27); p=0.57     | 27.6 vs 27.2 |
| CONVINCE   | 3     | 285 | EGFR mutated stage IIIB/IV NSCLC                                                    | Icotinib 125 mg three times daily vs 3 week cycles of chemotherapy (75 mg/m² cisplatin plus 500 mg/m² pemetrexed on Day 1) | 39.6                             | 11.2 vs 7.9; HR=0.61 (0.43–0.87); p=0.006 | 30.5 vs 32.1; p=0.8854 | NR      |

**Abbreviations:** EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; NR, not reported; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; SCLC, small cell lung cancer; TKI, tyrosine kinase inhibitors.
### Table 3: Select Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors Combination Trials

| Trial        | Phase | N   | Patient Population                                                                 | Intervention                                                                 | Median Follow-Up (Median, Months) | PFS (Median, Months) | OS (Median, Months) | ORR (%) |
|--------------|-------|-----|-------------------------------------------------------------------------------------|-----------------------------------------------------------------------------|-----------------------------------|----------------------|---------------------|---------|
| IMPRESS[^3][^4] | 3     | 265 | Chemotherapy naïve patients with EGFR mutated advanced NSCLC with progression on gefitinib | Gefitinib 250 mg/day plus cisplatin plus pemetrexed vs placebo plus cisplatin plus pemetrexed | 11.2 | 5.4 vs 5.4; HR=0.86 (0.65–1.13); p=0.27 | 13.4 vs 19.5; HR=1.44 (1.07–1.94); p=0.016 | 32 vs 34; p=0.76 |
| INTACT-1[^5] | 3     | 1093| Chemotherapy-naive patients with unresectable stage II/IV NSCLC                      | Gefitinib 500 mg/day plus gemcitabine plus cisplatin up to 6 cycles vs gefitinib 250 mg/day plus gemcitabine plus cisplatin up to 6 cycles | 15.9 | 5.5 vs 5.8 vs 6.0; p=0.7633 | 9.9 vs 9.9 vs 10.9; p=0.4560 | 50.3 vs 51.2 vs 47.2 |
| INTACT-2[^5] | 3     | 1037| Chemotherapy naïve patients with unresectable stage II/IV NSCLC                      | Gefitinib 500 mg/day plus paclitaxel plus carboplatin up to 6 cycles vs gefitinib 250 mg/day plus paclitaxel plus carboplatin up to 6 cycles | Minimum of 12 | 4.6 vs 5.3 vs 5.0; p=0.0562 | 8.7 vs 9.8 vs 9.9; p=0.6385 | 30.0 vs 30.4 vs 28.7 |
| Noronha Vet al[^3] | 3     | 350 | Chemotherapy naïve patients with EGFR mutated advanced NSCLC                          | Gefitinib 250 mg/day plus pemetrexed 500 plus carboplatin for 4 cycles vs gefitinib 250 mg/day | 17.0 | 16.0 vs 8.0; HR=0.51 (0.39–0.66); p<0.001 | Not reached vs 17.0; HR=0.45 (0.31–0.65); p<0.001 | 75.3 vs 62.5; p=0.01 |
| NEJ-009[^5] | 3     | 345 | Chemotherapy naïve patients with EGFR mutated stage II/IV or relapsed nonsquamous NSCLC | Gefitinib 250 mg/day plus carboplatin plus pemetrexed for up to 6 cycles, followed by gefitinib plus pemetrexed maintenance vs gefitinib 250 mg/day | 45.0 | 20.9 vs 11.9; HR=0.49 (0.39–0.62); p<0.001 | 50.9 vs 38.8; HR=0.722 (0.55–0.95); p=0.021 | 84 vs 67; p<0.001 |
| NEJ026[^5] | 3     | 228 | Chemotherapy naïve patients with EGFR mutated stage II/IV NSCLC                     | Erlotinib 150 mg/day plus bevacizumab every 21 days vs erlotinib 150 mg/day | 12.4 | 16.9 vs 13.3; HR=0.605 (0.417–0.877); p=0.016 | NR | 72 vs 66 |

(Continued)
| Trial       | Phase | N  | Patient Population                                                                 | Intervention                                                                 | Median Follow-Up (Median, Months) | PFS (Median, Months) | OS (Median, Months) | ORR (%) |
|------------|-------|----|-------------------------------------------------------------------------------------|------------------------------------------------------------------------------|----------------------------------|----------------------|---------------------|---------|
| BeTa<sup>55</sup> | 3     | 636| Patients with advanced NSCLC who were recurrent or refractory to first line chemotherapy | Erlotinib 150 mg/day plus bevacizumab every 21 days vs erlotinib 150 mg/day | 19.0                             | 3.4 vs 1.7; HR=0.62 (0.52–0.75) | 9.3 vs 9.2; HR=0.97 (0.80–1.18); p=0.7583 | 13 vs 6 |
| RELAY<sup>61</sup>      | 3     | 449| Treatment naïve patients with EGFR mutated stage IV NSCLC                             | Erlotinib 150 mg/day plus ramucirumab every 14 days vs erlotinib 150 mg/day | 20.7                             | 19.4 vs 12.4; HR=0.59 (0.46–0.76); p<0.0001 | 1-year OS: 93% vs 94% 2-year OS: 83% vs 79% | 76 vs 75 |
| Scagliotti GV et al<sup>66</sup> | 3     | 579| Stage IIIB/IV or recurrent disease with non-adenocarcinoma NSCLC who had previously received ≥1 platinum-based regimen | Erlotinib 150 mg/day plus figitumumab every 21-day cycle vs erlotinib 150 mg/day | NR                               | 2.1 vs 2.6; HR=1.08 (0.90–1.29); p=0.43    | 5.7 vs 6.2; HR=1.09 (0.91–1.31); p=0.35 | 5.5 vs 3.8 |
| Gatzemeier et al<sup>67</sup>        | 3     | 1172| Chemotherapy naïve patients with unresectable, locally advanced, recurrent or metastatic NSCLC | Erlotinib 150 mg/day plus gemcitabine plus cisplatin vs gemcitabine plus cisplatin | NR                               | 5.5 vs 5.7; HR=0.98 (0.86–1.11); p=0.74    | 10.0 vs 10.3; HR=1.06 (0.90–1.23); p=0.49 | 31.5 vs 29.9 |
| TRIBUTE<sup>68</sup>         | 3     | 1059| Treatment naïve patients with stage IIIB/IV NSCLC                                    | Erlotinib 150 mg/day plus carboplatin plus paclitaxel vs placebo plus carboplatin plus paclitaxel followed by maintenance erlotinib 150 mg/day | NR                               | 5.1 vs 4.9; HR=0.937; p=0.36               | 10.6 vs 10.5; HR=0.995 (0.86–1.16); p=0.95 | 21.5 vs 19.3; p=0.36 |

