

# Second-generation EGFR and ErbB tyrosine kinase inhibitors as first-line treatments for non-small cell lung cancer

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**Abstract:** The discovery that mutations in the *EGFR* gene are present in up to 50% of patients with lung adenocarcinoma, and the development of highly efficacious EGFR tyrosine kinase inhibitors (TKIs), has revolutionized the way this common malignancy is treated. Three generations of EGFR TKIs are now approved for use in *EGFR* mutation-positive non-small cell lung cancer (NSCLC); the first-generation agents erlotinib, gefitinib, and icotinib; the second-generation ErbB family blockers afatinib and dacomitinib; and most recently, osimertinib, a third-generation EGFR TKI. The second-generation agents have demonstrated impressive efficacy relative to both standard platinum-based chemotherapy and first-generation EGFR TKIs, significantly improving response and progression-free and overall survival. Data from real-world studies suggest that afatinib is as effective and well tolerated in routine clinical practice as it is in clinical studies and is effective in patients with certain uncommon *EGFR* mutations, patients with brain metastases, and older patients. Few real-world data are available for dacomitinib in the first-line setting. Afatinib and dacomitinib have similar safety profiles, with acne/skin dryness, diarrhea, stomatitis, and paronychia the most common adverse events (AEs) reported in clinical and real-world studies. Numerous studies have shown that tolerability-guided dose reductions can help manage afatinib-related AEs without reducing efficacy. As the number of therapeutic options for advanced NSCLC increases, the optimal choice for first-line treatment will be determined by considering patient factors such as the presence of brain metastases, the type of *EGFR* mutation, tolerability, and subsequent therapy options for long-term treatment.

**Keywords:** afatinib, dacomitinib, epidermal growth factor receptor, non-small-cell lung cancer

## Plain language summary

The EGFR plays an important role in cell signaling, but when incorrectly formed, may stimulate the uncontrolled growth of normal cells. The discovery that mutations in the epidermal growth factor receptor (*EGFR*) gene are present in up to 50% of patients with lung adenocarcinoma, and the development of highly effective treatments targeting tumor cells with these mutations, has revolutionized the way non-small-cell lung cancer is treated. In this article, we describe the development and clinical use of the second-generation EGFR tyrosine kinase inhibitors (TKIs), afatinib and dacomitinib. Many patients do not respond to first-generation EGFR TKIs, or subsequently become resistant to the anti-cancer effects of EGFR TKIs. The second-generation EGFR TKIs were developed to try and address these problems. Results from clinical studies have shown that afatinib and dacomitinib improve response and survival compared with chemotherapy and first-generation EGFR TKIs. The drugs are generally well tolerated, but in patients experiencing unbearable side effects, the dose of afatinib can be reduced without reducing its effectiveness. Data from patients receiving afatinib in

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routine clinical practice have demonstrated that it is as effective and well tolerated in the real-world setting as it is in clinical studies. Further, it has demonstrated efficacy in patients with brain metastases, in older individuals, and in patients with certain uncommon *EGFR* mutations.

## Introduction

Despite advances in treatment, lung cancer continues to be the world's most lethal malignancy, taking the lives of an estimated 1.76 million individuals in 2018, more than double the amount claimed by the next biggest killer, colorectal cancer.<sup>1</sup> Around 85–90% of lung cancer is non-small-cell lung cancer (NSCLC) and within NSCLC, adenocarcinoma and squamous cell carcinoma are the most frequently encountered subtypes.<sup>2</sup> In recent years, a number of molecular alterations involved in the development of NSCLC have been identified, including rearrangements in the *ALK* gene<sup>3</sup> and mutations or deletions in the *EGFR* gene.<sup>4,5</sup> *EGFR* encodes the EGFR (also known as ErbB1), a member of the ErbB family of receptor tyrosine kinases (RTKs). Other family members include HER2 (neu, ErbB2), HER3 (ErbB3), and HER4 (ErbB4).<sup>6</sup> The ErbB RTKs are involved in intracellular signaling cascades that promote cell proliferation and survival, but can also drive malignant transformation.<sup>7,8</sup>

Mutations in the *EGFR* gene are observed frequently in patients with lung adenocarcinoma,<sup>9</sup> but are rare in squamous cell carcinoma.<sup>10</sup> Approximately 50% of Asian adenocarcinoma patients carry *EGFR* mutations,<sup>11,12</sup> including 49% of Chinese patients,<sup>13</sup> compared with 14–17% of Caucasian adenocarcinoma patients.<sup>5,9,14</sup> The most common *EGFR* mutations, also known as the classical mutations, are in-frame deletions in exon 19 (del19; 49–72% of *EGFR* mutations) and a nucleotide substitution within codon 858 of exon 21 (L858R; 28–43%).<sup>4,14–21</sup> Other *EGFR* mutations have been detected in 7–23% of patients and include the G719X (~30% of uncommon mutations), L861Q (13–35%), and S768I (~5%) mutations.<sup>11,14,17,18,22–25</sup>

In recent years, numerous therapies targeting the EGFR have been developed and subsequently integrated into routine clinical use. The EGFR tyrosine kinase inhibitors (TKIs) are small molecules that bind to, and interfere with, the catalytic activity of EGFR.<sup>26</sup> Three first-generation EGFR TKIs are currently in routine clinical use: erlotinib, gefitinib, and icotinib. In the United States, erlotinib is approved for the first or subsequent line treatment of *EGFR* mutation-positive (exon 19 deletions or L858R mutations) patients with metastatic NSCLC;<sup>27</sup> similar approvals are in place in Europe and elsewhere.<sup>28</sup> In

contrast, gefitinib is indicated in both the United States and Europe as first-line therapy only.<sup>29,30</sup> Icotinib is only available in China and is approved for the treatment of *EGFR* mutation-positive NSCLC patients in any treatment line.<sup>31</sup>

