Review

Tyrosine Kinase Inhibitors for the Treatment of *EGFR* Mutation-Positive Non–Small-Cell Lung Cancer: A Clash of the Generations

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Abstract

The availability of 3 generations of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) with different pharmacologic characteristics and clinical profiles has provided oncologists with a potentially confusing choice for the treatment of *EGFR* mutation-positive non–small-cell lung cancer. Although recent head-to-head clinical trials have demonstrated improved efficacy with second-generation (ie, afatinib, dacomitinib) and third-generation (ie, osimertinib) TKIs compared with the first-generation TKIs (eg, erlotinib, gefitinib), acquired resistance has been inevitable, regardless of which agent has been chosen as first-line therapy. Thus, the potential availability of subsequent treatment options is an important consideration. Recent data have demonstrated that osimertinib confers an overall survival benefit compared with first-generation EGFR TKIs, and dacomitinib has shown an overall survival benefit compared with gefitinib in an exploratory analysis. However, the relative benefits of different sequential EGFR-TKI regimens, especially those involving second- and third-generation agents, have remained uncertain and require prospective evaluation. Few such data currently exist to inform treatment choices. In the present review, we examined the pharmacologic characteristics and current clinical data for EGFR TKIs, including emerging information on the molecular mechanisms of resistance across the different generations of TKIs. Given the uncertainties regarding the optimal treatment choice, we have focused on the factors that might help determine the treatment decisions, such as efficacy and safety in patient subgroups. We also discussed the emerging real-world data, which have provided some insights into the benefits of sequential regimens in everyday clinical practice.

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Introduction

Non–small-cell lung cancer (NSCLC) is the leading cause of cancer mortality worldwide.[1] Because most patients will have a diagnosis of advanced disease, localized intervention will rarely be an option. Until recently, the mainstay of systemic treatment was platinum-based chemotherapy doublets, which have typically conferred modest survival benefits, with most patients developing disease progression after 3 to 5 months.[2] The development of newer treatment options for NSCLC has proved challenging, largely because of the remarkable heterogeneity of the disease in terms of its histologic features, genomics, and molecular biology. However, during the past decade, several oncogenic drivers have been identified that can be actively targeted, albeit in a few patients.

To date, the best characterized oncogenic driver in NSCLC is the mutated form of the epidermal growth factor receptor (EGFR). EGFR (also known as human epidermal growth factor receptor [HER1] or ErbB1), and its structurally related receptors, HER2 (Neu, ErbB2), HER3 (ErbB3), and HER4 (ErbB4), constitute the ErbB family of tyrosine kinases.[3,4] These receptors form an array of homodimers and heterodimers on the tumor cell surface that plays a critical role in the regulation of cellular proliferation. However, dysregulated signaling through these receptors, either through overexpression or the acquisition of activating somatic mutations, can lead to tumorigenesis in a range of human cancers.[3,4] In NSCLC, activating *EGFR* mutations have been reported in ~10% to 15% of cases of adenocarcinoma in white patients and 50% of cases in Asian patients.[5] Because *EGFR*-mutated tumors tend to be dependent on EGFR activity to stimulate downstream signaling

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pathways,[3,4] an opportunity exists to treat such tumors with oral tyrosine kinase inhibitors (TKIs) that block EGFR signaling.

A plethora of robust clinical evidence has provided the proof of concept for targeting *EGFR* mutation-positive NSCLC with TKIs, and data showing that EGFR TKIs are superior to chemotherapy in this setting have supported their use as first-line standard of care. The first EGFR TKIs developed for NSCLC were erlotinib and gefitinib. Since their approval, however, other agents have become available. The characteristics of the different EGFR TKIs and the order in which the agents were developed have led to their grouping into 3 "generations" as follows: the first-generation reversible EGFR inhibitors, erlotinib and gefitinib; the second-generation irreversible ErbB family blockers, afatinib and dacomitinib; and the third-generation irreversible, wild-type–sparing EGFR TKI, osimertinib.

The availability of several agents has added a level of complexity to the treatment decisions that oncologists face when considering the optimal therapy for their patients, and the question of which agent to use for which patient has arisen. Clearly, this is a complex question, the answer to which depends on a number of factors including (but not limited to) the efficacy and tolerability with respect to the individual patient characteristics, the effect of the different agents on health-related quality of life (QoL), the physician's experience with each drug and their personal preference, and considerations of treatment sequencing, cost, and reimbursement issues.

In the present review, we have examined the pharmacologic characteristics of available EGFR TKIs and highlighted the differences in the mechanisms of action among the different generations. We assessed the available data on mechanisms of acquired resistance to different TKIs and the implications for subsequent therapy. In addition, we have reviewed the available clinical data, including recent head-to-head trials and real-world studies that assessed TKIs for patients with *EGFR* mutation-positive NSCLC. Finally, we have shared our perspectives on the further developments required to achieve the goal of turning *EGFR* mutation-positive NSCLC into a chronic disease.

First-, Second- and Third-generation EGFR TKIs Have Different Pharmacologic Profiles, Modes of Action, and Mechanisms of Resistance

First-generation EGFR TKIs

Gefitinib and erlotinib are first-generation EGFR TKIs that reversibly bind to the kinase domain of EGFR and potently inhibit the receptor when it has been constitutively activated by common mutations (deletions in exon 19 [Del19] or the exon 21 substitution, L858R). They also inhibit, to a lesser extent, wild-type EGFR.[6] These agents interrupt EGFR signaling by competing with adenosine triphosphate (ATP) at the intracellular catalytic (kinase) domain of the receptor, inhibiting autophosphorylation of the domain and, thus, attenuating the activation of intracellular signaling cascades.[7,8]

Both gefitinib and erlotinib have been approved for the treatment of *EGFR* mutation-positive NSCLC tumors in the first-line setting. However, with time, most patients will develop resistance to these agents. There appears to be 3 main categories of acquired resistance: target alteration owing to the emergence of tertiary *EGFR* mutations, such as the so-called gatekeeper T790M mutation in exon 20; activation of other signaling pathways that circumvent EGFR inhibition; and histologic changes, including the epithelial-to-mesenchymal transition or a transition to small cell histologic features.[9] The most common resistance mechanism, identified in 50% to 70% of tumors, is T790M.[10-12] This mutation increases the affinity of EGFR for ATP, reducing the potency of ATP-competitive TKIs.[13] In terms of compensatory signaling pathways, other members of the ErbB family have also been implicated in the development of resistance to EGFR TKIs. For example, *HER2* amplification has been identified in 12% to 13% of tumors resistant to first-generation EGFR TKIs.[14] Furthermore, mutations in the kinase domain of HER2 have been identified that facilitate the activation and transphosphorylation of EGFR even in the presence of EGFR TKIs.[15] Continuous exposure to EGFR TKIs can also trigger overexpression of HER3.[16] Other alternative pathways that can continue to drive tumor development despite EGFR inhibition include compensatory signaling via the MET and insulin-like growth factor 1 receptors[17-19] and the PI3K/Akt/mTOR (phosphatidylinositol 3-kinase/protein kinase B/mammalian target of rapamycin) and JAK2/STAT3 (Janus kinase/signal transducers and activator of transcription) signaling pathways.[20] Recent data have indicated that approximately one third of *EGFR* mutation-positive tumors will carry genetic alterations involving EGFR downstream effectors or bypass pathways such as *PIK3CA*, *BRCA1*, and *NOTCH* that could lead to the development of TKI-resistant subclones.[21] Accordingly, a rationale exists for the development of treatment strategies that will target multiple intracellular signaling pathways in *EGFR* mutation-positive NSCLC.