Abbreviations: EGFR, epidermal growth factor receptor; HR, hazard ratio; NSCLC, non-small cell lung cancer; NR, Not reported; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.
mineral grade 3 or higher toxicities. Along with the tumor cells, EGFR is also expressed in healthy epithelial cells, mainly in the skin and gastrointestinal (GI) tract. EGFR TKIs inhibit overexpressed EGFR in both cancer cells and in normal cells. This inhibition results in release of inflammatory cytokines, which subsequently leads to cutaneous and GI toxicities. Cutaneous AEs can affect 20%–89% of patients. These AEs may be mild to moderate but can be severe in up to 18% of patients, with GI AEs affecting 21–95% of patients. A survey of 110 oncologists conducted by Boone et al showed that 76% of patients experienced treatment interruptions and 32% of patients discontinued their treatment due to skin rash. Furthermore, a 10–50% dose reduction was made in 60% of patients due to cutaneous toxicities. The survey also showed that EGFR TKI-related diarrhea was associated with lethargy and sleep interruptions, affecting patient’s quality of life. Therefore, management of AEs is imperative to ensure treatment adherence and to improve quality of life.

**Cutaneous Toxicities of EGFR TKIs**

Various types and grades of cutaneous toxicities are seen in patients taking EGFR TKIs. This is mainly due to the inhibition of healthy EGFR found in the epidermis of skin, which plays a crucial role in epithelial maintenance. The earliest and most commonly reported AE is an acneiform rash (also termed papulopustular rash), which occurs in 90% of patients as early as 1–2 weeks of treatment, and is common in the sebaceous epithelium or glands. Osimertinib has shown to have a lower incidence of overall rash as well as grade ≥3 rash when compared to first-generation-EGFR TKIs. The rash usually progresses through four distinct phases, starting from dysesthesia, erythema and edema, followed by erythematous papules and pustules, followed by purulent crusts at 3–6 weeks and telangiectasia. There are several proposed systems for grading, but the most commonly used system is the NCI CTCAE (National Cancer Institute Common Terminology Criteria for Adverse Events) version 4.03, which classifies the rash in 5 grades (Table 4). The eruptions may decrease over 3–4 weeks despite the continuation of TKI but may persist as mild erythema or follicular papules throughout the course of treatment.

Xerosis is the second most reported AE which occurs in almost 50% of patients, usually after 30–50 days of treatment. EGFR TKIs alter the epidermal barrier leading to dry skin. Xerosis presents as dry, scaly patches, but may advance to painful fissuring and xerotic eczema with risk of secondary infections with staphylococcus aureus or herpes simplex virus. It usually has widespread involvement and can affect any part of the body. NCI CTCAE version 4.03 classifies xerosis in 3 grades (Table 4).

Paronychia is the other cutaneous AE, which occurs in 5–20% of patients, usually after 4 to 8 weeks of treatment. This occurs due to the inhibition of keratinocytes in the nail matrix due to TKIs. It usually presents as painful periungual inflammation, but in severe cases can cause periungual abscess and pyogenic granuloma. It can also lead to onycholysis or onychodystrophy. It is graded per CTCAE 4.03 guidelines (Table 4).

Abnormalities of hair growth can sometimes occur presenting as hirsutism, hypertrichosis and trichomegaly. This usually occurs after 2–5 months of treatment and is due to an increased terminal differentiation caused by EGFR inhibition. If it involves the eyelashes, conjunctivitis, corneal irritation and ulceration can occur. Scarring or non-scarring alopecia is unusual, but can affect 5–6% of patients and develops after 2–4 months of treatment. Scalp inflammation and extensive scalp pustules are also uncommon but can occur.

**Management of Cutaneous Toxicity**

Since cutaneous toxicities are almost universally anticipated, all patients starting on EGFR TKIs should be educated about general skincare measures. This includes skin cleansing and washing with lukewarm water and with the use of soap/alcohol-free products. It is also recommended to use thick alcohol-free emollients and sunscreen lotion with SPF ≥ 25.
| Grade | Cutaneous Toxicities | Xerosis | Paronychia | Diarrhea |
|-------|----------------------|---------|------------|---------|
| 1     | Papules and/or pustules covering <10% BSA, with or without symptoms of pruritus or tenderness. | Dry skin covering <10% BSA, with no associated erythema or pruritus. | Nailfold edema and/or erythema with cuticle disruption. | Increase of less than 4 stools per day over normal |
| 2     | Papules and/or pustules covering 10–30% BSA with or without symptoms of pruritus or tenderness; with psychological impact and limiting instrumental ADL. | Dry skin covering 10–30% BSA with erythema or pruritus and limiting instrumental ADL. | Painful nail fold bogginess and/or discharge with onycholysis. | Increase of 4–6 stools per day over normal, limiting instrumental ADL |
| 3     | Papules and/or pustules covering >30% BSA with or without symptoms of pruritus or tenderness; limiting self-care ADL associated with local superinfection for which oral antibiotics is indicated. | Dry skin covering >30% BSA with pruritus and limiting self-care ADL. | Ingrown nails with intense pain; pyogenic granuloma and/or exuberant periungual granulation tissue. | Increase of 7 or more stools per day over normal; or incontinence; hospitalization indicated; limited self-care ADLs. |
| 4     | Papules and/or pustules covering any percentage of BSA with or without symptoms of pruritus or tenderness; associated with extensive superinfection for which intravenous antibiotics is indicated; can have life threatening consequences. | Life threatening consequences, urgent intervention required. | |
| 5     | Death | | | Death |