In the first-line setting, erlotinib, gefitinib, and icotinib are associated with median progression-free survival (PFS) of 5.7–13.1 months, compared with 4.6–7.9 months with platinum-based chemotherapy.<sup>16,32–37</sup> However, in the first-line setting, none of the first-generation EGFR TKIs has demonstrated an overall survival (OS) benefit vs chemotherapy, and almost all patients develop resistance to first-generation agents. Although numerous resistance mechanisms have been identified, the most common is an acquired missense mutation in exon 20 of *EGFR* (T790M), which has been detected in over half of patients with acquired resistance.<sup>38–40</sup> Other resistance mechanisms include amplification of the *MET* receptor tyrosine kinase, acquired *PIK3CA* mutations, or *EGFR* amplifications.<sup>40–42</sup> A number of *EGFR* mutation-positive patients are resistant to first-line EGFR TKI treatment; this may be due to additional mutations in *ErbB2* or mutations elsewhere in *EGFR*, such as exon 20.<sup>43,44</sup> Clearly, agents with inhibitory profiles extending beyond the common activating mutations were needed, and this provided the rationale for the development of the second-generation EGFR TKIs.

## Literature search strategy

We searched the published literature (English language only) for articles and presentations that reported clinical efficacy and safety of the second-generation EGFR TKIs afatinib and dacomitinib. Relevant publications were identified by means of searches of U.S. National Library of Medicine (NLM) PubMed, using the search terms [efficacy] OR [safety] AND [Drug name (for each EGFR TKI)]. Reports of clinical trials and real-world evidence were included. Other relevant publications were identified from citations in the key publications identified via NLM PubMed and searches of abstracts published at recent major oncology meetings over the past 3 years, including annual meetings of the American Society of Clinical Oncology, European Society of Medical Oncology, European Lung Cancer Congress, and the World Conference on Lung Cancer. Further information was obtained from the US and EU prescribing information for each agent.

## Clinical development of second-generation ErbB family TKIs

The second-generation ErbB family TKIs afatinib and dacomitinib were developed to address the issue of

acquired resistance in patients with *EGFR* mutation-positive NSCLC and extend the inhibitory profile to *EGFR* mutations that were resistant to the first-generation TKIs. Afatinib is an ATP-competitive anilinoquinazoline derivative (Figure 1A) that binds to its targets by forming a covalent adduct with the active site sulfhydryl group of a cysteine residue through Michael addition reaction, thereby irreversibly blocking the kinase activity of all ErbB family members.<sup>26</sup> Importantly, formation of this covalent adduct seems central to the activity of afatinib across all ErbB family members. Like afatinib, dacomitinib is an irreversible pan-ErbB inhibitor (Figure 1B), which also covalently binds to key residues within EGFR and inhibits kinase activity.<sup>45</sup> These agents have a broader inhibitory profile than the first-generation TKIs; this more complete blockade of the ErbB family was expected to enhance the effect on important signaling pathways. Initial *in vitro* studies demonstrated that afatinib potently suppressed the kinase activity of wild-type and activated EGFR and ErbB2 mutants, including erlotinib-resistant isoforms.<sup>46</sup> Further, afatinib inhibited the survival of lung cancer cell lines harboring wild-type or L858R/T790M-mutant *EGFR*, or mutated *ErbB2*, and induced tumor regression in xenograft models expressing the double mutation L858R/T790M or mutated *ErbB2*.<sup>46–48</sup> Similarly, dacomitinib was shown to be a potent inhibitor of cells harboring *EGFR*-activating mutations as well as T790M resistance mutations<sup>45</sup> and caused marked regressions in a variety of human tumor xenograft models that expressed and/or over-expressed ErbB family members or contained L858R/T790M-mutant *EGFR*.<sup>49</sup> Additionally, dacomitinib is a highly effective inhibitor of wild-type

ErbB2.<sup>45</sup> Notably, preclinical data showed afatinib and dacomitinib to be more potent than first-generation TKIs against wild-type cells, those harboring the common activating mutations, and those with less common mutations, including T790M.<sup>45–47,49</sup>

## Clinical efficacy in EGFR mutation-positive advanced NSCLC patients treated in the first-line setting

### Afatinib

The global, Phase III LUX-Lung 3 study randomized 345 patients with *EGFR* mutation-positive NSCLC (del19, L858R, or uncommon mutations) to first-line treatment with afatinib or cisplatin and pemetrexed.<sup>20</sup> Patients receiving afatinib had significantly longer PFS (HR=0.58,  $p=0.001$ ) and significantly higher objective response rates (ORR) than those receiving cisplatin-pemetrexed (Table 1), although median OS was similar between the two arms (31.6 vs 28.2 months,  $P=0.11$ ) (Figure 2A).<sup>50</sup> Similarly, the Phase III LUX-Lung 6 study randomized 364 Asian patients with *EGFR* mutation-positive NSCLC (del19, L858R, or uncommon mutations) to afatinib or cisplatin and gemcitabine.<sup>21</sup> Like LUX-Lung 3, ORR and PFS were both significantly improved with afatinib vs cisplatin-gemcitabine.<sup>21</sup> However, despite the observed PFS and ORR benefits, no differences in OS were seen (Figure 2B).<sup>50</sup> In the Phase IIb LUX-Lung 7 study (n=319), PFS was significantly prolonged with afatinib compared with gefitinib, although the difference in median PFS was only small.<sup>51</sup> ORR was also significantly higher with afatinib (Table 1),

