Lung Cancer: Targets and Therapy

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REVIEW

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 time point. 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.[6] 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.[7,8] *EGFR* has an extracellular binding domain, trans-membrane segment, and cytoplasmic tyrosine kinase domain.[9] 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.[8] 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.[10,11] Sensitizing *EGFR* mutations have been found in up to 50% of Asian patients and about 10% of Caucasian patients.[12] 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.[13–17] Figure 1 summarizes the timeline of events regarding *EGFR* treatment.[18–22]

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.[23–26] 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.[23]

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).[24–26] 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.[46] 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.[47] 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 Therapy Interactions			Metabolism/Transport Effects		
					PPI	H2RA	Antacids	Substrate	Inhibitor	Inducer
Afatinib[13]	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	N/A	BCRP, PGP	N/A	N/A
Erlotinib[14]	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[15]	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	N/A	CYP2D6, CYP3A4, BCRP	N/A	N/A
Osimertinib[16]	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	N/A	CYP3A4, BCRP, PGP	BCRP, PGP	N/A
Dacomitinib[17]	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	N/A	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.

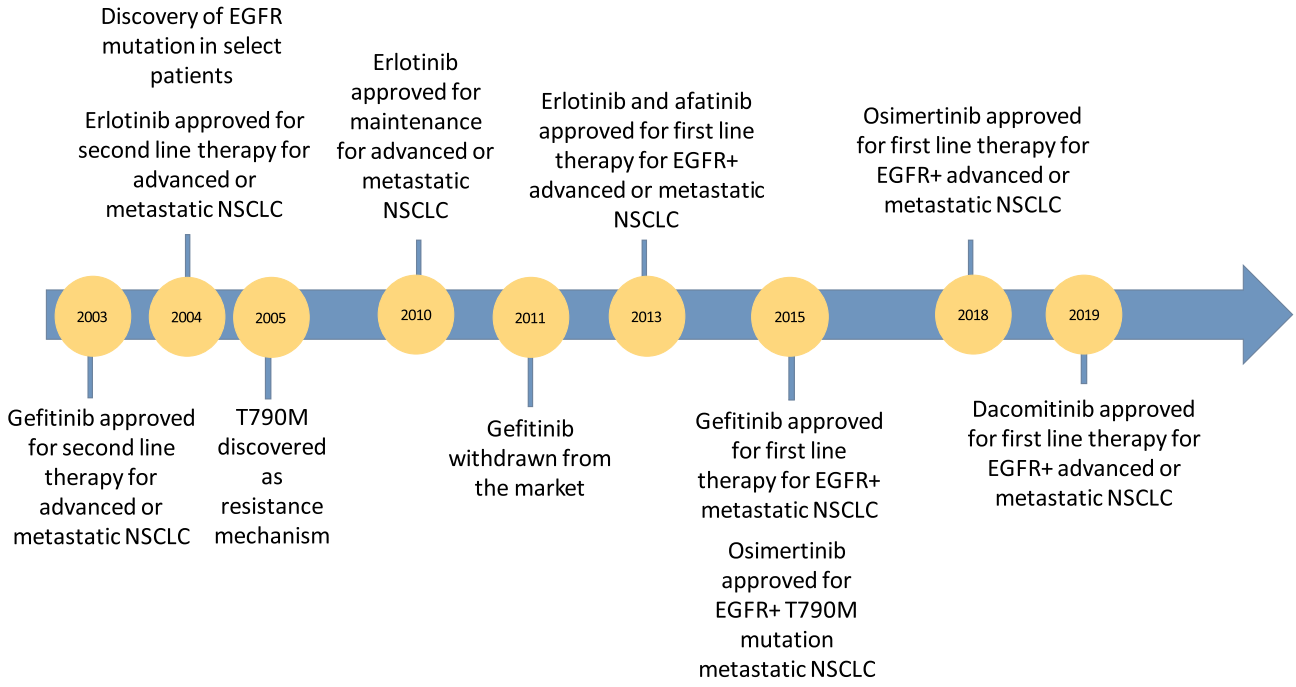

Figure 1 Epidermal growth factor receptor timeline.