**Notes:** Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0, November 2017, National Institutes of Health, National Cancer Institute. Available at: [https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf](https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf)

**Abbreviations:** ADL, activities of daily living; BSA, body surface area.

dermatology referral. In addition to oral antibiotics and topical steroids, oral steroids (prednisone 0.5 mg/kg/day for 5 days) are recommended. Occasionally, low dose isotretinoin is used, but under the supervision of a dermatologist. TKI therapy is interrupted until the rash is grade ≤2, and a reduced dose of TKI is resumed (Table 5).74,79

Secondary bacterial infection can follow cutaneous toxicities. If superinfection is suspected, antibiotics like cloxacillin or cephalaxin are recommended for a week before the initiation of prophylactic anti-inflammatory antibiotics. Potassium permanganate compresses for a few days, in addition to a topical steroid-antibiotic cream, helps the infected lesions heal faster.74

**Xerosis/Pruritus**

Symptomatic treatment of xerosis includes skincare with oil-in-water moisturizing creams or emollients like petroleum jelly, Eucerin, Aquaphor or zinc oxide (30%). Eczematous lesions can be treated with a topical steroidal cream for 1–2 weeks. Patients with pruritis are treated with topical or systemic steroids, anti-histamines, or GABA agonists.74,79 For grade 3 xerosis, TKI treatment should be interrupted and resumed at a lower dose once the xerosis is grade ≤2. Dermatology referral is recommended for grade 3 xerosis or if there is no improvement with conventional methods.

**Paronychia**

All patients starting TKIs should be educated about nail hygiene. Aggressive manicures/pedicures, strong irritants, and prolonged exposure to water or hot water should be avoided.80 Paronychia requires treatment with topical steroids, antimicrobials, and silver nitrate. Soaking fingers or toes in white vinegar for 15 minutes every day maybe useful. Grade 1 lesions are treated with topical steroids like betamethasone valerate 0.1% twice per day. Along with topical steroids, grade 2
Table 5 Management of Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors Induced Acneiform Rash (Reactive Treatment)\textsuperscript{77}

| Grade | Treatment of Rash                                                                                                                                                                                                 | TKI Treatment                                                                                   |
|-------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|
| 1     | Topical anti-inflammatory antibiotics 1% Clindamycin BID. Topical steroids like 2.5% hydrocortisone is considered, especially if the rash is itchy.                                                                 | Continue treatment at the current dose and monitor for bacterial super-infection or worsening of the rash. |
| 2     | Oral anti-inflammatory antibiotics like Minocycline 100 mg daily or Doxycycline 100 mg BID with topical steroid cream (hydrocortisone 2.5%, desonide, alclometasone 0.05% to the face and neck or fluocinonide 0.05% cream to chest and back) | Continue treatment at the current dose and monitor for bacterial super-infection or worsening of the rash. |
| ≥3    | Dermatology referral. Oral prednisone (0.5 mg/kg/day X 5 days) in addition to oral anti-inflammatory antibiotics like minocycline 100 mg daily or doxycycline 100 mg BID with topical steroid cream. Low dose isotretinoin (20 to 30 mg/day) is also considered. | Interrupt the treatment. Restart the TKI at a reduced dose once the rash is ≤ 2. Discontinue the TKI, if the rash does not improve. |

Abbreviation: TKI, tyrosine kinase inhibitors.

Table 6 Management of Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors Induced Diarrhea\textsuperscript{77}

| Grade | Treatment of Diarrhea                                                                                                                                                                                                 | TKI Treatment                                                                                   |
|-------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|
| 1     | Start non-pharmacologic strategy. Start Loperamide (4 mg, followed by 2 mg every 2–4 hours or after every loose stool until there is no bowel movement for 12 hours).                                                                 | Maintain current dose of TKI.                                                                 |
| 2     | As grade 1. - Add diphenoxylate/atropine (2 tablets every 6 hours) or Codeine (30 mg every 4 hours).                                                                                                              | Maintain current dose of TKI. If diarrhea does not respond to loperamide at 48 hours, TKI should be temporarily discontinued until diarrhea returns to grade 1, after which TKI is resumed as: Erlotinib: Lower dose by 50 mg to a minimum of 50 mg. Afatinib: Lower dose by 10 mg to a minimum of 20 mg. Gefitinib: Resume at original dose. |
| ≥3 or with complication | As grade 2. Octreotide (100 to 150 mcg subcutaneous three times a day) or tincture of opium is added if diarrhea continues. Octreotide is titrated up to 2000 mcg three times a day based on the response. Endoscopic evaluation is considered, if diarrhea continues despite use of loperamide and octreotide for 24 hours. | Interrupt the treatment. Resume TKI as above once diarrhea is grade 1 or lower. If diarrhea does not reach grade 1 or lower despite supportive measures and holding TKI by 14 days, permanently discontinue TKI. |

Abbreviation: TKI, tyrosine kinase inhibitors.

lesions require topical antimicrobials. Exuberant granulation tissue is treated with silver nitrate and dermatology referral is recommended if the lesions do not heal. If the granulation does not respond to topical agents, electrodesiccation or carbon dioxide laser ablation is usually performed. Secondary prophylaxis with doxycycline is recommended.\textsuperscript{74,80} Grade 3 lesions will require treatment interruptions and TKI should be resumed at a lower dose once the lesion is grade ≤2.

Gastrointestinal Toxicities of EGFR TKIs

Various types of GI toxicities are seen in patients taking EGFR TKIs, mainly due to the inhibition of normal EGFR found in squamous epithelium in the tongue, esophagus and GI tract.\textsuperscript{71} The most commonly reported GI AE is diarrhea.\textsuperscript{47,79} Diarrhea is thought to occur not only due to inhibition of normal EGFR but also due to excess chloride secretion caused by inhibition of calcium-dependent
chloride transport. NCI CTCAE v4.03 classifies diarrhea in 5 grades (Table 4).

