

# Development of treatment options for Chinese patients with advanced squamous cell lung cancer: focus on afatinib

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**Abstract:** Lung cancer is the leading cause of cancer death in China, and approximately one third of these cancers are squamous cell carcinoma (SqCC) of the lung. Ethnic diversity and country-specific environmental factors can account for interindividual variations in response to and tolerability of anticancer therapies. Although several targeted therapies have recently been approved for patients with relapsed/refractory SqCC of the lung, only afatinib, an irreversible ErbB family blocker, has data of Chinese patients. In the Phase III LUX-Lung 8 trial, afatinib demonstrated a significant clinical benefit vs the reversible first-generation EGFR tyrosine kinase inhibitor erlotinib in both the overall population and the Chinese subset, with a manageable safety profile. Emerging biomarker data from LUX-Lung 8 suggest that patients with ErbB mutations, especially ErbB2, and those classified as “good” in the VeriStrat® proteomic test, may benefit from afatinib treatment in particular, regardless of ethnicity, and may get a long-term response. In conclusion, afatinib is a valid second-line option for Chinese patients with SqCC of the lung, and specific biomarkers may help guide in treatment decision-making. Ongoing studies will provide further guidance on afatinib’s place in the treatment algorithm, alongside the other novel targeted therapies.

**Keywords:** squamous cell carcinoma, NSCLC, Chinese, afatinib, EGFR, ErbB, biomarker

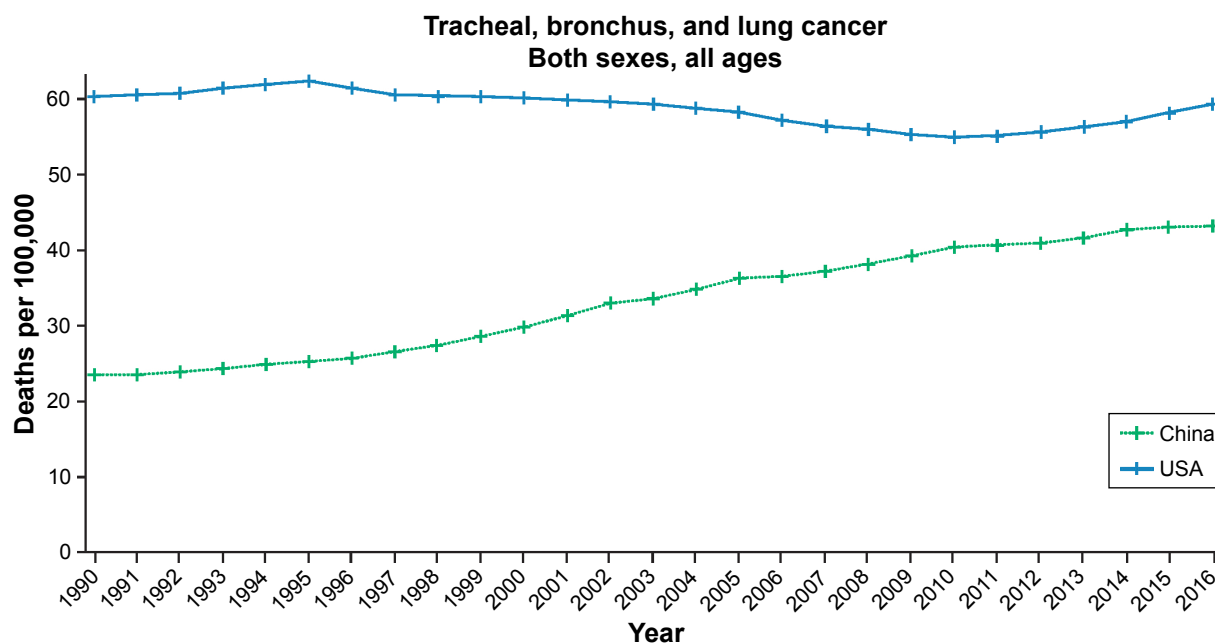
## Introduction

In China, lung cancer is the leading cause of cancer death<sup>1</sup> and the rates of lung cancer diagnoses are rising.<sup>2</sup> Although smoking rates in China have declined in recent years,<sup>3</sup> cigarette smoking is still common, with 52.9% of Chinese men and 2.4% of women being smokers in 2010, representing about one third of the world’s smoking population.<sup>4,5</sup> The trend in smoking prevalence in China over the past 20–30 years has followed patterns in the USA observed in the 1970s and 1980s,<sup>6</sup> and the burden of lung cancer is therefore increasing in China, as it did previously in the US population (Figure 1).<sup>5–7</sup>

Squamous cell carcinoma (SqCC) of the lung is strongly associated with smoking,<sup>8</sup> and about 30% of lung cancers in China are SqCC histology.<sup>7</sup> Although this is similar to the percentage of cases of SqCC of the lung in the US,<sup>8</sup> the actual patient numbers are much higher due to the size of the Chinese population. Therefore, there is an urgent need to identify optimal treatments for SqCC of the lung in the Chinese population.

While molecularly targeted therapy has revolutionized the treatment of patients with EGFR mutation-positive and anaplastic lymphoma kinase-positive non-small-cell

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**Figure 1** Deaths caused by lung cancer in China and the USA from 1990 to 2016.

**Notes:** Institute for Health Metrics and Evaluation (IHME). GBD Compare. Seattle, WA: IHME, University of Washington; 2017. Available from: <http://vizhub.healthdata.org/gbd-compare>. Accessed January 15, 2019.<sup>87</sup>

lung cancer (NSCLC), progress in the treatment of SqCC of the lung, which is typically EGFR wild-type, has been slower. Although platinum-doublet chemotherapy remains the standard first-line treatment for patients with advanced stage of SqCC of the lung in China, as elsewhere,<sup>9,10</sup> outcomes are generally modest. In addition, second-line treatment options are limited. Until recently, erlotinib (an EGFR tyrosine kinase inhibitor [TKI]) and docetaxel were the only agents approved in this setting,<sup>9,11</sup> highlighting the unmet need in this patient population.

Since 2014, several targeted therapies have been approved for the treatment of SqCC of the lung.<sup>9</sup> These include the following: necitumumab, an anti-EGFR monoclonal antibody, which is approved for the first-line use, in combination with standard chemotherapy;<sup>12,13</sup> the immunotherapies pembrolizumab, nivolumab, and atezolizumab; the vascular endothelial growth factor receptor-2 (VEGFR-2) antibody, ramucirumab (in combination with docetaxel); and the second-generation EGFR-targeted TKI, afatinib (an irreversible ErbB family blocker that inhibits signaling from all ErbB heterodimers and homodimers), all of which have been approved as the second-line therapy.<sup>9,12,14–17</sup> This recent expansion of therapeutics approved for the second-line use necessitates a discussion about optimal treatment choice.

Pharmacoethnicity, or ethnic diversity in drug response or toxicity, is recognized as an important factor accounting for an interindividual variation in anticancer therapy responsiveness.<sup>18</sup> In addition to the environmental factors

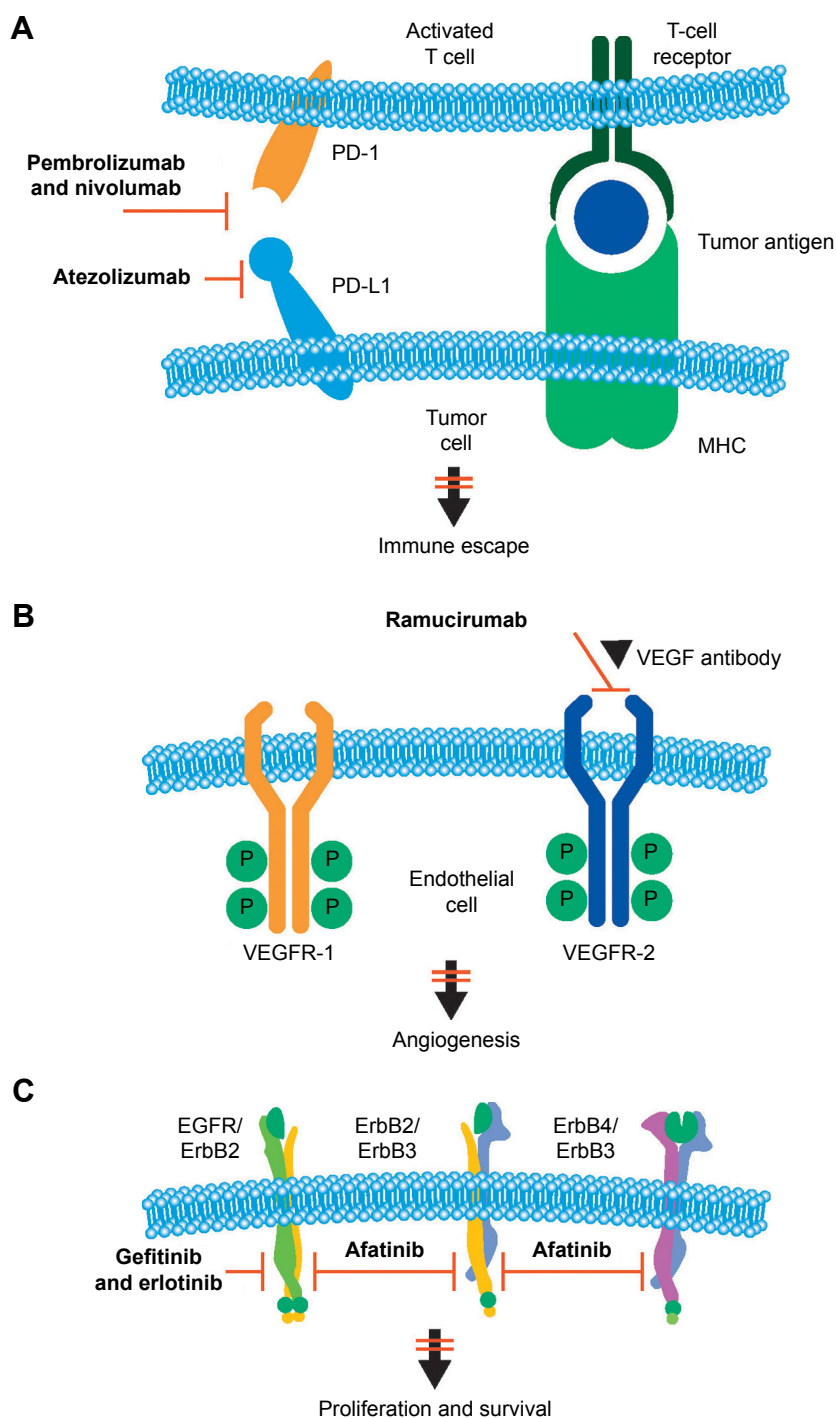
that influence bioavailability and metabolism, such as the frequency of smoking, the expression levels of the drug target and the prevalence of mutations in the target population must also be taken into account.<sup>19</sup> Therefore, potential biomarkers to help guide clinicians as to the optimal treatment choice for their patients with SqCC of the lung, including those of Asian ethnicity, also need to be considered.