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.[14,29-32,48] 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.[4] 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.[30] 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 IIIB 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.[29] 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.[14]

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-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.[38] 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.[52] 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 regimens 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 front-line 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 IIIA 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 front-line 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

Table 2 Select Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors Trials

Trial	Phase	N	Patient Population	Intervention	Median Follow-Up (Median, Months)	PFS (Median, Months)	OS (Median, Months)	ORR (%)
IPASS[23,27]	3	1217 261 (EGFR +)	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[24,28]	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[25]	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[26]	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[29]	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

OPTIMAL[30,31]	3	154	EGFR mutated stage IIIB/IV NSCLC	Erlotinib 150 mg/day vs gemcitabine plus carboplatin	25.9	13.1 vs 4.6; HR=0.16 (0.10–0.26); p<0.0001	22.8 vs 27.2; HR=1.19 (0.83–1.71); p=0.2663	83 vs 36
ENSURE[32]	3	217	EGFR mutated stage IIIB/IV NSCLC	Erlotinib 150 mg/day vs gemcitabine and cisplatin up to 4 cycles	28.9 vs 27.1	11.0 vs 5.5; HR=0.34 (0.22–0.51); p<0.0001	26.3 vs 25.5; HR=0.91 (0.63–1.31); p=0.607	62.7 vs 33.6
LUX-LUNG1[33]	2B/3	585	EGFR mutated Stage IIIB/IV NSCLC who had received 1 or 2 previous chemotherapy regimens and had disease progression after 12 weeks of treatment with erlotinib or gefitinib	Afatinib 40 mg/day vs placebo	NR	3.3 vs 1.1; HR=0.38 (0.31–0.48); p<0.0001	10.8 vs 12.0; HR=1.08 (0.86–1.35); p=0.74	NR
LUX-LUNG3[34]	3	345	EGFR mutated stage IIIB/IV NSCLC	Afatinib 40 mg/day vs up to 6 cycles of cisplatin plus pemetrexed chemotherapy	16.4	11.1 vs 6.9; HR=0.58 (0.43–0.78); p=0.001	28.2 vs 28.2; HR=0.88 (0.66–1.17); p=0.39	56.1 vs 22.6
LUX-LUNG6[35]	3	364	Treatment naïve EGFR mutated advanced NSCLC	Afatinib 40 mg/day vs gemcitabine and cisplatin for up to 6 cycles	16.6	11.0 vs 5.6; HR=0.28 (0.20–0.39); p<0.0001	23.1 vs 23.5; HR=0.93 (0.72–1.22); p=0.61	66.9 vs 23.0
LUX-LUNG7[36,37]	2B	319	EGFR mutated stage IIIB/IV NSCLC	Afatinib 40 mg/day vs gefitinib 250 mg/day	42.6	11.0 vs 10.9; HR=0.73 (0.57–0.95); p=0.017	27.9 vs 24.5; HR=0.86 (0.66–1.12); p=0.258	70 vs 56
LUX-LUNG8[38]	3	795	Stage IIIB/IV SCLC after progression of ≥4 cycles of platinum-based chemotherapy	Afatinib 40 mg/day vs erlotinib 150 mg/day	18.4	2.4 vs 1.9; HR=0.82 (0.68–1.00); p=0.0427	7.9 vs 6.8; HR=0.81 (0.69–0.95); p=0.0077	22 vs 11
ARCHER 1050 (Wu YL 2017)[39,40]	3	452	Treatment naïve EGFR mutated advanced NSCLC	Dacomitinib 45 mg/day vs gefitinib 250 mg/day	31.1	14.7 vs 9.2; HR=0.59 (0.47–0.74); p<0.0001	34.1 vs 26.8; HR=0.760 (0.582–0.993)	74.9 vs 71.6

(*Continued*)

Table 2 (Continued).

Trial	Phase	N	Patient Population	Intervention	Median Follow-Up (Median, Months)	PFS (Median, Months)	OS (Median, Months)	ORR (%)
ARCHER 1009[41]	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[42]	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[43]	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[44]	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[45]	3	285	EGFR mutated stage IIIB/IV NSCLC	Icotinib 125 mg three times daily vs 3 week cycles of chemotherapy (75 mg/mg^2 cisplatin plus 500 mg/m^2 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[59,60]	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[62]	3	1093	Chemotherapy-naïve patients with unresectable stage III/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 vs placebo 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[63]	3	1037	Chemotherapy naïve patients with unresectable stage III/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 vs placebo 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 V et al[57]	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[58]	3	345	Chemotherapy naïve patients with EGFR mutated stage IIIB/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[64]	3	228	Chemotherapy naïve patients with EGFR mutated stage IIIB/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*)

Table 3 (Continued).