Second-generation EGFR TKIs

Accumulated knowledge of the mechanisms of acquired resistance to first-generation EGFR TKIs led to the development of second-generation EGFR TKIs that overcome the resistance by simultaneously and irreversibly inhibiting multiple ErbB receptors. Several such agents have been developed, including afatinib[22] and dacomitinib.[23]

Afatinib irreversibly inhibits EGFR, HER2, and HER4 by blocking transphosphorylation of tyrosine residues in the C-terminus (the first step in the activation of ErbB receptors).[24,25] It also blocks the transphosphorylation of HER3 via its partner in HER3-containing heterodimers.[24] Consequently, afatinib has the capacity to block signaling via all HER homodimers and heterodimers at the cell surface.[25,26] In addition to a broader inhibitory profile, afatinib has demonstrated superior in vitro affinity and potency compared with first-generation EGFR TKIs against both wild-type EGFR and EGFR harboring L858R or Del19.[25,26] Afatinib has been approved for the treatment of *EGFR* mutation-positive NSCLC, including tumors harboring uncommon sensitizing *EGFR* mutations and is also indicated for the treatment of squamous cell carcinoma of the lung after failure of first-line chemotherapy. Recent data have demonstrated that, just as with first-generation EGFR TKIs, T790M is the most predominant mechanism of resistance to afatinib, detected in ~50% to 70% of cases.[27-30] Recent data have suggested that the allelic frequency of T790M (ie, the proportion of tumor cells that carry T790M) will be greater in afatinib-resistant

tumor cells than in erlotinib-resistant tumor cells, indicating a greater level of cellular homogeneity and, thus, potentially making them more susceptible to T790M-directed drugs such as osimertinib.[31] Preclinical data have indicated that other mechanisms of resistance to afatinib include MET amplification, FGFR (fibroblast growth factor receptor) overexpression, increased JAK/STAT signaling, and the emergence of other tertiary *EGFR* mutations, such as V843I.[32] Few clinical data are available regarding other mechanisms of resistance. However, patients with afatinib-resistant disease have been identified with the BRAF V600E mutation, MET amplification, epithelial-to-mesenchymal transition, and transition to small cell histologic features.[32-36]

Similar to afatinib, dacomitinib irreversibly inhibits EGFR, HER2, and ErbB4, although it is more potent in inhibiting EGFR than other members of the HER family.[23] It was recently approved for the first-line treatment of *EGFR* mutation-positive NSCLC (Del19 or L858R) based on the results from the phase III ARCHER 1050 trial (dacomitinib vs. gefitinib).[37] In vitro data have indicated that T790M confers resistance to dacomitinib[38]; however, few clinical data assessing resistance mechanisms are available at present.

Third-generation EGFR TKIs

The finding that, in many cases, T790M underlies the acquired resistance, prompted the quest for small molecules that potently inhibit T790M-positive tumors and spare the wild-type form of the receptor. The most clinically advanced third-generation EGFR TKI is osimertinib, an irreversible inhibitor of both EGFR-sensitizing and T790M-resistance mutations, with selectivity over the wild-type form of the receptor.[39] Because of the striking clinical activity in patients with T790M-positive tumors, osimertinib was originally indicated for patients with metastatic *EGFR* T790M mutation-positive NSCLC after failure of first-line TKIs. However, following the phase III FLAURA trial[40] (osimertinib vs. erlotinib or gefitinib), osimertinib has also been approved in the first-line setting for patients with *EGFR* mutation-positive NSCLC.

The mechanisms of resistance to osimertinib appear to be more heterogeneous than those with first- and second-generation EGFR TKIs. A recent analysis of plasma samples from 91 patients treated with first-line osimertinib in the FLAURA trial indicated that the most common resistance mechanism was MET amplification (15%). The tertiary *EGFR* mutation, C797S, was present in 7% of the patients.[41] Other aberrations that were identified included HER2 amplification and mutations in RAS or PIK3CA. No putative resistance mechanism was identified in ~60% of the tumors analyzed. An analysis of plasma samples from the AURA3 trial, which had assessed osimertinib after failure of first-line EGFR TKIs, showed that the most predominant mechanism of resistance in previously treated patients appears to be the emergence of *EGFR* mutations (21% of patients analyzed), predominantly C797S (14% of patients analyzed).[42] When C797S occurred with T790M, it appeared in cis (within the same allele) in all cases. Accordingly, in these cases, the receptor would carry both mutations and would unlikely be sensitive to first-generation TKIs. The next most common putative resistance mechanism was MET amplification (19%). Other more uncommon mechanisms of resistance in previously treated patients have included transformation to small cell histologic features, amplification of HER2 or FGFR, and mutations in *BRAF*.[43] A recent analysis of tissue biopsies (rather than liquid biopsies) of 71 patients with acquired resistance to osimertinib indicated that transformation to squamous or small cell histologic type was the predominant mechanism of resistance, especially for patients treated with first-line osimertinib (19%).[44] These changes would not have been detectable with liquid biopsies, highlighting the importance of tissue biopsy for patients with disease resistance to osimertinib. On-target mutations (C797S or other tertiary *EGFR* mutations) were more common in patients treated with later-line osimertinib (18%) than first-line osimertinib (6%). Regarding the histologic transformation, other recent data have indicated that concurrent *RB1*/*TP53* mutations, detectable in plasma ctDNA samples, might predict for transformation in patients with *EGFR* mutation-positive NSCLC, suggesting that the baseline screening for these mutations could be of value.[45]

Identifying the Most Effective EGFR TKI: Lessons From Randomized Controlled Trials

EGFR TKIs Versus Doublet Chemotherapy

The first-generation EGFR TKIs, gefitinib and erlotinib, and the second-generation TKI, afatinib, were originally assessed in phase III trials against various platinum-doublet chemotherapy regimens (Table 1). Although these trials had similar designs and undoubtedly supported the use of EGFR TKIs as the first-line treatment of choice for patients with *EGFR* mutation-positive NSCLC, cross-trial comparisons to determine which TKI was most suitable for which patient were not possible.

Multiple phase III trials have demonstrated the superiority of erlotinib, gefitinib, and afatinib compared with standard platinum-doublet chemotherapy with respect to progression-free survival (PFS) for treatment-naive patients with advanced *EGFR* mutation-positive NSCLC (Table 1). In the phase III EURTAC study, erlotinib conferred significant PFS benefit compared with platinum-based doublet chemotherapy (9.7 vs. 5.2 months; $P < .0001$) in European patients.[47] Significant PFS benefit with erlotinib versus gemcitabine/carboplatin was also reported for Chinese patients in the phase III OPTIMAL trial (13.1 vs. 4.6 months; $P < .0001$).[49] The results from a further phase III study, ENSURE, confirmed the PFS benefit with erlotinib versus gemcitabine/cisplatin in a broader Asian population from China, Malaysia, and the Philippines (11.0 vs. 5.5 months; $P < .0001$).[46] In the IPASS,[50,58] NEJ002,[52] and WJTOG3405[54] trials, gefitinib significantly improved PFS compared with paclitaxel/carboplatin (9.5 vs. 6.3 months; $P < .001$; *EGFR* mutation-positive subgroup), paclitaxel/carboplatin (10.8 vs. 5.4 months; $P < .001$), and cisplatin/docetaxel (9.2 vs. 6.3 months; $P < .0001$). Finally, in the LUX-Lung 3[55] and LUX-Lung 6[56] phase III trials, afatinib significantly prolonged PFS compared with cisplatin/pemetrexed (13.6 vs. 6.9 months; $P = .001$) and cisplatin/gemcitabine (11.0 vs. 5.6 months; $P < .0001$), respectively, in patients with common *EGFR* mutations.