This article reviews targeted agents, including the recently approved afatinib for the treatment of SqCC of the lung, the only targeted therapy with data of Chinese patients available from its registration trial. This article also considers the use of biomarkers to identify suitable patient populations, and of afatinib in the treatment algorithm alongside the other novel agents, including immunotherapies.

## Targeting EGFR and other ErbB family proteins in SqCC of the lung

Both first-line afatinib<sup>20,21</sup> and the first-generation, reversible EGFR TKIs, gefitinib<sup>22–24</sup> and erlotinib<sup>25–27</sup> (Figure 2C), have been demonstrated to be superior to chemotherapy in patients with NSCLC and *EGFR*-activating mutations; more recent trials showed the second-/third-generation EGFR TKIs, afatinib, dacomitinib, and osimertinib, to be superior to the first-generation TKIs.<sup>28–31</sup> Because *EGFR* mutations are relatively common in Asian patients, most of the trials were conducted in Asian populations.<sup>21,32,33</sup>

Although *EGFR* mutations are relatively uncommon in SqCC (Western population = 3.3%; Asian population = 4.6%;



**Figure 2** Mechanism of action of (A) immune checkpoint inhibitors, (B) VEGFR inhibitors, and (C) EGFR/ErbB inhibitors.

**Abbreviations:** MHC, major histocompatibility complex; PD-1, programmed cell death protein-1; PD-L1, programmed cell death ligand-1; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

Table 1),<sup>34</sup> EGFR overexpression is frequently observed (50%–80%)<sup>35–39</sup> and 7%–10% of tumors also have alterations in *EGFR* gene copy number.<sup>35,39,40</sup> There is therefore a clear rationale for evaluating EGFR-targeted agents in SqCC of the lung, either combined with the first-line chemotherapy<sup>20,21</sup> or as a monotherapy in patients with relapsed/refractory SqCC of the lung.<sup>41</sup>

In the Phase III SQUIRE trial in patients with previously untreated SqCC of the lung, the addition of necitumumab to gemcitabine plus cisplatin significantly improved overall survival (OS) vs gemcitabine plus cisplatin alone (median = 11.5 vs 9.9 months, respectively [HR = 0.84, 95% CI = 0.74–0.96;  $P=0.01$ ]).<sup>13</sup> However, a higher rate of grade  $\geq 3$  adverse events (AEs) and serious AEs occurred

**Table 1** Incidence of individual mutations in Western and Asian SqCC<sup>34</sup>

Gene	Incidence of mutation, n/N (%)	
	Western	Asian
<i>TP53</i> *:	62/113 (54.9)	64/179 (35.8)
<i>EGFR</i> *:	11/334 (3.3)	22/474 (4.6)
<i>KRAS</i> *:	12/187 (6.4)	5/284 (1.8)
<i>LKB1</i> *:	13/137 (9.5)	0/166 (0.00)
<i>EML4-ALK</i>	4/89 (4.5)	5/277 (1.8)
<i>PTEN</i> *:	0/12 (0.0)	12/123 (9.8)
<i>BRAF</i> *:	1/408 (0.2)	0/124 (0.0)
<i>PIK3CA</i>	1/71 (1.4)	8/124 (6.5)
<i>ErbB2</i>	2/117 (1.7)	1/259 (0.4)

**Notes:** \*Significantly different,  $P < 0.001$ . Copyright © 2013, Oxford University Press. Dearden S, Stevens J, Wu YL, Blowers D. Mutation incidence and coincidence in non small-cell lung cancer: meta-analyses by ethnicity and histology (mutMap). *Ann Oncol.* 2013;24(9):2371–2376.<sup>34</sup>

**Abbreviation:** SqCC, squamous cell carcinoma.

in patients treated with necitumumab plus gemcitabine and cisplatin. Of note, 8% of the patients were East Asian, but no efficacy data were reported for this subgroup.<sup>13</sup> A meta-analysis of 2018 unselected patients with an advanced NSCLC also suggested that the addition of the anti-EGFR

antibody cetuximab to standard platinum-doublets can provide a clinical benefit in patients with SqCC of the lung.<sup>42</sup> While 7% of the patients were Asian, again no efficacy data were reported for this subgroup.

In the second-line setting, the subanalysis of the Phase III studies BR.21 (erlotinib vs placebo in relapsed/refractory NSCLC)<sup>43,44</sup> and TAILOR (erlotinib vs docetaxel in patients with *EGFR* wild-type advanced NSCLC)<sup>45</sup> indicated that erlotinib also has an activity against SqCC of the lung (Table 2). No data are available from either trial on the efficacy of erlotinib in Asian patients.

In addition to *EGFR*, other members of the ErbB family, particularly ErbB2 and ErbB3 and their downstream signaling pathways, also have a key role in the pathogenesis of SqCC of the lung.<sup>12,46–48</sup> Approximately 18% of SqCC tumors express ErbB2,<sup>49</sup> and around 30% of SqCC tumors overexpress ErbB3.<sup>48</sup> Therefore, targeting just one branch of these degenerated ErbB pathways may offer a suboptimal treatment for squamous tumors.<sup>12</sup> It was postulated that broader irreversible ErbB blockade with afatinib might

**Table 2** Clinical activity of approved EGFR- and VEGFR-targeted agents and immunotherapies for the second-line treatment of patients with SqCC of the lung

Therapy type	Trial	Patient population	Treatment arms	Efficacy (OS and PFS) in SqCC	Reference
Immunotherapies	Checkmate-017; Phase III	Metastatic SqCC of the lung (N=272); progression during or after platinum-based chemotherapy; six Asian pts (2%)	Nivolumab vs docetaxel	Significant OS and PFS improvement: 9.2 vs 6.0 months (HR =0.59, 95% CI =0.4–0.8; $P < 0.001$ ) median PFS 3.5 vs 2.8 months (HR =0.62, 95% CI =0.5–0.8; $P < 0.001$ ); Asian subset data not reported	69
	Keynote-010; Phase II/III	Previously treated, PD-L1-positive, advanced NSCLC; 222 pts with SqCC of the lung (21%); 217 Asian pts (21%)	Pembrolizumab vs docetaxel	Trend for benefit in patients with SqCC of the lung; OS (HR =0.74, 95% CI =0.5–1.1); PFS (HR =0.86, 95% CI =0.6–1.2); Asian subset data not reported	71
	POPLAR Phase II	Previously treated NSCLC; 97 (34%) SqCC of the lung; no information on ethnicity	Atezolizumab vs docetaxel	OS significantly improved: 10.1 vs 8.6 months; (HR =0.8, 95% CI =0.5–1.3); PFS not reported	73
	OAK Phase III	Previously treated NSCLC; 222 (26%) SqCC of the lung; 180 (21%) Asian pts	Atezolizumab vs docetaxel	OS trend for improvement: 8.9 vs 7.7 months; (HR =0.73, 95% CI =0.5–1.08, $P = 0.0038$ ); PFS not reported; Asian subset data not reported	74
VEGFR-targeted agents	REVEL Phase III	Stage IV NSCLC after platinum-based therapy; 328 pts (26%) SqCC of the lung; 89 (7%) East Asian pts	Ramucirumab plus docetaxel vs placebo plus docetaxel	Median OS 9.5 vs 8.2 months (HR =0.88, 95% CI =0.7–1.1); trend for benefit in East Asian patients; PFS for subgroups not reported	77

(Continued)