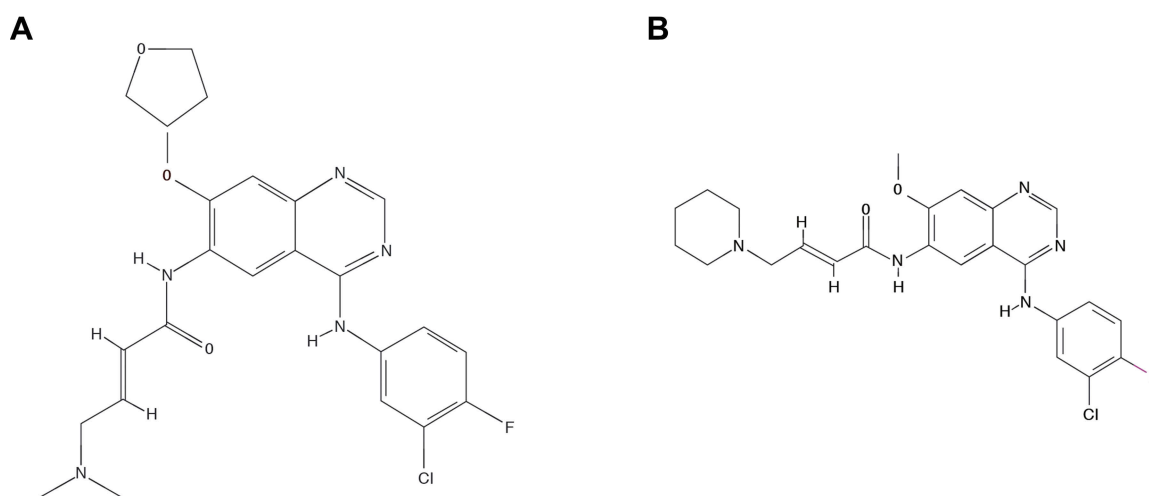
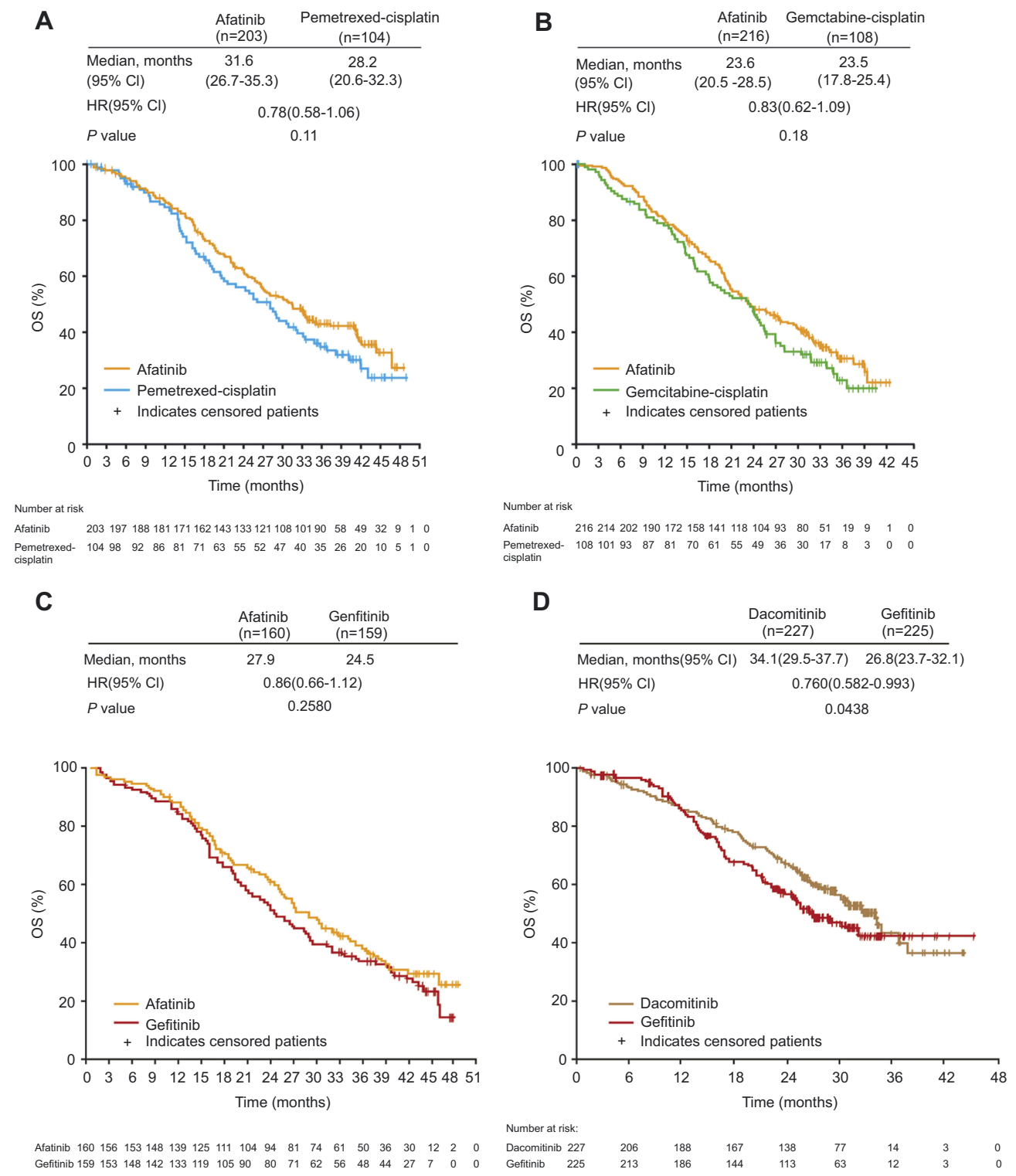


Figure 1 Chemical structures of (A) afatinib and (B) dacomitinib.