Despite the difficulties in cross-trial comparisons, the absence of head-to-head data at the time necessitated a number of meta-analyses that aimed to compare the outcomes for available agents in the first-line setting.[59-63] Most of these studies did not identify significant differences in PFS between first- and second-generation

Table 1 PFS Achieved in Trials of Patients With *EGFR* Mutation-positive Non–Small-cell Lung Cancer Treated With EGFR TKIs in a First-line Setting[a]

EGFR TKI	Study	Comparator	Median PFS, mo (HR[b] [95% CI])					
			Common Mutations		Del19		L858R	
Erlotinib	ENSURE[46]	Gemcitabine + cisplatin	n = 110	11.0 (0.34 [0.22-0.51])[c]	n = 57	11.1 (0.20 [0.11-0.37])[c]	n = 52	8.3 (0.57 [0.31-1.05])[c]
	EURTAC[47,48]	Platinum doublet	n = 86	9.7 (0.37 [0.25-0.54])[c]	n = 57	11.0 (0.30 [0.18-0.50])[c]	n = 29	8.4 (0.55 [0.29-1.02])[c]
	OPTIMAL[49]	Platinum doublet	n = 82	13.1 (0.16 [0.10-0.26])[c]	n = 43	15.3 (0.13 [0.07-0.25])[c]	n = 39	12.5 (0.26 [0.14-0.49])[c]
Gefitinib	IPASS[50,51]	Carboplatin + paclitaxel	n = 132	NR	n = 66	11.0 (0.38 [0.26-0.56])[c]	n = 64	9.2 (0.55 [0.35-0.87])[c]
	NEJ002[51-53]	Carboplatin + paclitaxel	n = 114	10.8 (0.30 [0.22-0.41])[c]	n = 58	11.5[c]	n = 49	10.8[c]
	WJTOG3405[54]	Cisplatin + docetaxel	n = 86	9.2 (0.49 [0.34-0.71])[c]	n = 50	NR (0.45 [0.27-0.77])[c]	n = 36	NR (0.51 [0.29-0.90])[c]
Afatinib	LUX-Lung 3[55]	Pemetrexed + cisplatin	n = 204	13.6 (0.47 [0.34-0.65])	n = 113	13.7 (0.28 [0.18-0.44])	n = 91	10.8 (0.73 [0.46-1.17])
	LUX-Lung 6[56]	Gemcitabine + cisplatin	n = 216	11.0 (0.25 [0.18-0.35])	n = 124	13.7 (0.20 [0.13-0.33])	n = 92	9.6 (0.32 [0.19-0.52])
	LUX-Lung 7[57]	Gefitinib	n = 160	11.0 (0.73 [0.57-0.95])	n = 93	12.7 (0.76 [0.55-1.06])	n = 67	10.9 (0.71 [0.48-1.06])
Dacomitinib	ARCHER 1050[37]	Gefitinib	n = 227	14.7 (0.59 [0.47-0.74])	n = 134	16.5 (0.55 [0.41-0.75])	n = 93	12.3 (0.63 [0.44-0.88])[c]
Osimertinib	FLAURA[40]	Gefitinib or erlotinib	n = 279	17.7 (0.45 [0.36-0.57])	n = 175	21.4 (0.43 [0.32-0.56])[c]	n = 104	14.4 (0.51 [0.36-0.71])[c]

Abbreviations: CI = confidence interval; Del19 = exon 19 deletion; EGFR = epidermal growth factor receptor; HR = hazard ratio; NR = not reported; PFS = progression-free survival; TKI = tyrosine kinase inhibitor.
[a]Central independent review, unless stated otherwise.
[b]HR for PFS between the TKI and the chemotherapy comparator in each study.
[c]Investigator review.

EGFR TKIs. However, 1 network meta-analysis (a method designed to simultaneously compare multiple treatments using direct and indirect evidence)[64] showed a trend toward improved PFS with afatinib compared with erlotinib or gefitinib.[63] This signal of improved efficacy with second-generation versus first-generation TKIs was subsequently substantiated by head-to-head data (discussed in the next section, "Head-To-Head Trials Comparing EGFR TKIs").

The overall survival (OS) observed with first- and second-generation TKIs in randomized controlled trials is shown in Table 2. In most trials, treatment with EGFR TKIs did not confer a significant OS benefit versus the comparator. This could possibly be attributable to the high levels of crossover. In the LUX-Lung 3 (crossover rate of 74%) and LUX-Lung 6 (crossover rate of 54%) studies, analysis of OS according to specific *EGFR* mutations was prespecified on the basis that Del19 and L858R mutations would have differential effects on the structure of the receptor and should be regarded as different biologic entities.[71] OS was significantly improved with afatinib compared with chemotherapy in patients with Del19 mutations in both studies (LUX-Lung 3: median, 33.3 vs. 21.1 months; hazard ratio [HR], 0.54; 95% confidence interval [CI], 0.36-0.79; $P = .0015$; LUX-Lung 6: median, 31.4 vs. 18.4 months; HR, 0.64; 95% CI, 0.44-0.94; $P = .023$).[67] No significant differences were found in OS between the treatment groups for patients with L858R mutations (LUX-Lung 3: median, 27.6 vs. 40.3 months; HR, 1.30; 95% CI, 0.80-2.11; $P = .29$; LUX-Lung 6: median, 19.6 vs. 24.3 months; HR, 1.22; 95% CI, 0.81-1.83; $P = .34$).[67] The findings of an OS benefit with afatinib compared with first-generation TKIs in patients with Del19 mutations were corroborated in a meta-analysis.[72] These findings could reflect differences in the mechanisms of action between first- and second-generation TKIs.

An interesting observation from the afatinib, gefitinib, and erlotinib trials is that the results suggested that *EGFR* Del19 and L858R mutations should be regarded as distinct biologic entities. Patients with tumors harboring Del19 mutations have consistently shown improved outcomes compared with patients with L858R mutations when treated with EGFR TKIs.[73-75] Although TKIs have generally conferred a PFS benefit compared with chemotherapy for patients with a L858R mutation,[74] this has not translated into an OS benefit. One hypothesis proposed to explain why patients with the L858R mutation have NSCLC that is not as responsive to EGFR TKIs as the disease of patients with Del19 is that de novo T790M gatekeeper mutations occur more frequently within L858R tumors than within Del19 tumors.[76] Another hypothesis is that different *EGFR* mutations activate different intracellular signaling pathways. In in vitro experiments, the phosphorylation patterns of EGFR in response to epidermal growth factor were markedly different depending on which mutations were present. This could lead to differences in the activation of intracellular signaling cascades.[71,77] Del19 and L858R mutations cause different conformational changes to EGFR, which might underlie their different sensitivities to TKIs. Del19 mutations remove amino acid residues from the ATP binding cleft of the receptor (the target of EGFR TKIs), but L858R mutations are remote from the ATP binding cleft.[78]