**Table 2** (Continued)

Therapy type	Trial	Patient population	Treatment arms	Efficacy (OS and PFS) in SqCC	Reference
EGFR-targeted agents	BR.21; Phase III	NSCLC; progressed after first-/second-line chemotherapy; 222 pts (38%) SqCC of the lung; 42 (7%) Asian pts	Erlotinib vs placebo	Favorable OS and PFS outcomes; median OS 5.6 vs 3.6 months (HR =0.60, 95% CI =0.4–0.8); median PFS 2.3 vs 1.8 months (HR =0.48, 95% CI =0.4–0.7); no data reported for Asian subgroup	43, 44
	TAILOR Phase III	NSCLC; WT EGFR; prior platinum-based chemotherapy; 54 pts (25%); two (1%) Asian pts	Erlotinib vs docetaxel	OS and PFS in SqCC of the lung favor docetaxel, but no significant difference: OS (HR =0.90, 95% CI =0.5–1.7; <i>P</i> =0.14); PFS (HR =0.57, 95% CI =0.3–1.0; <i>P</i> =0.3); no data reported for Asian pts	45
	LUX-Lung 8; Phase III	SqCC of the lung (N=795); progression after ≥4 cycles of platinum-based chemotherapy; 67 (8.4%) Chinese pts	Afatinib vs erlotinib	Significant PFS and OS improvements; medium PFS 2.4 vs 1.9 months (HR =0.82, 95% CI =0.7–1.0; <i>P</i> =0.0427); median OS 7.9 vs 6.8 months (HR =0.81, 95% CI =0.7–1.0; <i>P</i> =0.0077); trend toward prolonged OS in Chinese subgroup: PFS benefit afatinib vs erlotinib comparable between Chinese pts (HR =0.70, 95% CI =0.4–1.3); 2.8 months in both arms; OS benefit afatinib vs erlotinib also comparable between Chinese pts (HR =0.69, 95% CI =0.9–1.2); 8.2 months in both arms	41, 50
	LUX-Lung 5; Phase III	NSCLC progressed on chemotherapy and erlotinib/gefitinib; part A: 91 (8%) SqCC of the lung Part B: 17 (8.4%) SqCC of the lung; 82 (41%) East Asian pts	Part A: afatinib monotherapy  Part B: Afatinib plus paclitaxel (for pts progressing on afatinib following clinical benefit in part A)	Median PFS 3.7 months  Median PFS 5.6 months; PFS (HR =0.15, 95% CI =0.0–0.6) vs adenocarcinoma; East Asian (HR =0.67, 95% CI =0.4–1.2) vs Caucasian pts	55  86

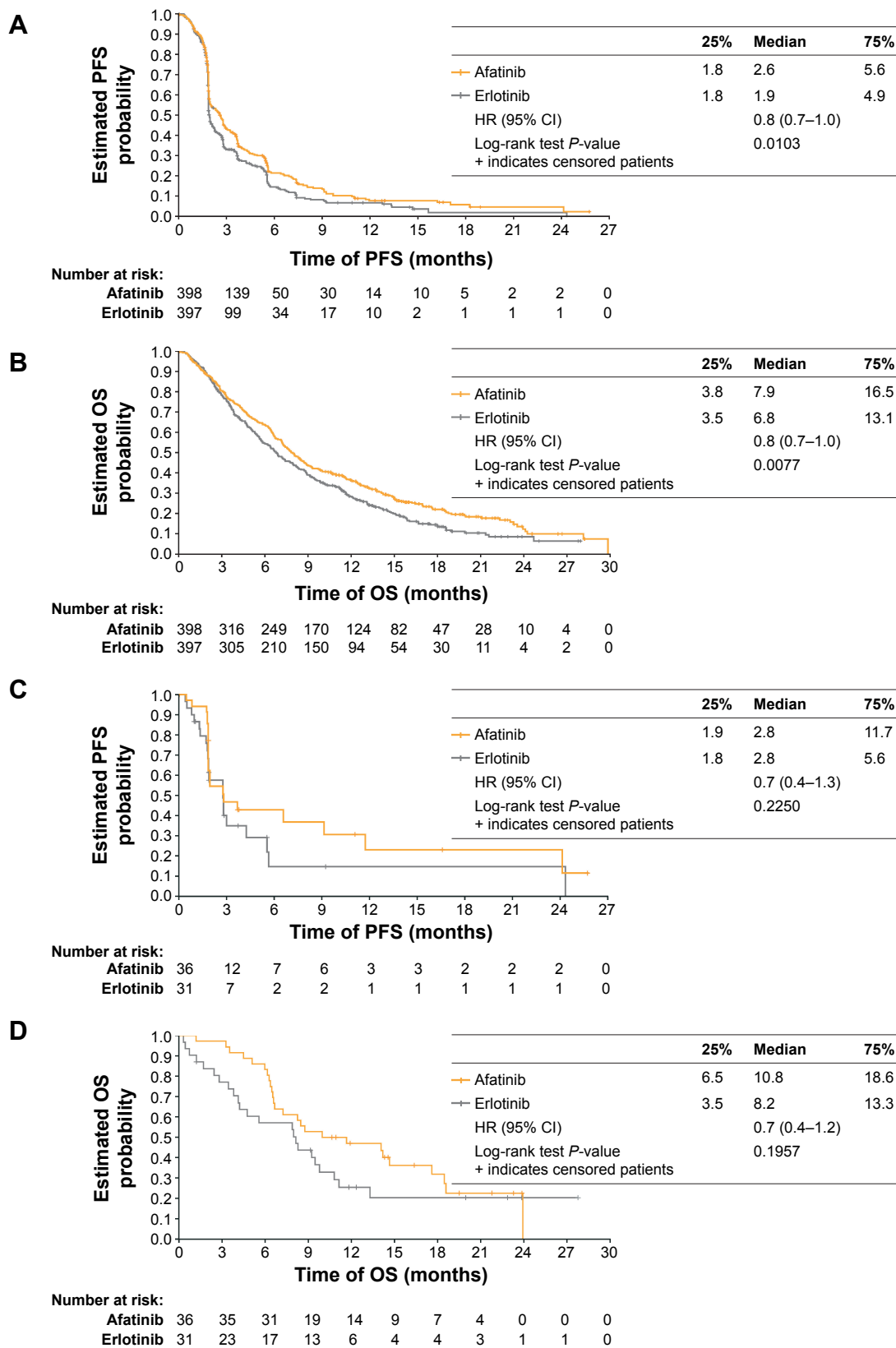
**Abbreviations:** NSCLC, non-small-cell lung cancer; OS, overall survival; PD-L1, programmed death ligand-1; PFS, progression-free survival; pts, patients; SqCC, squamous cell carcinoma; VEGFR, vascular endothelial growth factor receptor; WT, wild-type.

inactivate aberrant ErbB-dependent signaling cascades and, therefore, be effective in patients with SqCC of the lung.<sup>41,50</sup>

### LUX-Lung 8: afatinib vs erlotinib as the second-line treatment for SqCC of the lung

The LUX-Lung 8 trial was an open-label, randomized Phase III trial that compared afatinib (40 mg/day) with erlotinib (150 mg/day) in 795 patients with relapsed/refractory stage IIIB/IV SqCC of the lung who had progressed on or

after platinum-based chemotherapy.<sup>41</sup> Afatinib significantly improved progression-free survival (PFS; primary endpoint) and OS (key secondary endpoint) vs erlotinib (median PFS =2.6 vs 1.9 months, respectively [HR =0.82, 95% CI =0.68–1.00]; *P*=0.0103; median OS =7.9 vs 6.8 months, respectively [HR =0.81, 95% CI =0.69–0.95]; *P*=0.0077; Figure 3A and B).<sup>41</sup> Disease control rate (DCR) was also significantly higher with afatinib than with erlotinib (51% vs 40%; *P*=0.002).<sup>41</sup> Based on these data (Table 2), afatinib gained US approval in 2016 for the treatment of locally



**Figure 3** LUX-Lung 8: Kaplan–Meier plots for overall study population vs Chinese subgroup. **(A)** PFS (an independent review) and **(B)** OS for the overall treatment population; **(A and B)** Reprinted from Soria JC, Felip E, Cobo M, et al. Afatinib versus erlotinib as second-line treatment of patients with advanced squamous cell carcinoma of the lung (LUX-Lung 8): an open-label randomised controlled phase 3 trial. *Lancet Oncol.* 2015;16(8):897–907. Copyright © 2015, with permission from Elsevier.<sup>41</sup> **(C)** PFS (an independent review) and **(D)** OS for the Chinese subgroup **(C and D)** Copyright ©2013. Dove Medical Press. Republished from Lu S, Li W, Zhou C, et al. Afatinib versus erlotinib for second-line treatment of Chinese patients with advanced squamous cell carcinoma of the lung: a subgroup analysis of the phase 3 LUX-Lung 8 trial. *Oncotargets Ther.* 2018;11:8565–8573.<sup>50</sup>

**Abbreviations:** OS, overall survival; PFS, progression-free survival.

advanced or metastatic SqCC of the lung progressing on or after platinum-based chemotherapy.<sup>14</sup>

Of the 795 patients enrolled in the LUX-Lung 8 trial, 67 (8.4%) patients were from Mainland China.<sup>50</sup> Of these, 36 patients were randomized to receive afatinib and 31 patients to receive erlotinib.<sup>50</sup> Although this exploratory analysis was not powered to show significant differences between treatment groups, improvements in the Chinese subset were comparable to those in the overall treatment population (OTP).<sup>50</sup> There were more patients who had a long-term response in the Chinese subgroup than in the OTP (11% vs 5%), with a median treatment duration of 22.7 vs 17.6 months, respectively.<sup>50,51</sup> While median PFS was similar in Chinese patients who received afatinib and erlotinib (2.8 months in both the groups; HR =0.70; Figure 3C), there was a trend toward prolonged OS with afatinib compared with erlotinib (10.8 vs 8.2 months; HR =0.7; Figure 3D).<sup>50</sup> Overall response rates were improved with afatinib vs erlotinib in the Chinese subgroup, although the difference was not statistically significant. DCR was comparable between the two groups.<sup>50</sup> These data suggest that afatinib is a viable treatment option for Chinese patients with advanced SqCC of the lung.