Oral mucositis and stomatitis are also reported with EGFR TKIs, which can be debilitating. Mucositis is usually mild but can be painful and severe with extensive erythema causing aphthous-like stomatitis. Grade 1 is usually asymptomatic or mildly symptomatic. Grade 2 is associated with moderate pain, which does not interfere with eating or drinking. Grade 3 is associated with severe pain that interferes with intake of food or drink. Grade 4 is considered life-threatening and grade 5 is death.

Management of Gastrointestinal Toxicities

Diarrhea

Prior to TKI initiation, educating patients regarding the incidence of diarrhea is of utmost importance. Patients should call their provider immediately with increased frequency or changes in bowel habits. Management of TKI diarrhea includes non-pharmacological and pharmacological methods.

Non-Pharmacologic Strategy

At the first instance of diarrhea, patients should discontinue any baseline use of stool softeners and laxatives. Patients should be educated on adequate fluid intake and dietary modifications with any changes in bowel habits. Patients should maintain hydration with at least 3–4 liters of fluids daily, including fluids with salt and sugar to avoid electrolyte imbalances. Prophylactic dietary changes are not recommended. However, the BRAT (banana, rice, applesauce, toast) diet is recommended for patients with diarrhea. Vegetables, fibrous foods and legumes should be reduced. Spicy and fried foods should be avoided.\textsuperscript{82}

Pharmacologic Measures

Loperamide is the mainstay of treatment for diarrhea and should be started immediately at the onset of diarrhea. Patients with grade 1 and 2 diarrhea can be managed at home, but hospitalization may be required for diarrhea which is grade 3 or higher. Infective causes for diarrhea should be excluded. The maximum daily recommended dose for loperamide is 16 mg (4 mg immediately after symptoms begins, followed by 2 mg every 2–4 hours depending on the frequency of diarrhea). Diphenoxylate–atropine or codeine may be used in conjunction with loperamide if diarrhea is not controlled with loperamide alone. The maximum daily recommended dose for diphenoxylate 2.5 mg–atropine 0.025 mg is 20 mg (of diphenoxylate) (taken as 2 tablets every 6 hours) and for codeine is 120 mg (taken as 30 mg every 4 hours). Occasionally, octreotide or tincture of opium is required for grade 3 or higher diarrhea. Octreotide is initiated at 100 to 150 mcg subcutaneously three times a day, but the dose can be titrated up to 2000 mcg every 8 hours based on the response.\textsuperscript{82,83} TKI treatment is continued for grade 1 and 2 diarrhea. TKI is temporarily discontinued for grade 2 diarrhea if the symptoms are not improved within 48 hours of using loperamide. For grade 3 or higher diarrhea, TKI is interrupted until diarrhea reaches grade 1.

After interruption, erlotinib and afatinib are recommended to be resumed at a lower dose, but gefitinib is resumed at the original dose. The recommendation is to reduce the dose of erlotinib by 50 mg to a minimum dose of 50 mg and to reduce the dose of afatinib by 10 mg to a minimum dose of 20 mg (Table 6).\textsuperscript{82}

Mucositis/Stomatitis

A routine follow-up with the dentist prior to starting treatment, to diagnose and manage any underlying dental issues, is beneficial. It is important to educate the patient on dental and oral hygiene, including the use of a soft-bristle brush, floss, sodium-bicarbonate and alcohol-free mouthwash.\textsuperscript{84} For general mouth sensitivity, patients can gargle with benzydamine rinse, three times daily as needed. Ice chips or flavored popsicles can be used to numb the mouth and to temporarily ameliorate any symptoms. Acidic, spicy, salty, or coarse food should be avoided.\textsuperscript{74,83,84}

Triamcinolone in dental paste 2–3 times as needed is used for grade 1 mucositis. Oral erythromycin (250–350 mg daily) or minocycline (50 mg daily) is added for grade 2 mucositis. For grade 3 or higher mucositis, clobetasol ointment is used in dental paste along with erythromycin (500 mg daily) or minocycline (100 mg daily). TKI is not interrupted and dose reduction is not required for grade 1 and 2 mucositis. For grade 3 or higher mucositis, TKI is discontinued temporarily until it heals to grade 2 or less. At that point, TKI is reintroduced, usually at the initial dose.\textsuperscript{84}

Lung Toxicity with EGFR TKI

Although uncommon, pulmonary toxicity is seen with EGFR TKI, and is higher in smokers, patients with underlying lung
Table 7 Ongoing and Future Clinical Trials for Epidermal Growth Factor Receptor Mutated Non-Small Cell Lung Cancer