Head-To-Head Trials Comparing EGFR TKIs

Three seminal prospective head-to-head trials have been undertaken: LUX-Lung 7 (afatinib vs. gefitinib), ARCHER 1050 (dacomitinib vs. gefitinib), and FLAURA (osimertinib vs. gefitinib or erlotinib). These trials have demonstrated that second- and third-generation EGFR TKIs are superior to first-generation TKIs as first-line treatment options for patients with *EGFR* mutation-positive NSCLC.[37,40,57]

LUX-Lung 7: Afatinib Versus Gefitinib. The global phase IIb LUX-Lung 7 study was the first randomized trial to directly compare a first- and second-generation EGFR TKI in patients with *EGFR* mutation-positive NSCLC.[57] Afatinib was compared with gefitinib in 319 treatment-naive patients (160 randomized to

Table 2 OS (Overall Data Set and Stratified by Mutation) Achieved in Trials of Patients With *EGFR* Mutation-Positive Non–Small-Cell Lung Cancer Treated With EGFR TKIs in a First-line Setting

EGFR TKI	Study	Median OS, mo (HR[a] [95% CI])		
		Common Mutations	Del19	L858R
Erlotinib	ENSURE[46]	26.3 (0.91 [0.63-1.31])	NR (0.79 [0.48-1.30])	NR (1.05 [0.60-1.84])
	EURTAC[48]	22.9 (0.92 [0.63-1.35])	NR (0.94 [0.57-1.54])	NR (0.99 [0.56-1.76])
	OPTIMAL[65]	22.8 (1.19 [0.83-1.71])	27.0 (1.52 [0.92-2.52])	21.5 (0.92 [0.55-1.54])
Gefitinib	IPASS[50,51]	NR (1.00 [0.76-1.33])	27.2 (0.79 [0.54-1.15])	18.7 (1.44 [0.90-2.30])
	NEJ002[51,53]	27.7 (0.89 [0.63-1.24])[b]	28.9 (0.83 [0.52-1.34])	28.0 (0.82 [0.49-1.38])
	WJTOG3405[66]	34.8 (1.25 [0.88-1.78])	35.2 (NR)	32.2 (NR)
Afatinib	LUX-Lung 3[67]	31.6 (0.78 [0.58-1.06])	33.3 (0.54 [0.36-0.79])	27.6 (1.30 [0.80-2.11])
	LUX-Lung 6[67]	23.6 (0.83 [0.62-1.09])	31.4 (0.64 [0.44-0.94])	19.6 (1.22 [0.81-1.83])
	LUX-Lung 7[68]	27.9 (0.86 [0.66-1.12])	30.7 (0.83 [0.58-1.17])	25.0 (0.91 [0.62-1.36])
Dacomitinib	ARCHER 1050[69]	34.1 (0.76 [0.58-0.99])	34.1 (0.88 [0.61-1.26])	32.5 (0.71 [0.48-1.05])
Osimertinib	FLAURA[70]	38.6 (0.80 [0.64-1.00])	NR (0.68 [0.51-0.90])	NR (1.00 [0.74-1.40])

Abbreviations: CI = confidence interval; Del19 = exon 19 deletion; EGFR = epidermal growth factor receptor; HR = hazard ratio; NR = not reported; OS = overall survival; TKI = tyrosine kinase inhibitor.
[a]HR for OS between the TKI and the comparator in each study.
[b]Included 7 patients with uncommon mutations.

afatinib and 159 to gefitinib) with NSCLC harboring common *EGFR* mutations (Del19 or L858R). Three co-primary endpoints were selected: PFS (independently assessed), OS, and time-to-treatment failure (TTF; defined as the time from randomization to treatment discontinuation for any reason, including disease progression, treatment toxicity, or death). TTF was chosen as an endpoint to reflect "real-world" clinical practice, because many patients will continue treatment with TKIs after radiologic progression, at the discretion of the treating physician.

PFS was significantly improved with afatinib versus gefitinib (median, 11.0 vs. 10.9 months; HR, 0.73; 95% CI, 0.57-0.95; $P = .017$; Figure 1A).[57] Although the median PFS was almost identical in the 2 treatment arms, the curves subsequently separated, such that the 2-year PFS rate was greater with afatinib than with gefitinib (17.6% vs. 7.6%, respectively). Given that bypass signaling via other ErbB members has been implicated in the acquired resistance to EGFR TKIs observed in some patients,[17,79,80] this divergence in the PFS curves over time could be attributable to the broader inhibitory profile of afatinib compared with gefitinib, thus delaying the clonal evolution of a resistant tumor.[31] A subgroup analysis demonstrated that PFS improvement with afatinib compared with gefitinib was consistent, regardless of age and Eastern Cooperative Oncology Group (ECOG) performance status. The HRs favoring afatinib were similar between patients with Del19 (HR, 0.76; 95% CI, 0.55-1.06) and L858R (HR, 0.71; 95% CI, 0.47-1.06) mutations. The PFS benefit with afatinib was also independent of ethnicity, with similar HRs for Asians (HR, 0.76; 95% CI, 0.54-1.06) and non-Asians (HR, 0.72; 95% CI, 0.49-1.06). In addition to the PFS, the TTF was significantly longer with afatinib than with gefitinib in LUX-Lung 7 (median TTF, 13.7 vs. 11.5 months; HR, 0.73; 95% CI, 0.58-0.92; $P = .0073$).[57]

No significant difference was found in OS between afatinib and gefitinib, although the median OS was numerically longer with afatinib (27.9 vs. 24.5 months; HR, 0.86; 95% CI, 0.66-1.12; $P = .2580$).[68] Similar OS outcomes were found for patients with Del19 (30.7 vs. 26.4 months; HR, 0.83; 95% CI, 0.58-1.17; $P = .2841$) and L858R (25.0 vs. 21.2 months; HR, 0.91; 95% CI, 0.62-1.36; $P = .6585$) mutations.[68] It is likely that the OS analysis was confounded by the high rates of therapy after progression. Three quarters of the patients had received subsequent systemic anticancer therapy, and an additional 10% of patients in the gefitinib arm had received a subsequent EGFR TKI compared with in the afatinib arm (55.6% vs. 45.9%).[68]

Although not a primary endpoint, the overall response rate (ORR) data also favored afatinib compared with gefitinib (70% vs. 56%; odds ratio, 1.87; 95% CI, 1.18-2.99; $P = .0083$). In patients with tumors harboring Del19 mutations in the LUX-Lung 7 study, the ORR was 73% with afatinib and 66% with gefitinib. In patients with tumors harboring L858R mutations, a 24% difference in the ORR was found in favor of afatinib (66% with afatinib vs. 42% with gefitinib).[57]

Although the LUX-Lung 7 trial provided head-to-head evidence that afatinib is superior to gefitinib, a number of caveats must be considered.[57,68] First, LUX-Lung 7 was an exploratory phase IIb trial with no formal predefined hypothesis. It was designed with the aim of comparing afatinib and gefitinib for a range of endpoints. Second, although the absence of an OS benefit was not altogether surprising, given the widespread use of postprogression treatment, the study was not powered to detect an OS difference. The sample size was estimated based on controlling the width of the 95% CI for the HR of PFS. Finally, the study had an open-label trial design, which could have introduced some bias to certain endpoints.