Table 1 Summary of pivotal studies of first-line afatinib and dacomitinib

Second-generation EGFR TKI	Afatinib			LUX-Lung 6			LUX-Lung 7			Dacomitinib
Study name	LUX-Lung 3			LUX-Lung 6			LUX-Lung 7			ARCHER 1050
Study phase	3			3			2b			3
Comparator	Cisplatin-pemetrexed			Cisplatin-gemcitabine			Gefitinib			Gefitinib
Disease and stage	Stage IIIB/IV lung ADC			Stage IIIB/IV ADC			Stage IIIB/IV ADC			Stage IIIB/IV NSCLC
Reference	Sequist et al 2013 <sup>20</sup> Yang et al 2015 <sup>50</sup>	Kato et al 2015 <sup>53</sup>	Wu et al 2014 <sup>21</sup> Yang et al 2015 <sup>50</sup>	Wu et al 2018 <sup>54</sup>	Wu et al 2016 <sup>51</sup> Paz-Ares et al 2017 <sup>52</sup>	Wu et al 2017 <sup>58</sup> Mok et al 2018 <sup>59</sup>				
Analysis	ITT	Japanese patients	ITT	Mainland Chinese patients	ITT	ITT				ITT
Patients, N	345	83	364	327	319	452				452
Predominant ethnicity	72% East Asian	100% Japanese	100% Asian (~90% Chinese)	100% Chinese	~57% Asian	~77% Asian (~51% Chinese)				
EGFR mutations	del19, L858R, other (~11%)	Del19, L858R, other (~7%)	del19, L858R, other (~11%)	del19, L858R, other (~11%)	del19 or L858R	del19 or L858R				
ORR, %	56 vs 23 P=0.001	61 vs 21 P=0.0007	67 vs 23 P<0.0001	67 vs 24 P<0.0001	70 vs 56 P=0.0083	75 vs 72 P=0.42				
Median PFS, months	11.1 vs 6.9 HR=0.58; P=0.001	13.8 vs 6.9 HR=0.38; P=0.0014	11.0 vs 5.6 HR=0.28; P<0.0001	11.0 vs 5.6 HR=0.30; P<0.0001	11.0 vs 10.9 HR=0.73; P=0.017	14.7 vs 9.2 HR=0.59; P<0.0001				
Median OS in ITT population, months	28.2 vs 28.2 HR=0.88; P=0.39	46.9 vs 35.8 HR=0.75; P=0.38	23.1 vs 23.5 HR=0.93; P=0.61	23.1 vs 23.2 HR=0.96; P=0.78	27.9 vs 24.5 HR=0.86; P=0.26	34.1 vs 26.8 HR=0.76; P=0.044				
Median OS in del19-positive patients, months	33.3 vs 21.1 HR=0.54; P=0.0015	46.9 vs 31.5 HR=0.34; P=0.018	31.4 vs 18.4 HR=0.64; P=0.023	31.6 vs 16.3 HR=0.61; P=0.015	30.7 vs 26.4 HR=0.83; P=0.28	34.1 vs NR HR=0.88; P=0.49				
Median OS in L858R-positive patients, months	27.6 vs 40.3 HR=1.30; P=0.29	41.7 vs 40.3 HR=1.13; P=0.82	19.6 vs 24.3 HR=1.22; P=0.34	18.7 vs 24.5 HR=1.31; P=0.22	25.0 vs 21.2 HR=0.91; P=0.66	32.5 vs 23.2 HR=0.71; P=0.081				

**Abbreviations:** ADC, adenocarcinoma; del19, exon 19 deletion of EGFR; ITT, intent-to-treat population; L858R, leucine to arginine substitution in codon 858 of EGFR; NR, not reached; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.



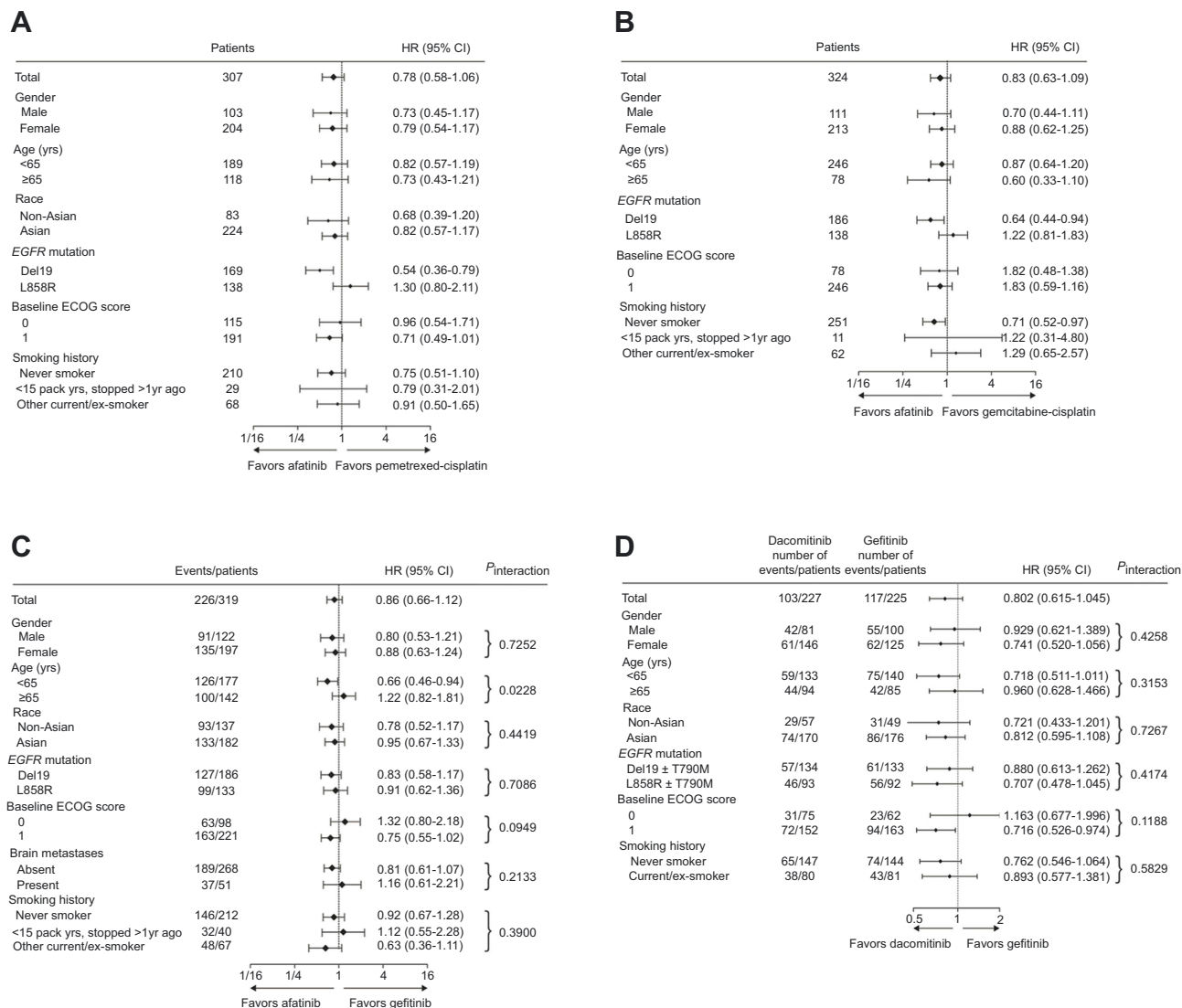
**Figure 2** Overall survival LUX-Lung 3 and LUX-Lung 6 (patients with Del19 and L858R mutations) and LUX-Lung 7 and ARCHER 1050. **(A)** LUX-Lung 3; **(B)** LUX-Lung 6. Reprinted from *The Lancet Oncology*, 16(2), Yang JC, Wu YL, Schuler M, et al, Afatinib versus cisplatin-based chemotherapy for EGFR mutation-positive lung adenocarcinoma (LUX-Lung 3 and LUX-Lung 6): analysis of overall survival data from two randomised, phase 3 trials, 141–151, Copyright © 2015, with permission from Elsevier.<sup>50</sup> **(C)** LUX-Lung 7. Reproduced from Paz-Ares L, Tan EH, O’Byrne K, et al, Afatinib versus gefitinib in patients with EGFR mutation-positive advanced non-small-cell lung cancer: overall survival data from the phase IIb LUX-Lung 7 trial, *Ann Oncol*, 2017, 28(2), 270–277, by permission of Oxford University Press.<sup>52</sup> **(D)** ARCHER 1050. Reprinted with permission. © 2018 American Society of Clinical Oncology. All rights reserved. Mok TS, Cheng Y, Zhou X, et al, Improvement in overall survival in a randomized study that compared dacomitinib with gefitinib in patients with advanced non-small-cell lung cancer and EGFR-activating mutations, *J Clin Oncol*, 36(22), 2244–2250.<sup>59</sup>