| Protocol Name | Phase | Patient Population | Treatment Regimen | Target Sample Size (n) | Primary Outcomes | Secondary Outcomes |
|---------------|-------|---------------------|-------------------|------------------------|------------------|-------------------|
| NCT04035486 (FLAURA2) | III | Treatment naïve EGFR mutated locally advanced or metastatic NSCLC | Osimertinib + pemetrexed + cisplatin or carboplatin | 586 | PFS | OS, ORR, DOR, DCR |
| NCT04099836 (TOP 1901) | II | EGFR mutated NSCLC in patients with progressive disease on osimertinib | Atezolizumab + bevacizumab | 39 | ORR | PFS, OS, safety |
| NCT04206787 | III | EGFR mutated advanced NSCLC receiving afatinib as first line treatment | Sequential afatinib treatments (observatory) | 825 | TOT | OS, PFS, ORR, DCR |
| NCT04335292 (OCELOT) | II | Previously treated with osimertinib and second line platinum and pemetrexed | Osimertinib | 200 | ORR | PFS, DOR, DCR, OS, QOL |
| NCT04239833 | III | Treatment naïve EGFR mutated locally advanced or metastatic NSCLC | SH-102B | 240 | PFS | ORR, DOR, DCR, OS, safety |
| NCT03255083 | I | EGFR mutated locally advanced or metastatic NSCLC who have progressed on an EGFR TKI | DS-1205c + osimertinib | 13 | Safety | PD, PK, ORR, DCR, PFS, OS |
| NCT03940703 | II | MET Amplified, EGFR mutated advanced or metastatic NSCLC having acquired resistance to prior EGFR TKI | Tepotinib + osimertinib | 90 | Safety, ORR | DOR, DCR, PFS, OS, QOL |
| NCT03599518 | I | EGFR mutated metastatic or unresectable NSCLC having acquired resistance to EGFR TKI | DS-1205c + gefitinib | 63 | Safety | PD, PK, ORR, DOR, DCR, PFS, OS |
| NCT03466147 | II | EGFR mutated advanced NSCLC who have progressed on EGFR TKI | ZN-e4 | 140 | Safety | Safety |
| NCT04351555 (NeoADAURA) | III | EGFR mutated resectable NSCLC | Osimertinib + pemetrexed + cisplatin or carboplatin | 351 | MPR | PCR, EFS, OS, DFS, QOL |
| NCT01352089 | II | Treatment naïve EGFR mutated metastatic NSCLC | Erlotinib + bevacizumab | 88 | PFS | OS, ORR, safety |
| NCT03909334 | II | Treatment naïve EGFR mutated locally advanced or metastatic NSCLC | Osimertinib + ramucirumab | 150 | PFS | ORR, DCR, OS, safety |
| NCT03382795 | II | EGFR mutated advanced NSCC NSCLC who have progressed on EGFR TKI and chemotherapy | Gefitinib or erlotinib | 69 | ORR | PFS, OS, safety |
| NCT02864251 (CheckMate722) | III | EGFR mutated advanced NSCLC who have progressed first or second line EGFR TKI | Nivolumab + chemotherapy or nivolumab + ipilimumab | 580 | PFS | OS, ORR, DOR |
| NCT02347839 (NEGOTIATE) | II | EGFR mutated stage III unresectable NSCLC | Neoadjuvant gefitinib followed by surgery + gefitinib | 37 | Resectability rate | Perioperative complications, EFS, OS |

(Continued)
Table 7 (Continued).

| Protocol Name | Phase | Patient Population | Treatment Regimen | Target Sample Size (n) | Primary Outcomes | Secondary Outcomes |
|---------------|-------|---------------------|-------------------|------------------------|------------------|---------------------|
| NCT04141644  | IB    | EGFR mutated locally advanced or metastatic NSCLC stable on osimertinib | Osimertinib + ipilimumab | 26 | Safety | ORR, PFS, OS |
| NCT04085315  | I     | EGFR mutated metastatic NSCLC who have progressed on or stable on osimertinib | Alisertib + osimertinib | 36 | Safety | ORR, DOR, DCR, PFS, OS, CNS DCR |
| NCT04248829  | III   | Treatment naive EGFR mutated locally advanced or metastatic NSCLC | Lazertinib | 380 | PFS | ORR, DOR, DCR, OS, QOL, CNS responses |
| NCT03532698  | II    | EGFR T790M mutated metastatic NSCLC who have progressed on osimertinib | Osimertinib + aspirin D-0316 | 100 | ORR | DCR, TTP, DOR |
| NCT03861156  | II    | EGFR mutated locally advanced or metastatic NSCLC who have progressed on osimertinib and have a T790M mutation | Osimertinib | 286 | ORR | CNS response |
| NCT0320850   | II/II | Treatment naive EGFR mutated advanced or metastatic NSCLC | Erlotinib + bevacizumab | 128 | PFS | ORR, OS |
| NCT02973763  | I     | EGFR mutated advanced NSCLC who have progressed on an EGFR TKI and have a T790M mutation | Aflatinib | 14 | Safety | PK, PD, ORR, DOR, PFS |
| NCT0302240   | III   | EGFR mutated locally advanced or metastatic non-squamous NSCLC who have progressed on an EGFR-TKI | Sintilimab ± IB305 + pemetrexed + cisplatin | 600 | PFS | OS, ORR |
| NCT03502850  | III   | EGFR mutated locally advanced or metastatic NSCLC who have progressed on an EGFR-TKI | ASK120067 | 135 | ORR | Safety, PFS, DOR, DCR, OS, PK, PD |
| NCT0307778   | II/II | EGFR mutated, exon 20 locally advanced or metastatic NSCLC who have progressed on an EGFR-TKI | TAK-788 | 63 | Safety | PK, PD, ORR, DOR, DCR, PFS, OS, QOL |
| NCT03799094  | III   | EGFR mutated locally advanced or metastatic NSCLC | Vitamin C + EGFR TKI | 150 | PFS | OS, QOL |
| NCT03769103  | II    | Treatment naive EGFR mutated metastatic NSCLC with BM | Osimertinib + SRS | 76 | CNS PFS | CNS OS, time to SRS/ WBRT, OS, QOL |
| NCT04137999  | I     | EGFR mutated locally advanced or metastatic NSCLC | CXCR5 Modified EGFR CAR-T | 11 | Safety, ORR | PK, PD, DOR, PFS |
| NCT03201466  | II    | Treatment naive EGFR mutated locally advanced or metastatic NSCLC | Apatinib + pemetrexed + cisplatin or carboplatin | 48 | ORR | PFS, DCR, OS |
| NCT02954523  | II    | Treatment naive EGFR mutated locally advanced or metastatic NSCLC | Osimertinib + dasatinib | 10 | Safety | PK, PD, PFS, OS, DOR |
| Trial ID | Stage | EGFR Status | Treatment | Duration | Outcome(s) |
|---------|-------|-------------|-----------|----------|------------|
| NCT03727724 | II | EGFR mutated, exon 20 locally advanced or metastatic NSCLC | Afatinib + cetuximab | 37 | ORR, safety, DOR, PFS, OS |
| NCT02716311 | II | Treatment naive EGFR mutated locally advanced or metastatic NSCLC | Afatinib + cetuximab | 118 | TTF, Safety, ORR, OS, PFS |
| NCT01897480 | II | Treatment naive EGFR mutated locally advanced or metastatic NSCLC who have disease control after an 8-week lead-in with erlotinib | LY2876358 + erlotinib | 150 | PFS, ORR, DOR, OS, PK |
| NCT02503722 | I | EGFR mutated advanced or metastatic NSCLC who have progressed on osimertinib | Sapanisertib + osimertinib | 36 | Safety, PK, PD, ORR, DCR, PFS |
| NCT03521154 | III | EGFR mutated stage III unresectable NSCLC | Osimertinib following chemoradiation | 200 | PFS, CNS PFS, OS, ORR, DOR, DCR, safety |
| NCT02789345 | I | EGFR mutated advanced NSCLC who have progressed on an EGFR TKI and have a T790M mutation | Osimertinib + ramucirumab or necitumumab | 74 | Safety, PK, PD, ORR, DCR, DOR, PFS, OS |
| NCT04129502 | III | Treatment naive EGFR mutated, exon 20 locally advanced or metastatic NSCLC | TAK-788 | 318 | PFS, ORR, OS, DOR, DCR, QOL |
| NCT03811054 | II | EGFR mutated advanced or metastatic NSCLC with slow progression on an EGFR TKI | Apatinib + EGFR-TKI | 60 | ORR, DCR, OS, PFS, safety |
| NCT03434418 | II | Treatment naive uncommon EGFR mutated locally advanced or metastatic NSCLC (exon 18 G719X, exon 20 S768I, or exon 21 L856Q) | Osimertinib | 37 | ORR, PFS, safety, OS |
| NCT0436682 | IIA | EGFR mutated, exon 20 locally advanced or metastatic NSCLC previously treated with platinum based chemotherapy | CLN-081 | 80 | Safety, ORR, DOR, DCR, PFS, OS, PK, PD |
| NCT04426825 | II | EGFR mutated advanced or metastatic NSCLC previously treated with an EGFR TKI | Atezolizumab + bevacizumab | 60 | PFS, ORR, DOR, OS, safety |
| NCT02820116 | II | EGFR mutated stage IIA - IIB NSCLC | Neoadjuvant icotinib | 67 | CRR, ORR, DCR, PFS, OS, safety |
| NCT03091491 | II | EGFR mutated advanced or metastatic NSCLC who have progressed on an EGFR TKI | Nivolumab + ipilimumab | 184 | ORR, PFS, DOR, OS, safety |
| NCT01982955 | IB/II | EGFR mutated advanced or metastatic MET positive NSCLC who have progressed on an EGFR TKI | Tepotinib + gefitinib | 70 | Safety, PFS, OS, ORR, DCR, PK, PD, QOL |
| NCT04148898 | II | EGFR mutated advanced or metastatic NSCLC with leptomeningeal metastasis | Osimertinib + bevacizumab | 80 | CNS PFS, ORR, CNS OS, PFS, safety |