Afatinib significantly improved patient-reported outcomes vs erlotinib in both the OTP and Chinese subgroups.<sup>41</sup> Many Chinese patients reported an improved global health status/quality of life (QoL; 52.8% afatinib vs 29.6% erlotinib;  $P=0.072$ ) compared with the OTP (36% afatinib vs 28% erlotinib;  $P=0.041$ ).<sup>41,50,52</sup> In the Chinese subgroup, “dyspnea walked” (shortness of breath while walking), time to deterioration of cough, and QoL rates were significantly improved, and time to deterioration of cough was significantly delayed with afatinib vs erlotinib.<sup>50,52</sup> Health-related QoL is an important consideration in the choice of appropriate treatments for patients with lung cancer. These data indicate that afatinib may improve health-related QoL outcomes in Chinese patients.

Afatinib demonstrated a predictable and manageable safety profile in patients with SqCC of the lung,<sup>41</sup> similar to that observed in the LUX-Lung 3 and LUX-Lung 6 trials<sup>20,21</sup> and consistent with the mechanistic profile of ErbB inhibition. In the OTP, the few discontinuations due to AEs, including the common class-related AEs of diarrhea (4%) and rash or acne (3%), suggested that the well-established recommended dose-adjustment schemes and supportive care measures enabled patients to remain on afatinib treatment for as long as they get a clinical benefit.<sup>14,41,53</sup> Among Chinese patients, the tolerability profile of afatinib was consistent with that observed in the OTP.<sup>50</sup> In the Chinese subgroup, there were no cases of grade  $\geq 3$  diarrhea, and none of

the patients discontinued treatment due to afatinib-related diarrhea,<sup>50</sup> which indicates that afatinib is well tolerated in Chinese patients. Overall, the LUX-Lung 8 trial data support afatinib as an effective and well-tolerated treatment option for Chinese patients with advanced SqCC of the lung.

In addition to the findings from LUX-Lung 8, because most patients in the LUX-Lung 3 trial<sup>20</sup> and all patients in the LUX-Lung 6 trial<sup>21</sup> were East Asian, it can be concluded that the safety profile of afatinib in East Asian patients is predictable and manageable. Afatinib has recently been approved in China, for treating both advanced NSCLC and SqCC of the lung.<sup>54</sup>

Other clinical studies have provided evidence of the activity of afatinib in patients with squamous tumors. In part A of the Phase III LUX-Lung 5 trial, patients with NSCLC who had progressed on chemotherapy and erlotinib/ gefitinib after initial disease control received afatinib monotherapy (50 mg/day).<sup>55</sup> In a subanalysis of 91 patients with SqCC of the lung, the DCR was 60% and the median PFS was 3.7 months.<sup>12,55</sup>

Similar to SqCC of the lung, other tumors with squamous histology, such as head and neck cancer, often show a high EGFR expression and/or an increased *EGFR* gene copy number and a low incidence of activating kinase domain mutations. In the Phase III LUX-Head and Neck 1 trial, afatinib monotherapy (40 mg/day) prolonged PFS vs methotrexate in patients with recurrent/metastatic head and neck SqCC.<sup>56</sup> In addition, in a recent Phase II study, the use of afatinib (40 mg/day) preoperatively led to an improved response compared with no treatment (NT) in patients with untreated head and neck SqCC.<sup>57</sup> Progressive disease (PD) occurred in 16.6% of the NT arm, whereas none of the patients receiving afatinib had PD. There were significantly more partial responses in the afatinib group (48%) than in the NT group (7%;  $P=0.005$ ), as measured by PET-computed tomography scan, using PET Response Criteria in Solid Tumors.<sup>57</sup>

## Emerging ErbB overexpression and mutation biomarker data for SqCC of the lung

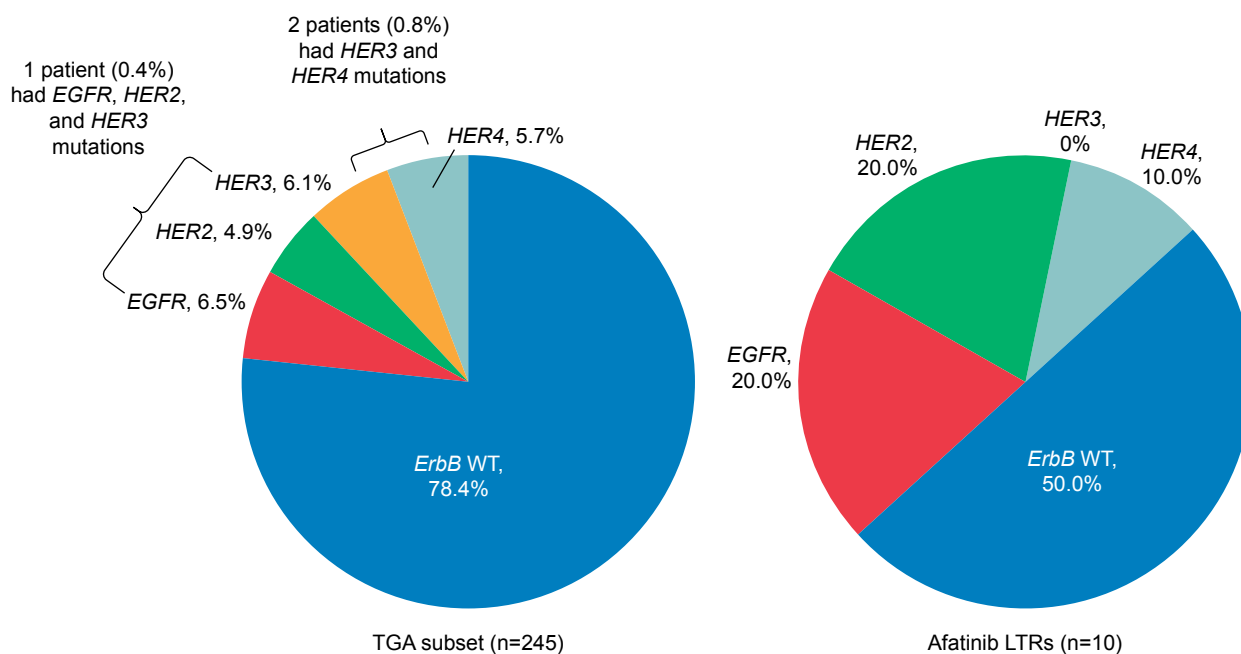
SqCC of the lung is genetically complex,<sup>34,41,46,58</sup> and the identification of predictive biomarkers may help to establish the optimal second-line treatment.<sup>59</sup> Although EGFR-activating mutations are rare, the cumulative frequency of ErbB mutations is much higher, ~1%–4%, 1%–2%, and 1%–2% for EGFR, ErbB2, and ErbB3, respectively.<sup>34,60–62</sup> A comprehensive analysis of squamous cell tumors identified genetic aberrations in several signaling molecules downstream of the ErbB receptors: KRAS, HRAS, BRAF,

RASA1, NF1, and NRG1.<sup>12,46,60</sup> Reported differences between the incidences of specific mutations (including EGFR and ErbB2) between Western and Asian patients (Table 1) underpin the need to study targeted therapies in different ethnic groups.<sup>34</sup> Given these findings in SqCC and the fact that SqCCs overexpress EGFR and other ErbB family proteins,<sup>36–38,61</sup> the analysis of the ErbB family was prespecified in the LUX-Lung 8 trial.