Trial	Phase	N	Patient Population	Intervention	Median Follow-Up (Median, Months)	PFS (Median, Months)	OS (Median, Months)	ORR (%)
BeTa[65]	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[61]	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[66]	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[67]	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[68]	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.

minimal grade 3 or higher toxicities.[43] Along with the tumor cells, *EGFR* is also expressed in healthy epithelial cells, mainly in the skin and gastrointestinal (GI) tract.[69,70] *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.[70] Cutaneous AEs can affect 20%-89% of patients.[30,34,71] 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.[30,34,71,72] 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.[73] 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 as 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.[30,34,71,74-76] Osimertinib has shown to have a lower incidence of overall rash as well as grade ≥3 rash when compared to first-generation-*EGFR* TKIs.[43] 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.[75,76] 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).[77,78] 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.[74,78]

Xerosis is the second most reported AE which occurs in almost 50% of patients, usually after 30–50 days of treatment.[30,34,71,74,78] *EGFR* TKIs alter the epidermal barrier leading to dry skin.[74] 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.[74,78] 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.[30,34,71,74,78] 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).[74,78]

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.[74,78] 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.[74]

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.[79]

Acneiform Rash

There is a lack of evidence-based guidelines from prospective, randomized controlled trials, and hence, the management of the rash differs by clinician.[79] In general, the management of the rash depends on the grade. Clindamycin gel 1% twice a day with topical hydrocortisone cream 2.5% is recommended for grade 1 rash and TKI dose adjustment is not required. For grade 2 rash, oral anti-inflammatory antibiotics such as doxycycline 100 mg twice daily or minocycline 100 mg daily are recommended, in addition to a topical steroidal cream. Dose adjustment is not required. The rash should be monitored carefully, and clinicians should be wary of the signs of bacterial super-infection. Grade 3 or higher rash warrants

Table 4 National Cancer Institute Common Terminology Criteria for Adverse Events V5.0 Grading Criteria for Common Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors Induced Toxicity[77]