(Continued)
Table 7 (Continued).

| Protocol Name | Phase | Patient Population | Treatment Regimen | Target Sample Size (n) | Primary Outcomes | Secondary Outcomes |
|---------------|-------|--------------------|-------------------|------------------------|------------------|--------------------|
| NCT03603262   | I     | EGFR mutated advanced or metastatic NSCLC who have progressed on an EGFR TKI | SH-1028           | 85                     | Safety, PK, PD   | ORR, PFS, DCR, OS |
| NCT02438722   | II/III| Treatment naive EGFR mutated locally advanced or metastatic NSCLC | Aftinib + cetuximab | 174                   | PFS, OS          | ORR, TTF, safety  |
| NCT04206072   | II/III| Treatment naive EGFR mutated locally advanced or metastatic NSCLC | D-0316            | 360                   | PFS              | ORR, DOR, DCR, OS, CNS PFS, safety |
| NCT01450579   | III   | EGFR mutated stage II-IIA (N1-N2) NSCLC | Gefitinib         | 222                   | DFS              | OS, safety, QOL   |
| NCT02716116   | II    | EGFR/HER2 mutated locally advanced or metastatic NSCLC (also includes exon 20) | TAK-788           | 306                   | ORR              | PK, PD, DOR, DCR, PFS, OS |
| NCT03755102   | I     | EGFR mutated advanced or metastatic NSCLC who have progressed on osimertinib | Dacomitinib + osimertinib | 24                     | ORR              | PFS, OS          |
| NCT03122717   | II    | Treatment naive EGFR mutated locally advanced or metastatic NSCLC | Osimertinib + gefitinib | 64                     | Safety           | ORR, PFS, OS     |
| NCT04425681   | II    | EGFR mutated advanced or metastatic NSCLC with leptomeningeal metastasis | Osimertinib + bevacizumab | 20                     | CNS PFS, ORR    | CNS OS, PFS, safety |
| NCT0396185    | II    | EGFR mutated stage IIA-IIB NSCLC | Icotinib following chemoradiation | 30                     | RFS              | OS, safety        |
| NCT03420822   | III   | EGFR mutated advanced or metastatic NSCLC with slow progression on an EGFR TKI | Apatinib + EGFR-TKI | 54                     | PFS              | OS, ORR          |
| NCT04233021   | II    | EGFR mutated advanced or metastatic NSCLC with brain or leptomicenegal metastasis | Osimertinib | 113                   | ORR              | OS, PFS, safety, QOL |
| NCT04143607   | III   | Treatment naive EGFR mutated locally advanced or metastatic NSCLC | ASK 120067        | 334                   | PFS              | ORR, DOR, DCR, OS |
| NCT04405674   | II    | EGFR mutated advanced or metastatic NSCC NSCLC who have progressed on an EGFR TKI | Tislelizumab + carboplatin + nab-paclitaxel | 66                     | PFS              | ORR, DCR, OS, DOR |
| NCT03392246   | II    | Treatment naive EGFR mutated locally advanced or metastatic NSCLC | Osimertinib + selumetinib | 25                     | Best ORR         | PFS, OS, safety  |
| NCT01553942   | II    | Treatment naive EGFR mutated stage III NSCLC | Aftinib + chemoradiation | 30                     | ORR              | PFS, safety, DCR |
| NCT03823807   | II    | EGFR mutated advanced NSCLC who have progressed on an EGFR TKI and have a T790M mutation | SH-1028           | 300                   | ORR              | Safety, PK, PD, PFS, DOR, DCR, OS |