with a longer median duration of response for patients treated with afatinib than gefitinib (10.1 vs 8.4 months; *P* not reported). In a subsequent survival analysis, there was no significant difference in OS, although median OS was numerically higher with afatinib vs gefitinib (Table 1; Figure 2C).<sup>52</sup>

In a pre-specified subgroup analysis, OS in both LUX-Lung 3 and LUX-Lung 6 was significantly longer with afatinib than chemotherapy in patients harboring the del19 *EGFR* mutation (*P*<0.05), but not in those

with the L858R mutation (Figure 3A and B).<sup>50</sup> Similar findings were reported in a sub-analysis of 83 Japanese patients from LUX-Lung 3<sup>53</sup> and in a sub-analysis of 327 patients from mainland China enrolled in the LUX-Lung 6 study (Table 1).<sup>54</sup> In LUX-Lung 7, there was no significant difference in OS between afatinib and gefitinib in patients with del19 mutations (Table 1; Figure 3C).

As a result of the above studies, afatinib is approved as first-line treatment of patients with advanced/metastatic



**Figure 3** Subgroup analyses of overall survival in (A) in LUX-Lung 3 (del19 and L858R mutations only). (B) LUX-Lung 6 (del19 and L858R mutations only). Reprinted from *The Lancet Oncology*, 16(2), Yang JC, Wu YL, Schuler M, et al, Afatinib versus cisplatin-based chemotherapy for EGFR mutation-positive lung adenocarcinoma (LUX-Lung 3 and LUX-Lung 6): analysis of overall survival data from two randomised, phase 3 trials, 141–151, Copyright © 2015, with permission from Elsevier.<sup>50</sup> (C) LUX-Lung 7. Reproduced from Paz-Ares L, Tan EH, O’Byrne K, et al, Afatinib versus gefitinib in patients with EGFR mutation-positive advanced non-small-cell lung cancer: overall survival data from the phase IIb LUX-Lung 7 trial, *Ann Oncol*, 2017, 28(2), 270–277, by permission of Oxford University Press.<sup>52</sup> (D) ARCHER 1050. Reprinted with permission. © 2018 American Society of Clinical Oncology. All rights reserved. Mok TS, Cheng Y, Zhou X, et al, Improvement in overall survival in a randomized study that compared dacomitinib with gefitinib in patients with advanced non-small-cell lung cancer and EGFR-activating mutations, *J Clin Oncol*, 36(22), 2244–2250.<sup>59</sup> **Abbreviations:** ECOG, Eastern Cooperative Oncology Group; PS performance status.

NSCLC whose tumors have nonresistant *EGFR* mutations.<sup>55,56</sup>

## Dacomitinib

The first clinical study of dacomitinib in a first-line setting was a Phase II, single-arm study that recruited patients with advanced NSCLC who were never- or former light smokers, and/or who were *EGFR* mutation-positive. The 4-month PFS rate was 77% in all 89 dacomitinib-treated patients and 96% in the 45 patients with *EGFR* mutations.<sup>57</sup> This study paved the way for the Phase III ARCHER 1050 study, in which 452 *EGFR* TKI-naïve patients with newly diagnosed or recurrent ( $\geq 12$  months since prior treatment) NSCLC received either dacomitinib or gefitinib (Table 1).<sup>58</sup> Median PFS was significantly longer with dacomitinib than gefitinib, although ORR was similar (Table 1). In patients who responded to treatment, however, duration of response was longer in the dacomitinib group (14.8 vs 8.3 months;  $P < 0.0001$ ). Further, although not a formal analysis due to hierarchical testing, an OS benefit was observed with dacomitinib (Table 1; Figure 2D).<sup>59</sup> Interestingly, OS in the subgroup of patients with exon 19 deletions was similar in both treatment arms (Table 1; Figure 3D), whereas median OS was longer with dacomitinib in patients with L858R mutations, although the difference was not significant (Table 1). Pre-specified subgroup analyses of PFS suggest that dacomitinib may be more beneficial in Asian patients (HR=0.51) than in non-Asian patients (HR=0.89). On the basis of the ARCHER 1050 results, dacomitinib has been approved by both the US FDA and the European Medicines Agency for the first-line treatment of *EGFR*-mutated metastatic NSCLC.