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
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 cephalexin 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)[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[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. -fAdd 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.[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.[71] The most commonly reported GI AE is diarrhea.[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.[81] 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.[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.[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).[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.[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.[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.[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)[90]	III	Treatment naïve EGFR mutated locally advanced or metastatic NSCLC	Osimertinib + pemetrexed + cisplatin or carboplatin	586	PFS	OS, ORR, DOR, DCR
NCT04099836 (TOP 1901)[91]	II	EGFR mutated NSCLC in patients with progressive disease on osimertinib	Atezolizumab + bevacizumab	39	ORR	PFS, OS, safety
NCT04206787[92]	III	EGFR mutated advanced NSCLC receiving afatinib as first line treatment	Sequential afatinib treatments (observatory)	825	TOT	OS, PFS, ORR, DCR
NCT04335292 (OCELOT)[93]	II	Previously treated with osimertinib and second line platinum and pemetrexed	Osimertinib	200	ORR	PFS, DOR, DCR, OS, TTF, QOL
NCT04239833[94]	III	Treatment naïve EGFR mutated locally advanced or metastatic NSCLC	SH-1028	240	PFS	ORR, DOR, DCR, OS, safety
NCT03255083[95]	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[96]	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[97]	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
NCT03446417[98]	I/II	EGFR mutated advanced NSCLC who have progressed on EGFR TKI	ZN-e4	140	Safety	Safety
NCT04351555 (NeoADAURA)[99]	III	EGFR mutated resectable NSCLC	Osimertinib + pemetrexed + cisplatin or carboplatin	351	MPR	PCR, EFS, OS, DFS, QOL
NCT01532089[100]	II	Treatment naïve EGFR mutated metastatic NSCLC	Erlotinib + bevacizumab	88	PFS	OS, ORR, safety
NCT03909334[101]	II	Treatment naïve EGFR mutated locally advanced or metastatic NSCLC	Osimertinib + ramucirumab	150	PFS	ORR, DCR, OS, safety
NCT03382795[102]	II	EGFR mutated advanced NSCC NSCLC who have progressed on EGFR TKI and chemotherapy	Gefitinib or erlotinib	69	ORR	PFS, OS, safety
NCT02864251 (CheckMate722)[103]	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)[104]	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
NCT01996098 (ICTAN)[105]	III	EGFR mutated stage IIA-IIIA unresectable NSCLC	Icotinib following chemotherapy	318	DFS	OS, safety, QOL
NCT04141644[106]	IB	EGFR mutated locally advanced or metastatic NSCLC stable on osimertinib	Osimertinib + ipilimumab	26	Safety	ORR, PFS, OS
NCT04085315[107]	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 (LASER301)[108]	III	Treatment naïve EGFR mutated locally advanced or metastatic NSCLC	Lazertinib	380	PFS	ORR, DOR, DCR, OS, QOL, CNS responses
NCT03532698[109] NCT03861156[110]	III II	EGFR T790M mutated metastatic NSCLC who have progressed on osimertinib EGFR mutated locally advanced or metastatic NSCLC who have progressed on EGFR TKI and have a T790M mutation	Osimertinib + aspirin D-0316	100 286	ORR ORR	DCR, TTP, DOR PFS, OS, DOR, DCR, CNS response
NCT03126799[111]	II	Treatment naïve EGFR mutated advanced or metastatic NSCLC	Erlotinib + bevacizumab	128	PFS	ORR, OS
NCT03904823[112]	II	Treatment naïve EGFR mutated locally advanced or metastatic NSCLC	Famitinib + HS-10,296	58	ORR	DOR, DCR, PFS, safety
NCT02973763[113]	I	EGFR mutated advanced NSCLC who have progressed on an EGFR TKI and have a T790M mutation	Alflutinib	14	Safety	PK, PD, ORR, DOR, PFS
NCT03802240 (ORIENT-31)[114]	III	EGFR mutated locally advanced or metastatic non-squamous NSCLC who have progressed on EGFR-TKI	Sintilimab ± IBI305 + pemetrexed + cisplatin	600	PFS	OS, ORR
NCT03502850[115]	I/II	EGFR mutated locally advanced or metastatic NSCLC who have progressed on EGFR-TKI	ASK120067	135	ORR	Safety, PFS, DOR, DCR, OS, PK, PD
NCT03807778[116]	I/II	EGFR mutated, exon 20 locally advanced or metastatic NSCLC who have progressed on EGFR-TKI	TAK-788	63	Safety	PK, PD, ORR, DOR, DCR, PFS, OS, QOL
NCT03799094[117]	III	EGFR mutated locally advanced or metastatic NSCLC	Vitamin C + EGFR TKI	150	PFS	OS, QOL
NCT03769103[118]	II	Treatment naïve EGFR mutated metastatic NSCLC with BM	Osimertinib + SRS	76	CNS PFS	CNS OS, time to SRS/WBRT, OS, QOL
NCT04153799[119]	I	EGFR mutated locally advanced or metastatic NSCLC	CXCR5 Modified EGFR CAR-T	11	Safety, ORR	PK, PD, DOR, PFS
NCT03201146[120]	I/II	Treatment naïve EGFR mutated locally advanced or metastatic NSCLC	Apatinib + pemetrexed + cisplatin or carboplatin	48	ORR	PFS, DCR, OS
NCT02954523[121]	I/II	Treatment naïve EGFR mutated locally advanced or metastatic NSCLC	Osimertinib + dasatinib	10	Safety	PK, PD, PFS, OS, DOR