## ErbB family mutation and EGFR overexpression analysis in LUX-Lung 8

By using a next-generation sequencing-based gene assay,<sup>63</sup> tumor genetic analysis (TGA) was conducted on tumor samples from 245 patients in the LUX-Lung 8 trial.<sup>61</sup> The most frequently observed genetic aberrations in the TGA cohort were single-nucleotide variations in TP53 (87.3% of patients), LRP1B (39.2%), MLL2 (33.1%), CDKN2A (28.6%), and FAT3 (27.3%) and copy number alterations in SOX2 (42.9%), KLHL6 (39.6%), PIK3CA (36.3%), MAP3K13 (32.2%), BCL6 (30.6%), and FGF12 (28.2%).<sup>61</sup> The findings are similar to those of the Cancer Genome Atlas Research Network study in SqCC of the lung.<sup>46,61</sup> None of the most frequently observed aberrations predicted clinical outcomes,<sup>61</sup> but by focusing on ErbB family mutations, some interesting trends emerged. In total, 21.6% of patients in the TGA subset had at least one ErbB family single-nucleotide variant mutation (Figure 4).<sup>61</sup> In the overall data

set, 21 patients (5.3%) were long-term responders (LTRs) to afatinib (received  $\geq 12$  months of treatment), ten of these were included in the TGA cohort, and five (50.0%) had ErbB mutations.<sup>61</sup> Among patients treated with afatinib (but not with erlotinib), PFS and OS were longer in those with vs without ErbB mutations (PFS = 4.9 vs 3.0 months, OS = 10.6 vs 8.1 months for afatinib; PFS = 2.7 vs 2.4 months, OS = 7.2 vs 6.4 months for erlotinib; Figure 5).<sup>61</sup> In the OTP for the LUX-Lung 8 trial, frequencies of *EGFR* mutation-positive tumors were low in both the treatment groups (6.8% afatinib vs 6.2% erlotinib).<sup>50,61</sup> Mutations in EGFR, in isolation, did not predict any clinical benefit with afatinib over erlotinib.<sup>61</sup> This indicates that clinical outcomes with afatinib vs erlotinib are unlikely to be driven by imbalances in EGFR mutations in the study groups.<sup>41,50</sup> By contrast, mutations in ErbB3, ErbB4, and in particular ErbB2 seem to drive the benefit of afatinib as compared with erlotinib.<sup>61</sup> In patients with an ErbB2 mutation (12 of 245; 4.9%), PFS (HR = 0.06, 95% CI = 0.01–0.59) and OS (HR = 0.06, 95% CI = 0.01–0.57) strongly favored afatinib vs erlotinib. Despite the small sample size, the interaction *P*-value ( $P_{int}$ ) was significant for both PFS ( $P_{int} = 0.006$ ) and OS ( $P_{int} = 0.003$ ), indicating that the presence of an ErbB2 mutation may predict better clinical outcomes with afatinib vs erlotinib in patients with SqCC of the lung.<sup>61</sup> Data on ErbB mutations were not available for the Chinese population included in LUX-Lung 8 trial. Further investigation into the impact of ErbB family

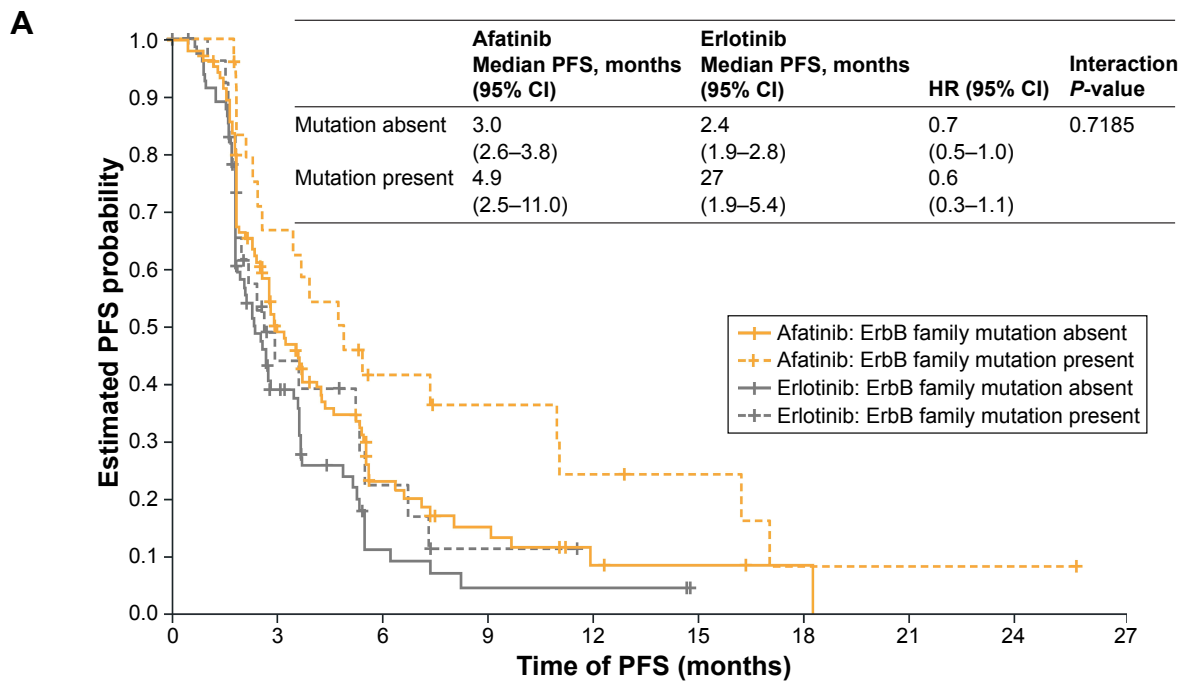


**Figure 4** LUX-Lung 8: frequency of ErbB family mutations in the overall TGA cohort and in patients who were LTRs to afatinib.<sup>61</sup>

**Note:** \*There were three LTRs to erlotinib (one had a tumor with an EGFR mutation and two had tumors which were EGFR WT).

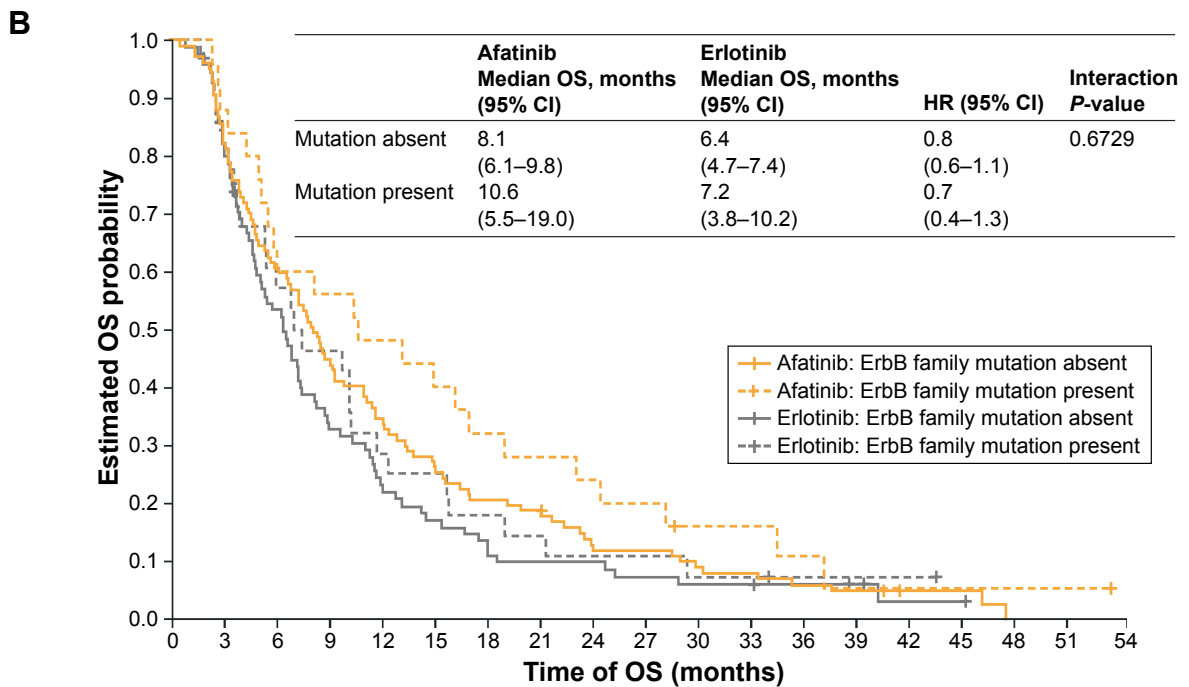
**Abbreviations:** LTRs, long-term responders; TGA, tumor genetic analysis; WT, wild-type.





**Number at risk:**

Afatinib: Absent	107	47	15	8	3	2	1	0	0	0
Afatinib: Present	25	16	8	6	4	3	1	1	1	0
Erlotinib: Absent	85	26	5	2	2	0	0	0	0	0
Erlotinib: Present	28	9	4	1	0	0	0	0	0	0



**Number at risk:**

Afatinib: Absent	107	88	65	48	37	28	22	20	13	12	9	8	6	5	2	2	0	0	0
Afatinib: Present	25	22	15	14	12	10	8	7	6	5	3	3	2	1	1	1	1	1	0
Erlotinib: Absent	85	69	44	27	19	14	11	8	8	6	5	5	4	3	1	1	0	0	0
Erlotinib: Present	28	23	16	13	8	7	5	4	3	3	2	2	1	1	1	0	0	0	0

**Figure 5** Comparison of (A) PFS and (B) OS between patients with the presence or the absence of ErbB family mutations.

**Note:** Reproduced with permission from Goss GD, Felip E, Cobo M, et al. Association of ERBB mutations with clinical outcomes of afatinib- or erlotinib-treated patients with lung squamous cell carcinoma: secondary analysis of the LUX-Lung 8 randomized clinical trial. *JAMA Oncol.* 2018;4(9):1189–1197. Copyright©2018 American Medical Association.<sup>61</sup>

**Abbreviations:** OS, overall survival; PFS, progression-free survival.

mutations on clinical outcomes with afatinib in this patient population is warranted.