While cross-trial comparisons should be avoided, it should be noted that both the study populations and the study designs of LUX-Lung 7 and ARCHER 1050 differed. In LUX-Lung 7, approximately 16% of patients had baseline central nervous system (CNS) metastases, whereas such patients were excluded from ARCHER 1050.<sup>51,58</sup> In addition, LUX-Lung 7 was a smaller, Phase IIb study and was underpowered to detect an OS difference.

## Meta-analysis

A network meta-analysis compared erlotinib, gefitinib, icotinib, afatinib, and dacomitinib using data from six head-to-head Phase III studies in patients with advanced *EGFR* mutation-positive NSCLC.<sup>60</sup> While the five TKIs were found to have similar therapeutic efficacy in terms of all

outcome measures (ORR, disease control rate, 1-year PFS, 1-year OS, and 2-year OS), rank probabilities indicated a preferable therapeutic efficacy for the second-generation TKIs relative to the first-generation TKIs. When compared with other agents, potential survival benefits (PFS and OS) were observed with dacomitinib, while afatinib had a higher rank probability in terms of ORR and disease control. The superiority of second-generation versus first-generation TKIs was also demonstrated in a recent meta-analysis including data from 18 randomized controlled trials and 20 retrospective cohort studies, with prolonged pooled PFS and OS reported with second-generation TKIs in the pooled dataset.<sup>61</sup> This superiority was demonstrated for patients with del19 and those with L858R mutations.

## Clinical efficacy in the real-world setting

Importantly, real-world studies support the findings from the pivotal Phase III studies and demonstrated the efficacy of afatinib in routine clinical practice. Several retrospective analyses have compared afatinib with first-generation TKIs in Asian populations,<sup>62–65</sup> while others report the use of afatinib only.<sup>11,66–69</sup> Median PFS ranged from around 12 months up to 19 months; in some comparative studies, afatinib was associated with significantly prolonged PFS vs both gefitinib and erlotinib,<sup>63,65</sup> but only gefitinib in others.<sup>64</sup> In a retrospective, population-based study of 467 patients with advanced NSCLC in South Korea, median PFS was 19.1 months with afatinib, compared with 13.7 and 14.0 months with gefitinib and erlotinib, respectively ( $P = 0.001$ ).<sup>63</sup> In this study, the benefit of afatinib was more pronounced in patients with del19 or uncommon *EGFR* mutations. A Canadian retrospective analysis also reported a survival benefit with second-generation compared with first-generation TKIs in patients with del19 mutations.<sup>70</sup> Data from a broad Asian population ( $n = 479$ ) in a large, Phase IIIb expanded access study, conducted in a setting similar to real-world practice, have further demonstrated the efficacy of afatinib in patients with common or uncommon *EGFR* mutations, with a median PFS of 12.1 months and time to symptomatic progression of 15.3 months.<sup>69</sup>

## First-line clinical efficacy in patient subgroups

While the pivotal clinical studies provide invaluable information on the use of afatinib and dacomitinib in broad clinical trial populations, certain patient subgroups that are frequently encountered in routine clinical practice may be excluded

from these trials due to strict inclusion or exclusion criteria. This includes patients whose tumors harbor uncommon mutations, those with brain metastases, and patients of advanced age. Fortunately, an increasing number of real-world studies are being reported, particularly on the real-world use of afatinib, providing a more detailed picture in these patient populations.

## Patients with uncommon mutations

While common *EGFR* mutations (del19 and L858R) are highly sensitive to EGFR TKIs, certain uncommon mutations may be less sensitive, with lower response rates and/or shorter survival reported in many studies.<sup>17,18,71–75</sup> However, studies suggest that some uncommon *EGFR* mutations, such as exon 19 insertions, L861Q, G719X, and S768I, are sensitive to certain TKIs, with response rates varying from 42% to 57% depending on the mutation and the TKI.<sup>18,71,72,76,77</sup>

In preclinical studies, cells harboring certain non-classical *EGFR* mutations, including L861Q, S768I, and G719A, were sensitive to treatment with afatinib; in contrast, sensitivity was markedly lower with erlotinib and gefitinib.<sup>78–80</sup> The clinical efficacy of afatinib in patients with uncommon mutations was assessed in a pooled post-hoc analysis of the LUX-Lung 2 (single arm, Phase II trial in *EGFR* mutation-positive patients with  $\leq 1$  prior treatment),<sup>81</sup> LUX-Lung 3, and LUX-Lung 6 studies and demonstrated that response and survival following afatinib treatment were highest in patients with point mutations or duplications in exons 18–21 and lowest in patients with exon 20 insertions.<sup>25</sup> In patients with the most frequent uncommon mutations, the ORR varied according to the mutation (78% G719X; 56% L861Q; 100% S768I) but was generally comparable to, or higher than, that seen in the overall study populations.

Findings from a retrospective, population-based study of patients with advanced NSCLC receiving first-line TKI therapy suggested that overall response may be higher with afatinib than with gefitinib or erlotinib in patients with uncommon mutations,<sup>63</sup> while in another retrospective analysis, PFS was numerically longer with afatinib than gefitinib or erlotinib in patients with uncommon *EGFR* mutations (median 19.7 vs 7.0 vs 7.0 months, respectively;  $P=0.506$ ).<sup>65</sup> A small retrospective study involving patients with advanced NSCLC and uncommon *EGFR* mutations, 89% of whom were receiving first-line treatment, reported significantly longer PFS in patients treated with afatinib compared with erlotinib/ gefitinib (median: 11.0 vs 3.6

months;  $P=0.03$ ).<sup>11</sup> In 24 patients with G719X, S768I, or L861Q mutations, median PFS was 18.3 months with afatinib and 2.6 months for both erlotinib and gefitinib. Subsequent to these reports, and on the basis of the results from the LUX-Lung 2, 3, and 6 trials, the United States FDA approval for afatinib was extended to include patients with these mutations.<sup>54</sup>

As the ARCHER 1050 study only included patients with common mutations (del19 or L858R), and no real-world data are available as yet, the efficacy of dacomitinib in patients with uncommon mutations is currently uncertain.