Tislelizumab + carboplatin + nab-paclitaxel.
| Study ID       | Design | Description                                                                 | Treatment                                                                 | Duration | Primary Outcome(s) | Secondary Outcome(s) |
|---------------|--------|-----------------------------------------------------------------------------|---------------------------------------------------------------------------|----------|---------------------|----------------------|
| NCT04204473   | I      | EGFR mutated advanced or metastatic NSCLC who have progressed on an EGFR TKI | TY-9591                                                                   | 126      | Safety, ORR         | PK, PD, PFS, DOR     |
| NCT04358562   | II     | EGFR mutated advanced NSCC NSCLC with unclear plasma ctDNA EGFR mutation after progression on gefitinib | Gefitinib + anlotinib                                                      | 240      | PFS                 | OS, ORR, safety      |
| NCT02098954   | II     | EGFR mutated advanced or metastatic NSCLC who have progressed on an EGFR TKI | Erlotinib + gemcitabine + cisplatin                                         | 40       | PFS                 | OS, ORR              |
| NCT03066206   | II     | EGFR mutated, exon 20 locally advanced or metastatic NSCLC                  | Poxetinib                                                                  | 80       | ORR                 | DCR, PFS, OS, DOR, safety |
| NCT01859026   | I      | EGFR or KRAS mutated advanced or metastatic NSCLC                           | MEK162 + erlotinib                                                        | 43       | Safety              | PFS                  |
| NCT02520778   | I      | EGFR mutated advanced or metastatic NSCLC who have progressed on an EGFR TKI | Osimertinib + navitoclax                                                  | 50       | Safety              | PK, PD, ORR          |
| NCT03653466   | II/III | Treatment naive EGFR mutated advanced or metastatic NSCC NSCLC              | Gefitinib + apatinib                                                      | 346      | Safety, PFS         | OS, ORR, DCR, DOR, QOL, PK, PD |
| NCT04007835   | II     | EGFR mutated advanced or metastatic NSCLC who have progressed on an EGFR TKI | AZD3759                                                                   | 432      | PFS                 | CNS PFS, ORR, DCR, DOR, ORR |
| NCT03819320   | II     | EGFR mutated advanced or metastatic NSCLC who have progressed on an EGFR TKI | Anlotinib + EGFR TKI                                                      | 120      | PFS                 | ORR, DCR, OS, safety |
| NCT03819320   | II     | EGFR mutated advanced or metastatic NSCLC who have progressed on an EGFR TKI | CB-839 + osimertinib                                                      | 53       | Safety, ORR         | PFS, OS, PK, PD      |
| NCT01746251   | II     | Treatment naive EGFR mutated advanced or metastatic NSCLC                  | Erlotinib + hydroxychloroquine                                             | 76       | PFS                 | Safety, ORR, OS      |
| NCT03141494   | II     | Treatment naive EGFR mutated advanced or metastatic NSCLC                  | Gefitinib + thalidomide                                                   | 128      | PFS                 | ORR, OS              |
| NCT0481663    | I      | EGFR mutated advanced or metastatic NSCLC who have progressed on an EGFR TKI | Osimertinib + necitumumab                                                 | 100      | Safety              | ORR, PFS, DCR, PK, PD |
| NCT01746251   | II     | EGFR mutated Stage I-II NSCLC                                              | Afatinib (adjuvant)                                                       | 92       | RFS                 | Safety, OS           |
| NCT04181060   | III    | Treatment naive EGFR mutated advanced or metastatic NSCLC                  | Osimertinib + bevacizumab                                                | 300      | PFS                 | OS, ORR, time to CNS metastases, safety |
| NCT02917993   | II     | EGFR mutated advanced or metastatic NSCLC who have progressed on an EGFR TKI | Itacitinib + osimertinib                                                 | 59       | Safety, ORR         | PK, PD, PFS, OS      |
| NCT0383811    | III    | EGFR mutated Stage IIB-IIIA NSCLC                                          | Icotinib + chemotherapy (adjuvant)                                       | 174      | DFS                 | Safety               |

(Continued)
Table 7 (Continued).

| Protocol Name                  | Phase | Patient Population                                                                                       | Treatment Regimen                                | Target Sample Size (n) | Primary Outcomes | Secondary Outcomes |
|--------------------------------|-------|----------------------------------------------------------------------------------------------------------|--------------------------------------------------|------------------------|-------------------|--------------------|
| NCT0326049[170]                | I     | EGFR mutated advanced or metastatic NSCLC who have progressed on an EGFR TKI                              | U3-I402                                          | 198                    | Safety, ORR       | PK, PD, DCR, DOR, PFS, OS |
| NCT04042558[171]               | II    | Advanced or metastatic NSCLC who have progressed on a targeted therapy                                     | Carboplatin + Pemetrexed + Atezolizumab + Bevacizumab | 149                    | ORR               | PFS, OS, DOR       |
| NCT02609776 (CHRYSLIS)[172]    | I     | EGFR mutated advanced or metastatic NSCLC who have progressed on an EGFR TKI                              | Lazertinib                                       | 460                    | Safety, ORR       | PK, PD, PFS, OS    |
| NCT03234712[173]               | I     | Advanced solid tumors with overexpression EGFR                                                           | ABBV-321                                        | 120                    | PK, PD            | PFS, DOR, DCR, OS, ORR |
| NCT01470716[174]               | II    | EGFR mutated Stage II–III A NSCLC                                                                      | Erlotinib (neoadjuvant)                          | 26                     | PFS               | ORR, OS, safety    |
| NCT03778229 (SAVANNAH)[175]    | II    | EGFR mutated advanced or metastatic NSCLC who have progressed on osimertinib                            | Osimertinib + savolitinib                       | 192                    | ORR               | PFS, QOL, OS, safety, DOR |
| NCT04201756[176]               | II    | EGFR mutated Stage III resectable NSCLC                                                                  | Afatinib (neoadjuvant)                          | 47                     | ORR               | DFS, OS, PFS, safety, QOL |
| NCT03623750 (EPICAL)[177]      | IB    | Treatment naive advanced or metastatic NSCLC                                                           | Afatinib + EGF-PTI + cyclophosphamide           | 30                     | Safety            | Clinical outcomes |