EGFR expression was assessed by immunohistochemistry in 345 tumor samples from the OTP of LUX-Lung 8 (apart from 11 patients, this population was different to that used for TGA).<sup>61</sup> High levels of EGFR overexpression (defined as an H-score  $\geq 200$ ) were observed: 45 of 157 (28.7%) afatinib-treated patients and 72 of 188 (38.3%) erlotinib-treated patients had EGFR overexpression.<sup>61</sup> EGFR overexpression did not predict a PFS or an OS benefit with afatinib vs erlotinib, suggesting that the efficacy of afatinib is not driven by EGFR overexpression in this patient group. EGFR overexpression was also assessed in 60 Chinese patients in the LUX-Lung 8 trial. In total, 19% of Chinese patients treated with afatinib and 25% treated with erlotinib had EGFR overexpression, which is similar to the frequency observed in the OTP.<sup>50,61</sup> Similarly, EGFR overexpression was not predictive of survival benefit with afatinib over erlotinib in the Chinese patients.<sup>50,61</sup>

In conclusion, a subgroup of patients with ErbB mutations may particularly benefit from afatinib treatment. This difference could be due to the broad mechanism of action of afatinib and the irreversible inhibition of signaling via all ErbB dimers. Mutations in ErbB members, particularly ErbB2, may be useful as predictive biomarkers for afatinib in this setting.

### ErbB family protein-specific blood-based assay in the LUX-Lung 8 trial

Another approach that could help differentiate subgroups of patients with SqCC of the lung who would benefit from specific second-line therapies is the use of a blood-based protein assay. The VeriStrat<sup>®</sup> test was developed for EGFR wild-type NSCLC or unknown mutation status. It uses matrix-laser desorption ionization mass spectrometry to analyze patients' pretreatment serum and compares the mass spectra obtained with a reference set. The classification as VeriStrat-good (VS-G) or VeriStrat-poor (VS-P) predicts good or poor survival, respectively, on EGFR TKIs.<sup>64</sup> This test has demonstrated a prognostic and predictive value in NSCLC for erlotinib.<sup>65,66</sup>

In a retrospective analysis of the LUX-Lung 8 trial, the ability of the VeriStrat<sup>®</sup> test to predict clinical benefit with afatinib vs erlotinib was investigated (Figure 6).<sup>59</sup> In the OTP, 675 of the 795 patients were classified, 412 as VS-G and 263 as VS-P.<sup>59</sup> Furthermore, 14.4% of the 675 VeriStrat-classified patients and 21.6% of the 795 patients in the OTP were East Asian.

In the VS-G group, OS was significantly longer with afatinib vs erlotinib (11.5 months on afatinib vs 8.9 months; HR =0.79, 95% CI =0.63–0.98), indicating that afatinib is

a valuable second-line option in this patient group.<sup>59</sup> In the VS-P group, there was no significant difference in OS between afatinib and erlotinib (HR=0.90, 95% CI=0.70–1.16).<sup>59</sup> However, there was no interaction between VeriStrat classification and treatment group for OS ( $P_{\text{int}}=0.5303$ ). The authors suggested that this may be due to the relatively small sample size and therefore broad 95% CIs of the VS-P group.<sup>59</sup> OS was significantly longer in VS-G than in VS-P patients, both for the overall VeriStrat-classified population (HR=0.41, 95% CI =0.35–0.49) and for the afatinib-treated patients (HR =0.40, 95% CI =0.31–0.51).<sup>59</sup> In the overall VeriStrat-classified population, 15% of VS-G and 13.3% of VS-P patients were from East Asia.<sup>59</sup> No further analysis was conducted on the Eastern Asian subgroup. The multivariate analysis showed that VeriStrat classification was an independent predictor of OS in afatinib-treated patients, regardless of race, performance status, or best response to the first-line chemotherapy.<sup>59</sup>

In conclusion, VS-G classification is strongly associated with favorable survival outcomes with either afatinib or erlotinib compared with VS-P classification. Patients who are classified as VS-G by the proteomic test derive a greater OS benefit from afatinib than from erlotinib. VeriStrat classification should therefore be considered when guiding in treatment decision-making in patients with SqCC of the lung.

### Biomarkers of long-term response in the LUX-Lung 8 trial

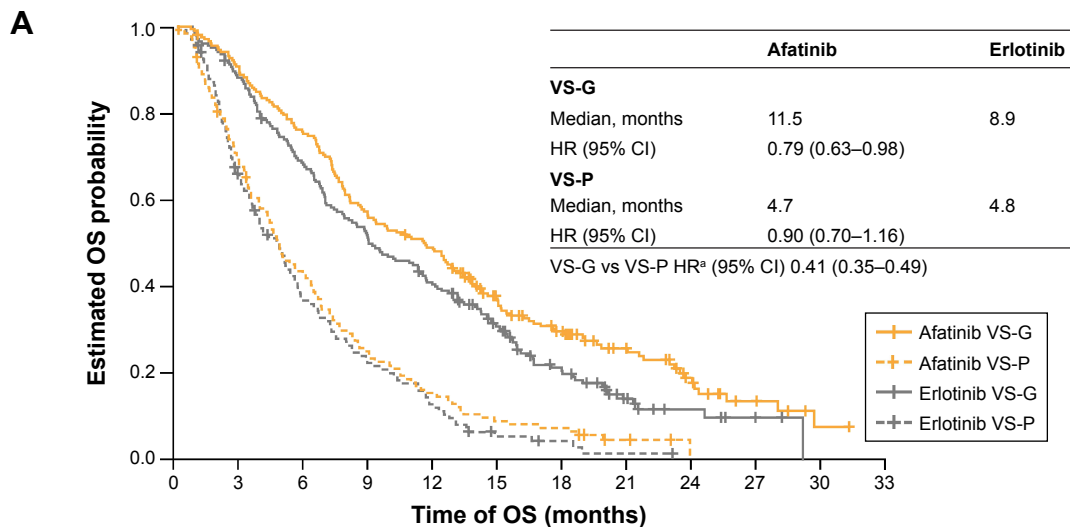
Clinical and molecular biomarkers indicative of long-term response ( $\geq 12$  months' afatinib treatment) were explored in the LUX-Lung 8 trial.<sup>51</sup> There were 21 LTRs (5%) in the afatinib treatment group (N=398; Figure 7); the median OS in the LTRs was 21.2 months. Fifteen of the 17 LTRs evaluated using the VeriStrat test (88%) were classified as VS-G.<sup>51</sup> None of the LTRs was East Asian.

The mutation profile of LTRs showed increased ErbB2, ErbB4, and EGFR mutations compared with the overall afatinib-treated population.<sup>51</sup> Long-term treatment with afatinib was well tolerated, with an AE profile similar to that of the overall afatinib-treated population. The findings from this analysis suggest that VS-G status and ErbB family mutations may be potential biomarkers of long-term response to afatinib.

### Immunotherapies and angiogenesis inhibitors for the treatment of SqCC of the lung

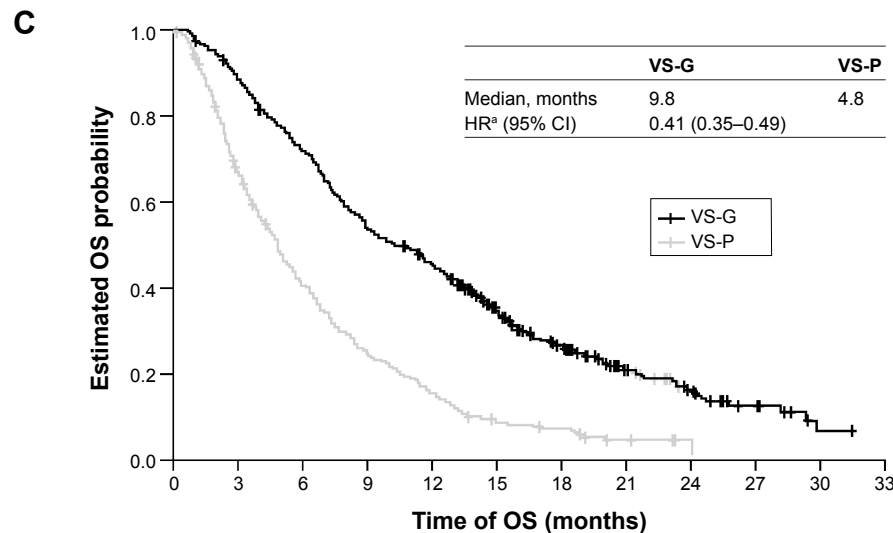
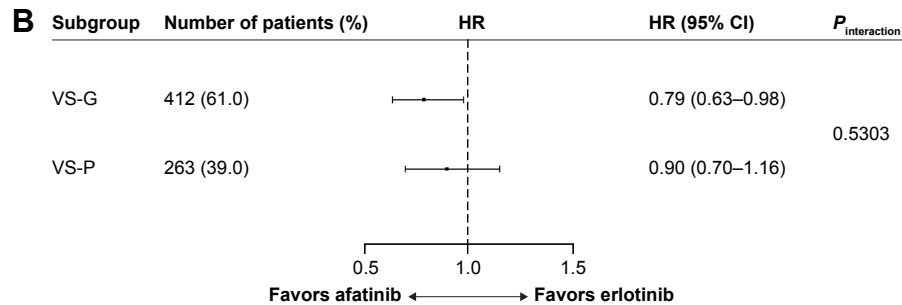
#### Immunotherapies

The overexpression of the immune checkpoint molecules, programmed cell death protein-1 (PD-1) and/or programmed



**Number at risk:**

	0	3	6	9	12	15	18	21	24	27	30	33
Afatinib VS-G	207	183	155	115	99	64	46	29	16	7	2	0
Afatinib VS-P	129	85	52	30	19	11	9	3	1	0	0	0
Erlotinib VS-G	205	179	137	101	81	52	30	13	6	3	0	0
Erlotinib VS-P	134	82	46	28	16	5	3	1	0	0	0	0