## Older patients

The LUX-Lung 3, LUX-Lung 6, and LUX-Lung 7 studies all permitted the enrolment of patients aged  $>65$  years and thus provide valuable data on the agent's efficacy and safety in older individuals. In prespecified analyses in LUX-Lung 3 and LUX-Lung 6, median PFS was prolonged with afatinib compared with chemotherapy in the subgroup of patients aged  $\geq 65$  years (LUX-Lung 3:  $n=134$ , median 11.3 vs 8.2 months, HR=0.64; 95% CI=0.39–1.03; LUX-Lung 6:  $n=86$ , median 13.7 vs 4.1 months, HR=0.16; 95% CI=0.07–0.39) as well as in younger patients (LUX-Lung 3: 11.0 vs 5.8 months, HR=0.53; 95% CI=0.36–0.76; LUX-Lung 6: 11.0 vs 5.6 months, HR=0.30; 95% CI=0.21–0.43).<sup>82</sup> In LUX-Lung 7, median PFS with afatinib was the same (11.0 months) in patients aged  $<65$  years and those aged  $\geq 65$  years.<sup>51</sup> In patients aged  $\geq 65$  years in LUX-Lung 3 and LUX-Lung 6, there was a trend toward improved OS with afatinib vs chemotherapy in the overall study populations, and in those with common *EGFR* mutations (del19/L858R); of note, in LUX-Lung 3, the OS difference was significant for elderly patients with del19 mutations (41.5 vs 14.3 months; HR=0.39; 95% CI=0.19–0.80).<sup>82</sup> Exploratory analyses of patients aged  $\geq 75$  years in LUX-Lung 7 demonstrated a trend toward improved PFS with afatinib vs gefitinib (median 14.7 vs 10.8 months; HR=0.69; 95% CI=0.33–1.44), consistent with the overall population and the younger subgroup. Median OS with afatinib or gefitinib was 27.9 vs 19.7 months (HR=1.05; 95% CI=0.50–2.21) in patients aged  $\geq 75$  years and 28.9 vs 25.2 months (HR=0.85; 95% CI=0.64–1.12) in patients aged  $<75$  years. In a single-arm, open-label, Phase IIIb study of Asian patients with *EGFR* mutation-positive NSCLC treated with first-line afatinib, median PFS was longer in patients aged  $\geq 65$  years compared with those aged  $<65$  years.<sup>69</sup> Similarly,



real-world data from the observational GioTag study demonstrated no difference in time on afatinib treatment in patients aged <65 years vs those aged ≥65 years (11.8 vs 12.2 months,  $P=0.241$ ).<sup>83</sup>

In the ARCHER 1050 study, subgroup analyses of PFS suggest that dacomitinib may be more effective in patients aged <65 years (HR=0.51; 95% CI=0.39–0.69) than in patients aged ≥65 years (HR=0.69; 95% CI=0.48–0.99).<sup>58</sup>

## Patients with brain metastases

Brain metastases are common in NSCLC, being identified at diagnosis in at least 10% of all patients and around one-quarter of patients with *EGFR* mutation-positive NSCLC.<sup>84,85</sup> Cumulative incidence rises over time, increasing to almost 50% in *EGFR* mutation-positive patients 3 years post-diagnosis.<sup>84</sup> Afatinib has been shown to penetrate the blood-brain barrier in mice<sup>86</sup> and in human subjects, with the concentration seen in the cerebrospinal fluid being well above the  $IC_{50}$  of afatinib against *EGFR* in *in vitro* studies.<sup>87–89</sup> A combined subgroup analysis of LUX-Lung 3 and LUX-Lung 6 demonstrated that among 81 patients with asymptomatic brain metastases at baseline, PFS was significantly improved with afatinib vs chemotherapy (8.2 vs 5.4 months; HR=0.50 [95% CI=0.52–0.95];  $P=0.0297$ ).<sup>90</sup> Further, the magnitude of PFS improvement with afatinib was similar to that observed in patients without brain metastases (LUX-Lung 3: HR=0.54 vs 0.48; LUX-Lung 6: HR=0.47 vs 0.22). Also, in both studies, ORR was significantly higher with afatinib than chemotherapy in patients with brain metastases. There were, however, no significant differences in OS between the afatinib and chemotherapy groups. A competing risk analysis using data from afatinib-treated patients with baseline brain metastases in LUX-Lung 3, LUX-Lung 6, and LUX-Lung 7 showed that the cumulative incidence of CNS progression (31%) was lower than that of non-CNS progression (52%).<sup>91</sup> Furthermore, the risk of *de novo* CNS progression with afatinib was very low, being observed in only 6% of patients who received afatinib in LUX-Lung 3 and LUX-Lung 6. Non-CNS progression for patients without baseline brain metastases was 78%.

Observations of CNS activity with afatinib in clinical trials are supported by a number of real-world studies. For example, data from a small retrospective review of 28 treatment-naïve patients with *EGFR* mutation-positive lung adenocarcinoma and brain metastases suggests that afatinib leads to comparable OS and time to treatment failure when given alone or in combination with whole-brain radiotherapy.<sup>92</sup>

ORR was over 80% for both treatment groups. Another analysis of data from 29 Korean patients with recurrent or metastatic NSCLC and brain metastases who received the first-line afatinib reported a 76% response rate to afatinib monotherapy and a median PFS of 15.7 months.<sup>93</sup> In a real-world study conducted in Singapore in patients with brain metastases prior to starting therapy, a lower afatinib starting dose (30 mg) was associated with significantly shorter PFS than a 40 mg starting dose (median: 5.3 vs 13.3 months;  $P=0.04$ ).<sup>67</sup> This may suggest that higher doses are required to achieve therapeutic levels within the CNS but may also simply be reflective of the subgroup of patients selected to receive a lower starting dose in this real-world study.

As patients with brain metastases were excluded from the ARCHER 1050 trial, no data on the CNS efficacy of dacomitinib are currently available.