ARCHER 1050: Dacomitinib Versus Gefitinib. Additional head-to-head data for second- versus first-generation TKIs were provided by the phase III ARCHER 1050 trial, which compared first-line dacomitinib and gefitinib in Asian or European (eg, Spain, Italy, Poland) patients with *EGFR* mutation-positive (Del19 or L858R) NSCLC. Dacomitinib significantly improved PFS (independent review; median, 14.7 vs. 9.2 months; HR, 0.59; 95% CI, 0.47-0.74; $P < .0001$; Figure 1B) and the median duration of response (14.8 vs. 8.3 months; $P < .0001$) versus gefitinib.[37] The PFS benefit was consistent across patient subgroups, including patients with Del19 (HR, 0.55; 95% CI, 0.41-0.75) and L858R (HR, 0.63; 95% CI, 0.44-0.88) mutations. The ORR was comparable between treatment arms (75% vs. 72%).

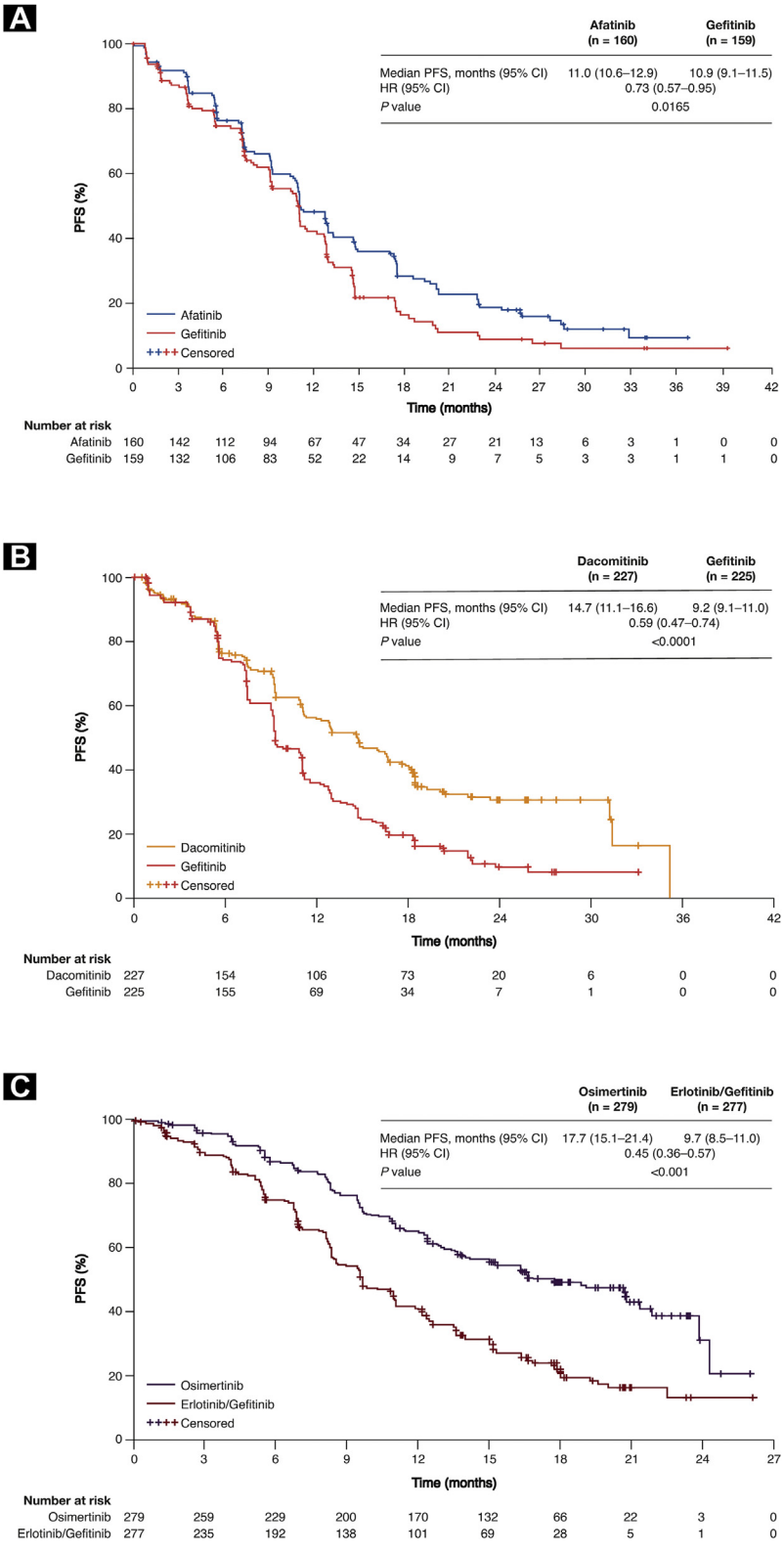
OS was prolonged with dacomitinib compared with gefitinib (median, 34.1 vs. 26.8 months; HR, 0.76; 95% CI, 0.58-0.99; $P = .044$). The OS data were similar across patient subgroups, including those with Del19 (HR, 0.88; 95% CI, 0.61-1.26) and L858R (HR, 0.71; 95% CI, 0.48-1.05) mutations.[69] The investigators of the study attributed these findings to the broader and irreversible inhibitory profile of dacomitinib compared with gefitinib. For example, dacomitinib appeared to provide a greater depth of response than did gefitinib, with 101 of 133 patients who responded having tumor shrinkage of > 50%. The uptake of subsequent therapy was similar across the treatment arms (50% after dacomitinib; 62% after gefitinib). The most common subsequent therapy was chemotherapy. Few patients had received third-generation EGFR TKIs, owing to their limited availability at the time of the study.

Although ARCHER 1050 had been prospectively powered on a single endpoint (PFS), a number of caveats must been considered when interpreting the data. The trial, similar to the LUX Lung 7 trial, was open label. Unlike LUX Lung 7, patients with brain metastases were excluded, enriching the study population with patients with a better overall prognosis. Moreover, some imbalances were present in the baseline characteristics across the treatment arms. For example, more patients with an ECOG performance status of 0 were in the dacomitinib arm. Finally, owing to a hierarchical statistical testing order of PFS, followed by ORR and then OS, the OS analysis was considered exploratory because no significant difference was found in the ORR.[81]

Taken together, the results from the LUX Lung 7 and ARCHER 1050 trails have indicated that irreversible ErbB inhibition is more effective than reversible EGFR inhibition as a first-line treatment strategy for patients with *EGFR* mutation-positive NSCLC. However, because of the differences in study design and the inherent difficulties in cross-trial comparisons, it was not possible to conclude any differences in the clinical activity of afatinib and dacomitinib.

FLAURA: Osimertinib Versus Erlotinib or Gefitinib. The double-blind phase III FLAURA trial was undertaken in patients with *EGFR* mutation-positive (Del19; L858R) NSCLC, including

Figure 1 Progression-free Survival Determined by Independent Assessment From Head-to-head Trials That Compared Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors. (A) LUX-Lung 7 Study (Reprinted From Park et al,[57] With Permission From Elsevier); (B) ARCHER 1050 Study (Reprinted From Wu et al,[37] With Permission From Elsevier); and (C) FLAURA Study. Reprinted From Soria et al,[40] With Permission From Massachusetts Medical Society



patients with stable brain metastases.[40] The primary endpoint was PFS. A striking improvement in PFS was found for the patients treated with osimertinib versus gefitinib or erlotinib (independent review; median, 17.7 vs. 9.7 months; HR, 0.45; 95% CI, 0.36-0.57; $P < .001$; Figure 1C). The PFS benefit was consistent across the patient subgroups, including patients with Del19 (HR, 0.43; 95% CI, 0.32-0.56) and L858R (HR, 0.51; 95% CI, 0.36-0.71) mutations. It is likely that the improvement in PFS with osimertinib was attributable to its activity against T790M. Recent studies have demonstrated that, in many cases, small numbers of cells within *EGFR* mutation-positive tumors will carry the T790M mutation concomitantly, and these cells will be selected for, and clonally expand, during treatment with first-generation TKIs.[31] In contrast, clonal expansion of pre-existing T790M cells, or the development of de novo T790M-positive clones, is likely to be prevented by osimertinib. No statistically significant difference was found in the response rate with osimertinib versus first-generation EGFR TKIs. However, the duration of response was prolonged with osimertinib (median, 17.2 vs. 8.5 months, respectively).[40]