Abbreviations: BM, brain metastases; CAR-T, chimeric antigen receptor autologous T-Cells; CNS, central nervous system; ORR, complete resection rate; DCR, disease control rate; DFS, disease-free survival; DOR, duration of response; EGF-PTI, EGF pathway targeting immunization; EGFR, epidermal growth factor receptor; EFS, event-free survival; MET, mesenchymal-epithelial transition; MPR, major pathological response; NSCC, non-squamous cell carcinoma; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PCR, pathological complete response; PD, pharmacokinetics; PK, pharmacodynamics; PFS, progression-free survival; QOL, quality of life; SRS, stereotactic radiosurgery; TKI, tyrosine kinase inhibitor; TOT, time on treatment; TTP, time to progression; TTF, time to treatment failure; WBRT, whole brain radiotherapy.
conditions or those who have been treated with radiation in the past. This usually consists of interstitial lung disease/pneumonitis. While the exact mechanism is unclear, this is thought to be due to inhibition of EGFR, which is expressed in type II pneumocytes, which helps in alveolar wall repair. Management is supportive, with immediate discontinuation of the drug, oxygen supplementation, and steroids. Osimertinib has shown to have a higher incidence of pulmonary toxicity compared to first-generation EGFR TKIs.

Cardiac Toxicity with EGFR TKI
Cardiac toxicity including QT prolongation, cardiac failure, pericardial effusion, myocarditis, atrial fibrillation although uncommon, has been seen with osimertinib. The exact mechanism is not known but is thought to be due to the inhibition of HER 2 (human epidermal growth factor-2). Treatment includes supportive measures, maximizing cardiac protection and sometimes discontinuation of the drug.

Evolving Treatment Paradigm for EGFR Positive Metastatic NSCLC
Currently, for patients who have EGFR positive metastatic NSCLC, treatment options consist of erlotinib, gefitinib, icotinib, afatinib, dacomitinib, osimertinib or erlotinib plus ramucirumab. Osimertinib has emerged as the preferred EGFR TKI due to its benefit in PFS and OS over erlotinib and gefitinib. The most common cause for secondary resistance to first and second-generation TKI is development of a secondary mutation in exon 20, T790M. Osimertinib is an effective second-line option for patients who were previously treated with first or second-generation TKI, particularly for those who develop the T790M mutation. Patients who progress on osimertinib have limited options. Resistance mechanisms include occurrence of tertiary mutations such as C797S, activation of alternate signaling pathways such as MET, and histological transformation to small cell or sarcomatoid tumors. Options after progression on osimertinib include continuing TKI while addressing areas of progression with local therapies or initiating systemic platinum-based or docetaxel chemotherapy. Checkpoint inhibitor therapy is generally ineffective in this patient population. Enrollment in clinical trials is ideal and should be strongly considered for these patients.

Conclusions and Future Directions
EGFR TKIs significantly improve outcomes in patients with advanced NSCLC that contains an activating mutation in EGFR compared with platinum-based chemotherapy doublets. Resistance inevitably occurs and identifying patients who are likely to have rapid progression is critical. This would not only help with monitoring patients on treatment but also help optimize outcomes by encouraging them to participate in clinical trials.

There are emerging data to support the use of EGFR TKIs with other systemic therapies in the front-line setting. While most of the published studies on combination therapies have involved first-generation TKIs, there are ongoing trials looking at combinations of various TKIs including osimertinib with other systemic agents as summarized in Table 7. It is possible that these combinations will push median survival even further for these patients, but the incremental benefit needs to be weighed against additional toxicities from adding other systemic agents. Currently, osimertinib is the preferred therapy of choice of EGFR-mutated NSCLC, but the promising data for combination therapies raise the question as to which option would be better suited as first-line therapy. PFS was similar amongst the trials, but osimertinib may be a suitable option after progression on combination therapy.

Developing effective treatment regimens for patients who progress on osimertinib, or those who develop tertiary mutations such as C797S, is urgently needed. Patients with less common EGFR mutations such as exon 20 insertions typically do not respond well to the available TKIs and there is an imminent need to develop agents that work effectively in this population (Table 7). Similarly, patients with refractory brain metastases or leptomeningeal disease desperately need efficient treatment options. Table 7 enlists some of the ongoing clinical trials that aim to address these unmet needs.

With multiple agents approved for EGFR-mutated NSCLC, it would be ideal to have standardization of clinical pathways, including guidelines on optimal utilization of tissue-based and blood-based next-generation sequencing. Multidisciplinary input, in addition to detailed genomic information, is of paramount importance to help create a personalized treatment plan for each patient. These therapies do come with unforeseen adverse effects, for which having an interdisciplinary team including oncologists, nurses, clinical pharmacists, dermatologists, gastroenterologists, dentist/oral health-care providers, and wound care
specialists, is of utmost importance. Patient education regarding toxicities prior to initiation of treatment, in conjunction with the utilization of patient-reported outcomes, and toxicity management algorithms, help improve patients’ quality of life. These strategies increase patient compliance while also reducing treatment interruptions, dose reductions, or treatment discontinuation.

**Conclusion**

EGFR mutated advanced NSCLC forms a special subset of lung cancer for which there are excellent treatment options. The current standard of care for patients diagnosed with this disease is treated with one of the several FDA-approved TKIs, which have all shown improved outcomes compared to chemotherapy. However, almost all patients with this disease develop resistance at some time point and there are no effective treatment options for patients who progress on the third-generation TKI, osimertinib. Ongoing trials with combination regimens and polyspecific antibodies will hopefully address unmet needs and transform EGFR-mutated lung cancer to a chronic disease with an excellent prognosis.

**Disclosure**

Nagashree Seetharamu has served on the advisory boards for Genentech, Amgen, Takeda and Astra-Zeneca in the last year outside the submitted work. The authors report no other conflicts of interest in this work.

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