## Resistance mechanisms and subsequent treatment options

As with the first-generation TKIs, resistance eventually develops to both afatinib and dacomitinib. T790M appears to be the key resistance mechanism to afatinib, being detected in 43–68% of patients from primarily Asian populations<sup>94–96</sup> and 73% of Caucasian patients<sup>97</sup> after afatinib failure. Other resistance mutations developing in the *EGFR* gene in response to afatinib include the C797S and L792F mutations and *MET* amplification, which have been observed *in vitro*.<sup>98</sup> Although the mechanisms of resistance to dacomitinib have not been as well characterized, *in vitro* data suggest that resistance to dacomitinib therapy primarily involves T790M mutations and, less frequently, C797S mutations.<sup>98</sup>

The third-generation TKI, osimertinib, is selective for both *EGFR*-sensitizing and *EGFR* T790M-resistance mutations and is approved for use in both the first- and second-line settings in metastatic NSCLC.<sup>99</sup> In the Phase III FLAURA study, PFS was significantly prolonged in patients with L858R or del19 *EGFR* mutations receiving the first-line osimertinib compared with first-generation TKIs (18.9 vs 10.2 months;  $P<0.001$ ),<sup>100</sup> and in a network meta-analysis, PFS appeared longer with the first-line osimertinib than erlotinib, gefitinib, afatinib, and dacomitinib.<sup>101</sup> However, no clear resistance mutation to the first-line osimertinib has been identified, limiting options for subsequent therapy.<sup>102</sup>

In patients with T790M-positive advanced NSCLC who had progressed after first-line TKI therapy,

osimertinib was associated with significantly longer PFS than patients who received platinum-pemetrexed (median: 10.1 vs 4.4 months;  $P < 0.001$ ).<sup>103</sup> Thus, osimertinib is an effective option after the failure of first- or second-generation TKIs to extend the duration of the therapeutic benefit obtained with targeted therapies. Encouraging OS results from 37 patients in the LUX-Lung 3, LUX-Lung 6, and LUX-Lung 7 trials who received osimertinib after afatinib, where median time on treatment was 20.2 months and median OS had not been reached after >4 years of follow-up, support the use of osimertinib in this setting.<sup>104</sup> Further, in a multicenter observational study of 204 patients who received second-line osimertinib after developing the T790M mutation with the first-line afatinib, the overall median time on treatment was 27.6 months.<sup>83</sup> However, further data are needed to determine the most appropriate sequential therapy and to determine whether osimertinib is best used upfront or reserved until after first-line TKI failure. The latter is a controversial topic following the first-line approval of osimertinib and in the context of the emerging challenge of osimertinib resistance.<sup>105–107</sup>

For patients who are T790M-negative and therefore not candidates for osimertinib, novel combinations of second-generation TKIs and other agents may overcome EGFR bypass mechanisms and provide alternative second-line options. Several agents have been tested in combination with afatinib, including cetuximab,<sup>108</sup> paclitaxel,<sup>109</sup> bevacizumab,<sup>110</sup> and pembrolizumab (NCT02364609), but further investigation is required.

## Safety

Adverse events (AEs) with second-generation TKIs are largely predictable and manageable,<sup>20,21,51,58</sup> although occurring more frequently than with first-generation TKIs,<sup>51,58,111</sup> likely reflecting the irreversible activity and broader inhibitory profile. Diarrhea and skin-related events such as acne or dryness, stomatitis, and paronychia were the most common AEs reported in pivotal clinical studies of afatinib and dacomitinib.<sup>20,21,51,57,58</sup> Similar AEs have been reported in large real-world studies of afatinib (diarrhea, rash/acne, stomatitis, and paronychia),<sup>63,67,69</sup> further demonstrating the predictable nature of these AEs. In a sub-analysis of the LUX-Lung 3, LUX-Lung 6, and LUX-Lung 7 studies, afatinib-associated AEs in older patients were consistent with the overall populations.<sup>82</sup> Of note, afatinib-related AEs can be controlled with tolerability-guided dose reductions that do not impact efficacy.<sup>63,65,66,68,112,113</sup> For example, in a Korean real-

world study, substantially more patients receiving afatinib required dose reductions compared with gefitinib and erlotinib; however, dose reductions did not adversely affect PFS in afatinib-treated patients (median: 23.5 vs 12.4 months for dose-reduced vs non-dose-reduced patients).<sup>63</sup>

Improvement in patient-reported outcomes such as time to deterioration of symptoms, cough, dyspnea, and pain symptoms, as well as overall health and quality of life, were reported for patients receiving afatinib relative to chemotherapy in the LUX-Lung 3 and LUX-Lung 6 studies.<sup>20,21</sup> In LUX-Lung 7, similar improvements in health status, as assessed by the EuroQoL-5D health status self-assessment questionnaire and the EuroQoL visual analog scale, were reported for afatinib and gefitinib. In ARCHER 1050, the improvement in global quality of life was significantly greater with gefitinib versus dacomitinib, although neither improvement was considered clinically meaningful.<sup>58</sup> In individual symptom scales, dacomitinib was associated with a greater improvement from baseline versus gefitinib in cough and chest pain symptoms, but a significant worsening in diarrhea and sore mouth symptoms.

## Conclusions

Second-generation TKIs have demonstrated improved efficacy vs first-generation TKIs and are an effective first-line therapeutic option for patients with advanced NSCLC, including Asian patients. As the number of therapeutic options for advanced NSCLC increases, the choice of first-line treatment will be determined by considering patient factors such as the presence of brain metastases, the type of *EGFR* mutation, tolerability, and subsequent therapy options for long-term treatment. In most clinical trials to date, the second-generation TKIs have been associated with manageable toxicity profiles and superior outcomes compared with first-generation TKIs, most likely due to their broader inhibitory profile. With striking efficacy in the first-line setting recently shown with the third-generation TKI, osimertinib, an important goal of future studies will be determining the optimal sequencing of the first-, second-, and third-generation TKIs to maximize patient response and survival across all lines of therapy.

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