Recently, an updated analysis of FLAURA demonstrated that osimertinib conferred significant OS benefit compared with gefitinib/erlotinib (median, 38.6 vs. 31.8 months; HR, 0.80; 95% CI, 0.64-1.00; $P = .046$).[70] The OS benefit was largely consistent across the patient subgroups, with the exception of Asian patients (HR, 1.00; 95% CI, 0.75-1.32) and patients with L858R-positive tumors (HR, 1.00; 95% CI, 0.75-1.32). The OS benefit with osimertinib was similar for patients with (HR, 0.83; 95% CI, 0.53-1.30) and without (HR, 0.79; 95% CI, 0.61-1.01) baseline brain metastases. In patients who had received subsequent therapy (48% and 65% in the osimertinib and gefitinib/erlotinib arms, respectively), the most common options were osimertinib (47%) for the gefitinib/erlotinib arm and chemotherapy (68%) for the osimertinib arm. The relatively low uptake of subsequent therapy in the osimertinib arm possibly reflected the present paucity of targeted therapy options after its failure, owing to the heterogeneity of the resistance mechanisms. Likewise, the uptake of subsequent therapies was likely to be influenced by the reimbursement policies in the individual countries participating in the FLAURA trial. Although the FLAURA data are very encouraging, afatinib and dacomitinib were not included in the comparator arm. Thus, it would not be appropriate to directly compare second-generation TKIs and osimertinib, because no head-to-head trials have been performed.

Clinical Trials That Assessed First-line TKIs Combined With Other Agents

Several randomized trials have assessed whether clinical benefit with first-line EGFR TKIs might be improved by combining them with other treatment modalities,[82] without negatively affecting tolerability too severely. The phase II JO25567 trial assessed the combination of erlotinib with the anti-VEGF monoclonal antibody, bevacizumab, compared with erlotinib alone in 154 Japanese patients with *EGFR* mutation-positive (Del19/L858R) NSCLC. Patients with brain metastases were excluded. The PFS was significantly longer in the erlotinib plus bevacizumab arm than in the erlotinib arm (median, 16.0 vs. 9.7 months; HR, 0.54; 95% CI, 0.36-0.79; $P = .0015$).[83] Because of these data, the combination of erlotinib plus bevacizumab has been approved by the European Medicines Agency for this setting. However, no significant differences were found in OS between the 2 arms (median, 48.4 vs. 48.5 months, respectively; HR, 0.91; 95% CI, 0.56-1.46; $P = .6838$).[84] Following on from the JO25567 trial, a phase III trial, NEJ026, was undertaken to compare erlotinib plus bevacizumab versus erlotinib in 224 Japanese patients.[85] Consistent with the previous study, significant improvement was found in the PFS (median, 16.9 vs. 13.3 months; HR, 0.61; 95% CI, 0.42-0.88; $P = .0157$), although the OS data are immature. Combinations with other anti-angiogenic agents are also being assessed. For example, an ongoing phase III study (ClinicalTrials.gov identifier, NCT02411448) is assessing the combination of erlotinib with the VEGFR2 antibody, ramucirumab, because of encouraging data from the phase Ib phase of the study.[86]

The results from a recent phase III NEJ009 study has prompted a debate on the potential benefits of combining first-line EGFR TKIs with chemotherapy.[87] In that study, 344 Japanese patients with *EGFR* mutation-positive (Del19/L858R) NSCLC were randomized to receive gefitinib plus carboplatin and pemetrexed versus gefitinib alone. Impressive OS was observed for the combination arm, which was significantly superior to that observed in the monotherapy arm (52.2 months vs. 38.8 months; $P = .013$). No data on the mechanisms of resistance or subsequent therapies are available for NEJ009; however, it is unlikely that many patients had received third-generation EGFR TKIs because they were not widely available at the time. It would be interesting to know the proportion of tumors that were T790M positive at the development of resistance. These data are of interest and suggest that the combination of EGFR TKIs plus chemotherapy could be a first-line treatment option for some patients, if tolerable.

Safety and Tolerability of First-, Second-, and Third-Generation EGFR TKIs

As described in the previous sections, second- and third-generation TKIs have been shown to be superior to first-generation TKIs in terms of clinical efficacy. An important question is whether this improved activity comes at a cost of reduced tolerability. Overall, certain class-based adverse events (AEs) have appeared to be more common with second-generation TKIs than with first- or third-generation TKIs and, presumably, are attributable to the broader and irreversible inhibition profile. However, the frequency of permanent treatment discontinuation because of AEs have been similar with afatinib, dacomitinib, and osimertinib. Thus, the AEs have generally been manageable, allowing patients to continue treatment for as long as they derive clinical benefit.

In the LUX-Lung 7 trial, the overall frequency and severity of AEs were similar between afatinib and gefitinib (all grades, 99% vs. 100%; grade $\geq$ 3, 57% vs. 52%).[57] Also, the AE profiles were consistent with previous experience, with no unexpected safety findings.[57] As expected, treatment-related diarrhea (all grades, 90% vs. 61%; grade $\geq$ 3, 13% vs. 1%) and rash/acne (all grades, 89% vs. 81%; grade $\geq$ 3, 9% vs. 3%) were more frequent with afatinib. In contrast, elevated treatment-related alanine transaminase/aspartate aminotransferase (all grades, 10% vs. 25%; grade $\geq$ 3, 0% vs. 9%) was more frequent with gefitinib.[57] More patients in the afatinib arm experienced a serious treatment-related AE than did those in

the gefitinib arm (11% vs. 4%, respectively). The most frequent serious treatment-related AEs were diarrhea (afatinib, 6%; gefitinib, 1%) and interstitial lung disease (afatinib, 0%; gefitinib, 3%). Dose reductions because of AEs were common for patients treated with afatinib (42%). However, only 6% of the patients had discontinued afatinib because of treatment-related toxicity, indicating that dose modification was effective in reducing the severity of the AEs.

Available data have demonstrated that the AEs with afatinib can be managed via tolerability-guided dose adjustment for individual patients. In most cases, dose reduction[88] and/or supportive care measures[89,90] will allow patients to continue treatment for as long as they experience clinical benefit with this agent. In the LUX-Lung 7 trial, no differences were found in the frequency of discontinuations because of treatment-related AEs (6% in each arm).[57] Post hoc analyses of the data from the LUX-Lung 3, LUX-Lung 6, and LUX-Lung 7 trials showed that dose reductions reduced the incidence of drug-related AEs but did not affect the efficacy.[88,91] In these studies, the median PFS was similar between those patients who had required a dose reduction during the first 6 months of treatment and those who had not.[88,91] The responses to the EuroQoL-5D health status self-assessment questionnaire and the EuroQoL visual analog scale did not show any differences in the QoL outcomes between afatinib and gefitinib. Furthermore, in a recent non-interventional study of 228 patients with *EGFR* mutation-positive NSCLC treated with afatinib, which included patients who would not normally be included in clinical trials (eg, those with an ECOG performance status of $\geq$ 2), 67% of the patients had required $\geq$ 1 dose reduction.[92] Neither the TTF nor the time to progression were negatively affected by dose modifications. In addition, 31% of the patients in this real-world setting had received a modified starting dose of $\leq$ 30 mg. Again, this had no effect on the TTF or time to progression.