NCT03727724 (AFACET)[122]	II	EGFR mutated, exon 20 locally advanced or metastatic NSCLC	Afatinib + cetuximab	37	DCR	ORR, safety, DOR, PFS, OS
NCT02716311 (ACE-Lung)[123]	II	Treatment naïve EGFR mutated locally advanced or metastatic NSCLC	Afatinib + cetuximab	118	TTF	Safety, ORR, OS, PFS
NCT01897480 (Balise)[124]	II	Treatment naïve EGFR mutated locally advanced or metastatic NSCLC who have disease control after an 8-week lead-in with erlotinib	LY2875358 + erlotinib	150	PFS	ORR, DOR, OS, PK
NCT02503722[125]	I	EGFR mutated advanced or metastatic NSCLC who have progressed on osimertinib	Sapanisertib + osimertinib	36	Safety	PK, PD, ORR, DCR, PFS
NCT03521154 (LAURA)[126]	III	EGFR mutated stage III unresectable NSCLC	Osimertinib following chemoradiation	200	PFS	CNS PFS, OS, ORR, DOR, DCR, safety
NCT02789345[127]	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[128]	III	Treatment naïve EGFR mutated, exon 20 locally advanced or metastatic NSCLC	TAK-788	318	PFS	ORR, OS, DOR, DCR, QOL
NCT03811054[129]	II	EGFR mutated advanced or metastatic NSCLC with slow progression on an EGFR TKI	Apatinib + EGFR-TKI	60	ORR	DCR, OS, PFS, safety
NCT03434418[130]	II	Treatment naïve uncommon EGFR mutated locally advanced or metastatic NSCLC (exon 18 G719X, exon 20 S768I, or exon 21 L861Q)	Osimertinib	37	ORR	PFS, safety, OS
NCT04036682[131]	I/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[132]	II	EGFR mutated advanced or metastatic NSCLC previously treated with an EGFR TKI	Atezolizumab + bevacizumab	60	PFS	ORR, DOR, OS, safety
NCT02820116[133]	II	EGFR mutated stage IIIA - IIIB NSCLC	Neoadjuvant icotinib	67	CRR	ORR, DCR, PFS, OS, safety
NCT03091491[134]	II	EGFR mutated advanced or metastatic NSCLC who have progressed on an EGFR TKI	Nivolumab + ipilimumab	184	ORR	PFS, DOR, OS, safety
NCT01982955 (INSIGHT)[135]	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[136]	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[137]	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[138]	II/III	Treatment naïve EGFR mutated locally advanced or metastatic NSCLC	Afatinib + cetuximab	174	PFS, OS	ORR, TTF, safety
NCT04206072[139]	II/III	Treatment naïve EGFR mutated locally advanced or metastatic NSCLC	D-0316	360	PFS	ORR, DOR, DCR, OS, CNS PFS, safety
NCT01405079[140]	III	EGFR mutated stage II–IIIA (N1-N2) NSCLC	Gefitinib	222	DFS	OS, safety, QOL
NCT02716116[141]	I/II	EGFR/HER2 mutated locally advanced or metastatic NSCLC (also includes exon 20)	TAK-788	306	ORR	PK, PD, DOR, DCR, PFS, OS
NCT03755102[142]	I	EGFR mutated advanced or metastatic NSCLC who have progressed on osimertinib	Dacomitinib + osimertinib	24	ORR	PFS, OS
NCT03122717[143]	I/II	Treatment naïve EGFR mutated locally advanced or metastatic NSCLC	Osimertinib + gefitinib	64	Safety	ORR, PFS, OS
NCT04425681 (OWBLM)[144]	II	EGFR mutated advanced or metastatic NSCLC with leptomeningeal metastasis	Osimertinib + bevacizumab	20	CNS PFS, ORR	CNS OS, PFS, safety
NCT03396185[145]	II	EGFR mutated stage IIIA-IIIB NSCLC	Icotinib following chemoradiation	30	RFS	OS, safety
NCT03428022 (AFLC)[146]	III	EGFR mutated advanced or metastatic NSCLC with slow progression on an EGFR TKI	Apatinib + EGFR-TKI	54	PFS	OS, ORR
NCT04233021 (ORBITAL)[147]	II	EGFR mutated advanced or metastatic NSCLC with brain or leptomeningeal metastasis	Osimertinib	113	ORR	OS, PFS, safety, QOL
NCT04143607[148]	III	Treatment naïve EGFR mutated locally advanced or metastatic NSCLC	ASK120067	334	PFS	ORR, DOR, DCR, OS
NCT04405674[149]	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[150]	II	Treatment naïve EGFR mutated locally advanced or metastatic NSCLC	Osimertinib + selumetinib	25	Best ORR	PFS, OS, safety
NCT01553942 (ASCENT Trial)[151]	II	Treatment naïve EGFR mutated stage III NSCLC	Afatinib + chemoradiation	30	ORR	PFS, safety, DCR
NCT03823807[152]	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