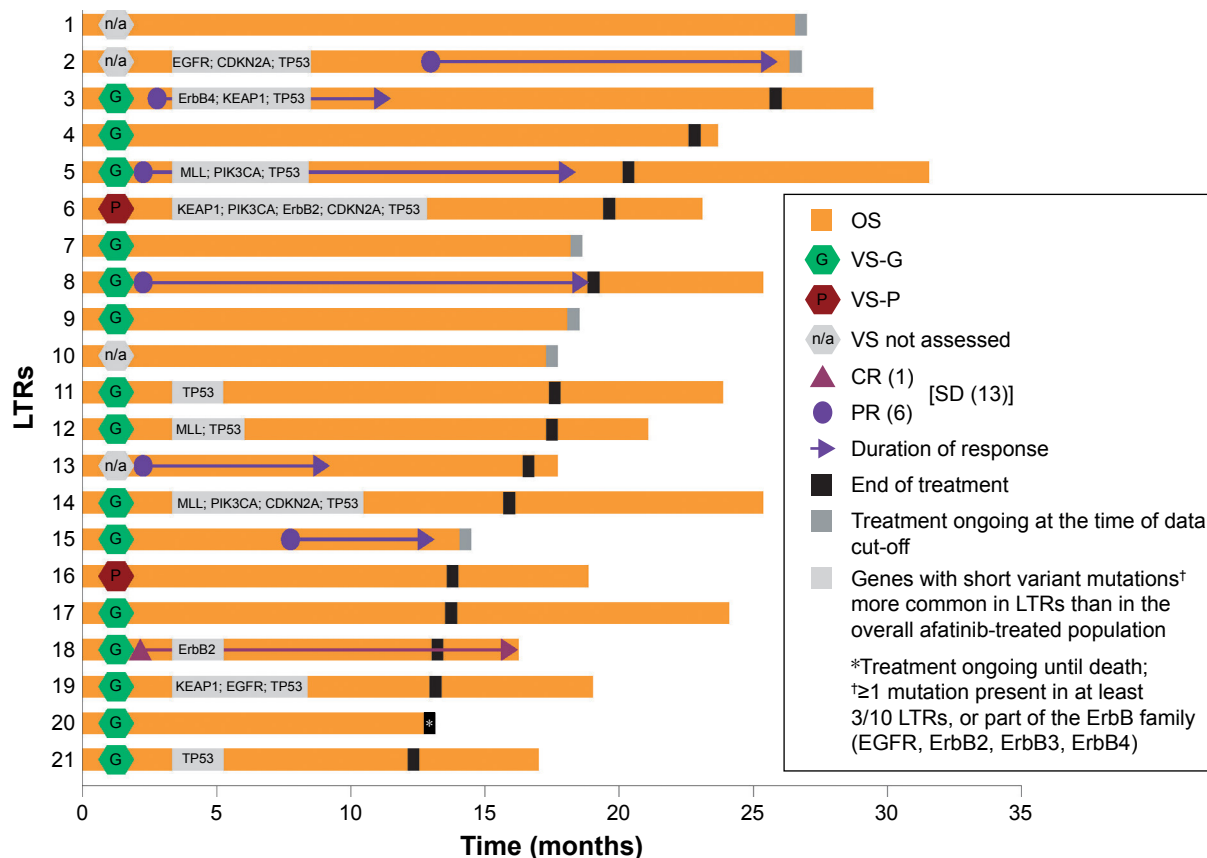
**Number at risk:**

	0	3	6	9	12	15	18	21	24	27	30	33
VS-G	412	362	292	216	180	116	76	42	22	10	2	0
VS-P	263	167	98	58	35	16	12	4	1	0	0	0

**Figure 6** LUX-Lung 8: relationship between VeriStrat classification, OS, and treatment group. **(A)** Kaplan–Meier curves of OS with afatinib vs erlotinib treatment and VS-G vs VS-P classification; **(B)** forest plot of OS by treatment group and VeriStrat classification; **(C)** relationship between VeriStrat classification and OS in all patients.

**Notes:** <sup>a</sup>Adjusted for treatment effect. This Figure was published in *Lung Cancer*. 2017;109:101–108, Gadgeel S, Goss G, Soria JC, et al. Evaluation of the VeriStrat® serum protein test in patients with advanced squamous cell carcinoma of the lung treated with second-line afatinib or erlotinib in the phase III LUX-Lung 8 study. Copyright © 2017 Elsevier.<sup>59</sup>

**Abbreviations:** OS, overall survival; VS-G, VeriStrat-good; VS-P, VeriStrat-poor.



**Figure 7** LUX-Lung 8: clinical outcomes, VeriStrat status, and biomarker frequency and biomarkers more commonly observed in LTRs than in the overall trial population.<sup>51</sup>  
**Abbreviations:** CR, complete response; LTRs, long-term responders; n/a, not assessed; OS, overall survival; PR, partial response; SD, stable disease; VS-G, VeriStrat-good; VS-P, VeriStrat-poor.

cell death ligand-1 (PD-L1), enables tumor cells to evade detection and destruction by the immune system.<sup>67</sup> Immune escape has been shown to be an important feature in the development of SqCC of the lung.<sup>68</sup>

The Food and Drug administration (FDA)-approved immune checkpoint inhibitors for SqCC of the lung are nivolumab and pembrolizumab (both PD-1 inhibitors) and atezolizumab (a PD-L1 inhibitor; Table 2; Figure 2A). Nivolumab was approved for patients with metastatic SqCC of the lung with progression during or after platinum-based chemotherapy based on data from the Phase III Checkmate-017 trial, in which nivolumab significantly improved OS and PFS compared with docetaxel (see Table 2 for further details).<sup>69</sup> Only 2% of the patients in this trial were Asian; therefore, conclusions cannot be drawn regarding the efficacy of nivolumab in the Asian population.<sup>69</sup> However, data from a small Phase II trial of nivolumab in 35 Japanese patients with advanced or recurrent SqCC of the lung who had progressed after platinum-containing chemotherapy indicate that nivolumab may be beneficial in Japanese patients, as OS (a secondary endpoint; 16.3 months; 95% CI=12.4–25.4) was consistent with the results of the Checkmate-017 trial in the Caucasian population.<sup>70</sup>

In the Phase II/III Keynote-010 trial<sup>71</sup> in previously treated PD-L1-positive, advanced NSCLC, OS was significantly longer for pembrolizumab than for docetaxel (Table 2).<sup>71</sup> Unlike nivolumab, pembrolizumab has not been evaluated specifically in patients with SqCC of the lung. However, a trend for clinical benefit was shown with pembrolizumab in the 21% of patients who had SqCC of the lung, although a subgroup analysis by ethnicity (21% were Asian) was not reported.<sup>71</sup> The addition of the first-line pembrolizumab to carboplatin plus paclitaxel or nab-paclitaxel was also shown to improve PFS and OS in patients with PD-L1-unselected, treatment-naïve, advanced squamous NSCLC, without adding substantial toxicity. In this study, 19% of patients were from East Asia, and the benefits of adding pembrolizumab to the chemotherapy regimen in terms of both PFS and OS appeared particularly marked in the East Asian subgroup.<sup>72</sup>

Atezolizumab gained FDA approval based on two randomized clinical trials, POPLAR<sup>73</sup> and OAK (Table 2).<sup>74</sup> In the POPLAR trial, 34% of patients had squamous histology, and a similar improvement in OS was observed in patients with squamous (HR =0.80, 95% CI=0.49–1.30) and nonsquamous histology (HR =0.69, 95% CI =0.47–1.01).<sup>73</sup>

In the Phase III OAK trial, 26% of the study population had SqCC of the lung.<sup>74</sup> A similar improvement in OS was observed in patients with squamous (HR =0.73, 95% CI =0.54–0.98;  $P=0.0383$ ) and nonsquamous histology (HR =0.73, 95% CI =0.60–0.89;  $P=0.0015$ ).<sup>74</sup> While both the POPLAR and OAK trials had study centers in East Asia, the number of Chinese patients included was not disclosed.

The safety profile of immune checkpoint inhibitors is generally favorable; however, they can be associated with immune-related AEs. These include dermatological (eg, rash), gastrointestinal (GI) tract (eg, diarrhea, colitis), hepatic and endocrine AEs, and other less common but potentially life-threatening inflammatory events, such as pneumonitis.<sup>75</sup> Temporary immunosuppression with corticosteroids is often necessary and helps manage and reverse these AEs.<sup>75</sup> Infusion-related reactions can occur with intravenous (IV) administration of immune checkpoint inhibitors, which may make them unsuitable for use in elderly patients and difficult to use effectively in areas with poor medical infrastructure.