Similar to the LUX-Lung 7 trial, some differences in the tolerability profile were observed in the ARCHER 1050 study. The most common AEs were diarrhea (all grades, 87% vs. 56%; grade $\geq$ 3, 9% vs. 1%), paronychia (all grades, 62% vs. 20%; grade $\geq$ 3, 7% vs. 1%), and dermatitis acneiform (all grades, 49% vs. 29%; grade $\geq$ 3, 14% vs. 1%).[37] Serious treatment-related AEs were more frequent with dacomitinib than with gefitinib (9% vs. 4%), as were dose reductions (66% vs. 38%). Improvements in the patient-reported measures of key disease-associated symptoms were similar between the treatment arms, with the exception of diarrhea and a sore mouth. For the latter, significant increases in patient-reported symptoms were identified with dacomitinib compared with gefitinib. Furthermore, a statistically significant difference was found in the global QoL score in favor of gefitinib.[37] Permanent discontinuation of the study drug because of treatment-related AEs was slightly greater with dacomitinib than with gefitinib (10% vs. 7%). The most frequent reasons for discontinuation of dacomitinib were skin and subcutaneous tissue disorders (3%), gastrointestinal disorders (2%), and interstitial lung disease or pneumonitis (1%). Just as with the LUX-Lung 7 study, the most common reason for discontinuation of gefitinib was elevated alanine transaminase/aspartate aminotransferase (3%) or interstitial lung disease/pneumonitis (1%). To date, few real-world data are available regarding the tolerability of dacomitinib in everyday clinical practice.

Because osimertinib is *EGFR* wild-type sparing, it appears to have a better tolerability profile than first-generation EGFR TKIs and might be expected to have a better tolerability profile than second-generation EGFR TKIs, although no head-to-head data exist.[40] In the FLAURA trial, the frequency of grade $\geq$ 3 AEs was lower with osimertinib than with gefitinib/erlotinib (34% vs. 45%). The common treatment-related AEs were rash/acne (all grades, 54% vs. 74%; grade $\geq$ 3, 1% vs. 7%), diarrhea (all grades, 49% vs. 51%; grade $\geq$ 3, 2% vs. 2%), and dry skin (all grades, 33% vs. 33%; grade $\geq$ 3, $<$ 1% vs. 1%). Cardiac effects (QT elongation) were more common with osimertinib (all grades, 10% vs. 5%; grade $\geq$ 3, 2% vs. $<$ 1%). The frequency of serious AEs (treatment-related or not) was 22% with osimertinib and 25% with gefitinib/erlotinib. Permanent discontinuation of the study drug because of treatment-related AEs was similar across the treatment arms (10% with osimertinib; 14% with gefitinib/erlotinib). No patient-reported outcome data were included in the primary analysis of FLAURA trial.

Finally, as expected, the combination of EGFR TKIs with other agents does appear to affect the tolerability. In the JO25567 trial, the overall incidence of grade $\geq$ 3 AEs (all cause) was 91% with erlotinib plus bevacizumab compared with 53% with erlotinib alone.[83] The incidence of some grade $\geq$ 3 AEs, including hypertension (60% vs. 10%), proteinuria (8% vs. 0%), and hemorrhagic events (3% vs. 0%) was notably greater in the combination arm. Similarly, elevated frequencies of hemorrhage, proteinuria, and hypertension were observed with erlotinib plus bevacizumab in the NEJ026 trial, although no other notable differences in toxicity versus erlotinib were observed.[85] In the NEJ009 trial, the incidence of grade $\geq$ 3 AEs was 65% in the combination arm and 31% in the gefitinib arm.[87] The most common AEs included anemia (all grades, 67% vs. 20%; grade $\geq$ 3, 21% vs. 2%), neutropenia (all grades, 60% vs. 4%; grade $\geq$ 3, 31% vs. $<$ 1%), and thrombocytopenia (all grades, 54% vs. 5%; grade $\geq$ 3, 17% vs. 0%).

Future Perspectives: Defining Optimal Treatment in Patients With *EGFR* Mutation-positive NSCLC

Head-to-head trials have shown that second- and third-generation EGFR TKIs are probably preferable to first-generation agents for first-line treatment of *EGFR* mutation-positive NSCLC. To date, the longest reported PFS benefit with a first-line EGFR TKI has been with osimertinib in the FLAURA trial.[40] This observation, in addition to its favorable tolerability profile, and recent demonstration of an OS benefit,[70] has positioned osimertinib as an attractive first-line treatment option, which has been reflected in the National Comprehensive Cancer Network guidelines. However, because second-generation TKIs were not included in the FLAURA trial, and other prospective data directly comparing dacomitinib, afatinib, and osimertinib are lacking, it remains unclear which TKI will provide the best OS benefit. Therefore, the selection of the most appropriate EGFR TKI for patients still requires some thought.

Important factors to consider in choosing the most appropriate EGFR TKI include the type of *EGFR* mutation (including uncommon mutations) and the presence of brain metastases or

leptomeningeal disease. The utility of different EGFR TKIs in these scenarios has recently been reviewed in detail.[93-95] In brief, osimertinib appears to be effective against existing central nervous system (CNS) lesions and in reducing the risk of CNS progression according to randomized trials[96,97] and real-world data.[98] For example, in the FLAURA trial, the CNS PFS (HR, 0.48; 95% CI, 0.26-0.86; $P = .014$) and CNS response rate (66% vs. 43%; $P = .01$) were significantly improved with osimertinib compared with erlotinib/gefitinib.[97] Also, the competing risk analysis showed that the probability of experiencing CNS progression (in the absence of non-CNS progression or death) after 12 months was 8% with osimertinib and 24% with erlotinib/gefitinib.[97] Although osimertinib has demonstrated greater penetration of the blood–brain barrier (BBB) than gefitinib and afatinib in preclinical studies, afatinib[99] also appears to permeate the BBB sufficiently to be pharmacologically active in patients with brain metastases and to reduce the risk of CNS progression.[100] For example, in a recent competing risk analysis of the LUX-Lung 3 and 6 trials, the risk of de novo CNS progression was only 5% after 24 months. In contrast, the risk of non-CNS progression was 71%.[93] CNS activity of afatinib has been demonstrated in real-world studies. In a case series of 5 patients with symptomatic brain metastases, afatinib conferred complete and durable CNS responses in all 5 patients.[101] Fewer data are available regarding dacomitinib; however, it also appears to delay CNS progression.[37] First-generation TKIs can cross the BBB, and intracranial activity has been demonstrated.[93] However, CNS penetration appears to be relatively inefficient. Therefore, several studies have assessed pulsed-dose regimens, which appear to delay CNS progression compared with standard dosing,[102,103] but do not improve PFS. Given that metastatic spread to the brain is especially prevalent in patients with *EGFR* mutation-positive NSCLC,[104] these observations have provided a further rationale for initiating treatment with osimertinib or second-generation TKIs.