NCT04204473[153]	I	EGFR mutated advanced or metastatic NSCLC who have progressed on an EGFR TKI	TY-9591	126	Safety, ORR	PK, PD, PFS, DOR
NCT04358562[154]	II	EGFR mutated advanced NSCC NSCLC with uncleared plasma ctDNA EGFR mutation after progression on gefitinib	Gefitinib + anlotinib	240	PFS	OS, ORR, safety
NCT02098954[155]	II	EGFR mutated advanced or metastatic NSCLC who have progressed on an EGFR TKI	Erlotinib + gemcitabine + cisplatin	40	PFS	OS, ORR
NCT03066206[156]	II	EGFR mutated, exon 20 locally advanced or metastatic NSCLC	Poziotinib	80	ORR	DCR, PFS, OS, DOR, safety
NCT01859026[157]	I	EGFR or KRAS mutated advanced or metastatic NSCLC	MEK162 + erlotinib	43	Safety	PFS, OS
NCT02520778[158]	I	EGFR mutated advanced or metastatic NSCLC who have progressed on an EGFR TKI	Osimertinib + navitoclax	50	Safety	PK, PD, ORR
NCT02824458[159]	III	Treatment naïve EGFR mutated advanced or metastatic NSCC NSCLC	Gefitinib + apatinib	346	Safety, PFS	OS, ORR, DCR, DOR, QOL. PK, PD
NCT03653546[160]	II/III	Treatment naïve EGFR mutated advanced or metastatic NSCLC with CNS metastases	AZD3759	432	PFS	CNS PFS, ORR, DCR, DOR, OS
NCT04007835[16]	II	EGFR mutated advanced or metastatic NSCLC who have progressed on an EGFR TKI	Anlotinib + EGFR TKI	120	PFS	ORR, DCR, OS, safety
NCT03831932[162]	I/II	EGFR mutated advanced or metastatic NSCLC who have progressed on an EGFR TKI	CB-839 + osimertinib	53	Safety, ORR	PFS,OS, PK, PD
NCT00977470[163]	II	Treatment naïve EGFR mutated advanced or metastatic NSCLC	Erlotinib + hydroxychloroquine	76	PFS	Safety, ORR, OS
NCT03341494[164]	II	Treatment naïve EGFR mutated advanced or metastatic NSCLC	Gefitinib + thalidomide	128	PFS	ORR, OS
NCT02496663[165]	I	EGFR mutated advanced or metastatic NSCLC who have progressed on an EGFR TKI	Osimertinib + necitumumab	100	Safety	ORR, PFS, DCR, PK, PD
NCT01746251[166]	II	EGFR mutated Stage I–III NSCLC	Afatinib (adjuvant)	92	RFS	Safety, OS
NCT04181060[167]	III	Treatment naïve EGFR mutated advanced or metastatic NSCLC	Osimertinib + bevacizumab	300	PFS	OS, ORR, time to CNS metastases, safety
NCT02917993[168]	I/II	EGFR mutated advanced or metastatic NSCLC who have progressed on an EGFR TKI	Itacitinib + osimertinib	59	Safety, ORR	PK, PD, PFS, OS
NCT03983811[169]	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
NCT03260491[170]	I	EGFR mutated advanced or metastatic NSCLC who have progressed on an EGFR TKI	U3-1402	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 (CHRYSALIS)[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–IIIA 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 naïve 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; CRR, 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.[69] Osimertinib has shown to have a higher incidence of pulmonary toxicity compared to first-generation *EGFR* TKIs.[43]

Cardiac Toxicity with *EGFR* TKI

Cardiac toxicity including QT prolongation, cardiac failure, pericardial effusion, myocarditis, atrial fibrillation although uncommon, has been seen with osimertinib.[43] The exact mechanism is not known but is thought to be due to the inhibition of HER 2 (human epidermal growth factor-2).[85] 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.[23–45,61] Osimertinib has emerged as the preferred *EGFR* TKI due to its benefit in PFS and OS over erlotinib and gefitinib.[43,54] 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.[86] Options after progression on osimertinib include continuing TKI while addressing areas of progression with local therapies or initiating systemic platinum-based or docetaxel chemotherapy.[87] Checkpoint inhibitor therapy is generally ineffective in this patient population.[88,89] 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.[43,57–61]

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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