Developments in *EGFR* mutation detection technologies, such as next-generation sequencing, have demonstrated that uncommon mutations are more prevalent than previously thought and can often exist subclonally within tumors carrying common *EGFR* mutations (so-called compound mutations).[105,106] Preclinical and clinical data have indicated that second-generation TKIs have a broader inhibitory profile against uncommon *EGFR* mutations, including compound mutations.[105-107] Afatinib has been approved for the treatment of tumors with G719X, S768I, and L861G mutations. The treatment options for some other uncommon mutations, notably exon 20 insertions, remain an unmet medical need. Therefore, the type of *EGFR* mutation is an important factor when assessing the treatment choice. Other potentially important factors, not discussed in the present report, are the relative efficacy of EGFR TKIs in patients with different ethnicities and the optimal treatment for elderly patients and/or patients with significant comorbidity burdens.

When considering how to maximize the OS for patients with *EGFR* mutation-positive NSCLC, it might be important to consider the likely availability of further treatment options after acquired resistance to first-line treatment. As discussed, third-generation EGFR TKIs were originally developed as a treatment option to target the T790M gatekeeper mutation and sparing the wild-type form of the receptor. Osimertinib confers a PFS benefit of ~10 months in this setting.[96,108] Although osimertinib has been established as a first-line treatment option, targeted treatments after failure of osimertinib have not yet been identified, reflecting the heterogeneous resistance mechanisms. However, some novel agents (eg, JNJ-372 [a bispecific EGFR/cMET antibody] and U3-1402 [a HER2 antibody–drug conjugate]) have shown early promise.[109,110] In contrast, because ~50% to 70% of patients treated with afatinib[27-30] and, presumably, a similar proportion of patients treated with dacomitinib, will exhibit T790M-positive–acquired resistance, sequential treatment with second- and third-generation TKIs might be a potential option for some patients and could prolong their net time with chemotherapy-free treatment compared with first-line osimertinib.

At present, clinical trial data that have compared sequential EGFR TKI regimens are limited. Further analysis of the final OS data from the FLAURA trial, especially for patients who have crossed over from erlotinib/gefitinib to osimertinib, and the OS analysis of the AURA3 trial will be informative. Moreover, a number of ongoing trials will be important, such as the phase II APPLE trial, which is comparing first- and second-line (after gefitinib) osimertinib with a primary endpoint of PFS at 18 months.[111] In the absence of prospective data, retrospective observations from the LUX-Lung 3, 6, and 7 trials have indicated that sequential afatinib and osimertinib might be an effective and viable option for some patients. For 37 patients who had received osimertinib after afatinib, the median OS was not reached, and the 3-year OS rate was > 90%.[112] Likewise, a post hoc analysis of the data from the ARCHER 1050 trial demonstrated promising OS for those patients who had received a third-generation EGFR TKI after dacomitinib (n = 22; median OS, 36.7 months).[69]

Although their findings cannot substitute for prospective data and are subject to selection bias, several real-world studies have demonstrated encouraging clinical outcomes for patients receiving sequential EGFR TKIs. For example, the recent observational, real-world, GioTag study assessed the outcomes of 204 patients who had received sequential first-line afatinib and second-line osimertinib.[113] The median TTF was 27.6 months overall and was 30.3 months for patients with Del19-positive tumors and 47.6 months for Asians. The median OS was 41.3 months (90% CI, 36.8-46.3) overall and 45.7 months (90% CI, 45.3-51.5) for patients with Del19-positive tumors (n = 149).[114] Notwithstanding its retrospective nature and potential for selection bias, the results from that study support further clinical investigation of sequential afatinib and osimertinib, especially for patients with Del19 tumors, because these patients have a greater likelihood of acquiring a T790M mutation (~75%) than do patients with L858R-positive tumors.[113] Another recent retrospective study compared the outcomes for 111 patients with *EGFR* mutation-positive NSCLC with T790M-positive acquired resistance who had received either sequential afatinib and osimertinib or sequential first-generation TKIs and osimertinib. Both the response rate (83% vs. 54%) and the PFS (median, 15.7 vs. 8.9 months) were greater in the former group,[115] which might be attributable to a greater allelic frequency of T790M after failure of afatinib compared with first-generation EGFR TKIs.[31] Finally, in a retrospective analysis of 1381 patients from 3 German lung centers, the median OS was 67 months for the patients who had received a third-generation TKI after a first- or second-generation TKI but was

only 23 months for the patients who had not.[116] Overall, these observations support further clinical evaluation of sequential second- and third-generation EGFR TKI regimens and their effect on OS compared with first-line osimertinib.

As discussed, major developments have occurred in the treatment of patients with T790M-positive tumors. However, the treatment options for patients with T790M-independent resistance mechanisms have remained limited. One option could be to combine EGFR TKIs with other treatment modalities such as chemotherapy or EGFR monoclonal antibodies. Observations from the phase II BELIEF trial have indicated that the combination of erlotinib and bevacizumab could have potential clinical applicability in the T790M-negative setting. In patients with *EGFR* mutation-positive metastatic or locally advanced NSCLC, the median PFS was 10.5 months for patients with T790M-negative tumors, and the ORR was 79.2% (complete response, 4.2%; partial response, 75.0%).[117] The combination of afatinib with bevacizumab has demonstrated promising activity in patients with T790M-negative tumors. In a phase II study of patients with *EGFR* mutation-positive NSCLC with acquired resistance (n = 32), the combination achieved an ORR of 22% and a median PFS of 7.1 months for patients with T790M-negative tumors.[118] Grade $\geq$ 3 AEs included hypertension (41%), paronychia (25%), and proteinuria (19%). No incidence of treatment-related interstitial lung disease or severe bleeding was reported.

Conclusions

During the past few years, huge strides have occurred in the effective treatment of patients with *EGFR* mutation-positive NSCLC. The seminal head-to-head trials, LUX-Lung 7, ARCHER 1050, and FLAURA, have demonstrated the benefits of second- and third-generation EGFR TKIs as first-line treatment compared with the first-generation EGFR TKIs. The results of the FLAURA trial, which demonstrated a PFS and an OS benefit with osimertinib compared with gefitinib/erlotinib, along with good tolerability and CNS activity, have positioned osimertinib as an attractive first-line treatment option. Nevertheless, given the absence of head-to-head data comparing second- and third-generation EGFR TKIs, the optimal sequence of TKIs remains a matter of debate. One could argue for withholding osimertinib from first-line use to allow its use as second-line therapy after second-generation TKIs, because it has demonstrated strong activity against T790M-positive tumors. This hypothesis requires prospective evaluation. Also, the optimal therapy remains uncertain for patients harboring tumors with uncommon *EGFR* activating mutations. In terms of the tolerability profile, second-generation EGFR TKIs are probably associated with a greater frequency of AEs than third-generation TKIs. However, the AEs appear to be generally manageable. In clinical trials, the discontinuation rate because of AEs was similar for afatinib, dacomitinib, and osimertinib, indicating that the AEs with each agent were similarly manageable, allowing patients to continue treatment for as long as they derive clinical benefit. Prospective trials are warranted to compare predefined sequential regimens or combination regimens given the recent promising data with the aim of maximizing OS and the duration of chemotherapy-free treatment and maintaining or improving patients' QoL and symptomatic burden. The definition of optimal therapy will require further improvements in the monitoring of the molecular evolution of tumors and the mechanisms of resistance during the course of several lines of therapy. Ultimately, further developments during the coming years will help to define the treatment regimens, tailored to individual patients according to their disease characteristics and the molecular features of their tumors to render *EGFR* mutation-positive NSCLC a chronic disease for most patients.

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