## Angiogenesis inhibitors

One of the key pathways that stimulate tumor angiogenesis involves the VEGFRs, which initiate signal cascades that trigger angiogenesis.<sup>76</sup> Ramucirumab is an anti-VEGFR-2 antibody that has been FDA-approved for NSCLC, including SqCC of the lung, when administered with docetaxel, based on superior efficacy shown in the Phase III REVEL trial (Table 2; Figure 2B).<sup>77</sup> A subgroup analysis conducted to assess outcomes in 89 East Asian patients, 35% of whom had SqCC of the lung, showed a trend for clinical benefit favoring the ramucirumab-containing regimen.<sup>78</sup> Due to the increased incidence of neutropenia and febrile neutropenia observed in East Asian patients, the starting dose of docetaxel was amended and reduced in 24 patients enrolled later into the trial.<sup>77,78</sup> Serious AEs related to the mechanism of action of ramucirumab include hemorrhage, GI perforation, and impaired wound healing.<sup>15</sup> As with immune checkpoint inhibitors, infusion-related reactions can occur with IV administration of anti-VEGFR inhibitors, so similar precautions and pre-medications are required.

Although these agents have been FDA-approved as the second-line treatment in patients with advanced SqCC of the lung, none of the pivotal trials included patients with SqCC of the lung from China and only the REVEL trial analyzed data from an Asian population. Consequently, there is a need for additional treatment options to improve the outcomes for patients with SqCC of the lung and also to investigate efficacy and tolerability particularly in Chinese patients.

## Future directions in the treatment of SqCC of the lung

### Global clinical trials of targeted therapies in SqCC of the lung

Key areas of the development of targeted therapies in SqCC of the lung include novel immunotherapies and expansion into the first-line treatment, novel combination regimens with immunotherapies, and agents against novel drug targets. Many of the ongoing clinical trials include centers in China (Table 3). The Keynote-407 trial of pembrolizumab plus paclitaxel in first-line SqCC of the lung includes Chinese study centers. Atezolizumab plus platinum-based chemotherapy is also being evaluated in advanced SqCC of the lung, one trial being in China. Other relevant studies in SqCC of the lung (not involving Chinese centers) include a trial of ramucirumab plus platinum-based chemotherapy in previously untreated NSCLC (including SqCC), a trial of afatinib plus pembrolizumab following the progression of SqCC during/after platinum-based therapy (not yet recruiting), and trials of the PD-L1 inhibitors, avelumab and durvalumab plus tremelimumab. Ipilimumab and tremelimumab (antibodies against CTLA-4) are also being evaluated. The results of a Phase II trial of ipilimumab plus paclitaxel and carboplatin suggested a greater clinical benefit in SqCC than in nonsquamous NSCLC;<sup>79</sup> this regimen is now being evaluated in Phase III trials, including study centers in China. A regimen comprising ipilimumab and nivolumab is also being evaluated (not in Chinese centers).

To the best of my knowledge, the only EGFR inhibitor in clinical trials specifically for the treatment of SqCC of the lung in China is nimotuzumab (NCT02577341). Nimotuzumab, which is approved for the treatment of head and neck SqCC in China, is being tested as the first-line and second-line treatments for SqCC of the lung in combination with chemoradiotherapy or chemotherapy. In addition, icotinib, a novel EGFR TKI developed in China, is currently being evaluated in a Phase II trial in China as a monotherapy for the treatment of patients with fully resected-stage IB NSCLC, including SqCC of the lung, harboring an EGFR mutation (NCT02264210).

Other genomic alterations that are therapeutic targets include *PIK3CA*, *FGFR*, and *DDR2*, which were identified by comprehensive genomic profiling SqCC of the lung.<sup>39,46</sup> Inhibitors of the proteins encoded by these genes are being investigated in early-phase clinical trials. For example, fibroblast growth factor receptor (FGFR)-1 inhibitors<sup>15</sup> show a potential activity in SqCC of the lung, with one of three patients with FGFR-expressing SqCC of the lung included

**Table 3** Targeted drugs for SqCC of the lung being investigated in clinical trials in China or including centers in China

Targeted drug	Target	In combination with	Phase	Setting	Locations	NCT number*
Atezolizumab	PD-L1	Platinum agent plus gemcitabine	III	Chemotherapy-naïve SqCC of the lung and nonsquamous	Global, including China	NCT02409342
Nimotuzumab	EGFR	Chemoradiotherapy	II	Unresectable locally advanced SqCC of the lung (first-line or previously treated)	China	NCT02577341
Nimotuzumab	EGFR	Gemcitabine and carboplatin	II	Unresectable locally advanced SqCC of the lung (first-line)	China	NCT02428764
Icotinib	EGFR	None	II	Resected-stage IB EGFR mutant NSCLC, including SqCC of the lung (first-line)	China	NCT02264210
Four novel target inhibitors (BYL719, INC280, LDK378, and MEK162)	PIK3CA; c-MET; ALK or ROS1; KRAS, NRAS, or BRAF	None	II	Advanced NSCLC, including SqCC of the lung; line of therapy unspecified	China	NCT02276027
Ipilimumab	CTLA-4	Paclitaxel and carboplatin	III	SqCC of the lung; line of therapy unspecified	Global, includes China	NCT01285609
Ipilimumab	CTLA-4	Paclitaxel and carboplatin	III	SqCC of the lung; line of therapy unspecified	Some European locations Korea, Singapore, and China	NCT02279732
Pembrolizumab	PD-1	Carboplatin and paclitaxel or nanoparticle albumin-bound paclitaxel (nab-paclitaxel)	III	SqCC of the lung (first-line)	China	NCT02775435

**Note:** \*Accessed from [ClinicalTrials.gov](http://ClinicalTrials.gov), September 2018.

**Abbreviations:** ALK, anaplastic lymphoma kinase; NCT, National Clinical Trial; NSCLC, non-small-cell lung cancer; PD-1, programmed death protein 1; PD-L1, programmed death ligand-1; SqCC, squamous cell carcinoma.

in a first-in-human trial achieving a partial response; FGFR1 is overexpressed in 10%–20% of SqCC.<sup>15,80</sup> In addition, phosphoinositide 3-kinase (PI3K) alpha inhibitors, such as BYL719, are also currently being clinically evaluated in SqCC of the lung (Table 3). The results of these trials are awaited with interest.

## Biomarker development for targeted therapies for SqCC of the lung

A further assessment of the use of predictive biomarkers will help facilitate decisions on second-line therapy. Both ErbB family mutations, especially ErbB2, and VS-G status seem to be particularly useful in identifying a patient group who demonstrates long-term response to afatinib. Indeed, there are two ongoing trials of afatinib in Asian patients with advanced NSCLC, one focusing on patients with EGFR mutations (NCT01953913) and the other on patients with ErbB2 mutations (NCT02597946). In addition, the US National Cancer

Institute–Molecular Analysis for Therapy Choice study of afatinib includes groups of patients with EGFR or ErbB2 activating mutations (NCT02465060). The results of these trials are also eagerly awaited.

An ongoing study, Lung-MAP,<sup>81</sup> conducted in the USA, is assessing the personalization of second-line therapy for patients with SqCC of the lung according to their tumor mutations. Based on their genetic characteristics, each patient will be assigned to the trial substudy, which will evaluate an investigational agent that is best matched to their tumor's genomic profile vs standard of care chemotherapy as the comparator. The investigational agents include the following: nivolumab plus ipilimumab; erlotinib plus rilotumumab (hepatocyte growth factor inhibitor); palbociclib (cyclin-dependent kinase inhibitor); AZD4547 (FGFR1 inhibitor); durvalumab; and tasisib (PI3K inhibitor; NCT02154490).

There is some evidence that PD-L1 expression is a predictive biomarker for PD-1 inhibitors.<sup>71</sup> Therefore, afatinib

may be a suitable treatment option for patients who do not overexpress PD-L1 but have ErbB family mutations.

## Chinese perspectives and conclusions

As lung cancer incidence and mortality continuously increase in China,<sup>1,2</sup> a consensus on optimal treatment strategies is urgently needed to ensure that patients receive the best possible care, which is in line with best practice elsewhere in the world.

Guidelines for the management of primary lung cancer in China were last published in 2015,<sup>10</sup> and since then, a number of targeted therapies have been approved for the treatment of SqCC of the lung, including necitumumab, pembrolizumab, nivolumab, ramucirumab, and afatinib.<sup>9</sup> The so-called “drug-lag” may be a factor contributing to the delayed availability of other new anticancer agents. In China, there is a large backlog of pending applications for both clinical trial registrations and drug approvals, which is thought to be a consequence of the complexity of the approval process, the volume of applications, and a lack of resource available to process these applications.<sup>82</sup> Whether the Chinese treatment guidelines should be updated immediately, or after other new anticancer agents that are available elsewhere have been approved for use in China, is a matter for debate.

As described above, the analyses of afatinib in a small number of Chinese patients suggest that improvements in long-term response<sup>50</sup> and patient-reported outcomes may be greater than that in Western populations.<sup>41,50,52</sup> Among different ethnic populations, pharmacoethnic differences induced by differences in environmental and local medical practices have been noted, in addition to pharmacogenomic differences, which may affect treatment response.<sup>19</sup> Therefore, factors related to patients’ ethnicity may affect response to anticancer agents in different populations. These include the following: environmental factors influencing bioavailability and metabolism, such as smoking frequency, alcohol or herbal medicine use, and/or variations in local dietary patterns; local factors such as differences in medical care preferences; ethnic-specific drug–drug interactions and variability of genetic polymorphisms in drug metabolizing enzymes and transporters; and ethnic-specific mutations in a drug’s receptor or target leading to a particular sensitivity or resistance to an individual drug.<sup>19</sup>

A number of specific challenges to effective cancer care in China have been identified, including disparities in health

care access, environmental contamination, and inherent traditional attitudes toward cancer.<sup>83</sup> While anticancer treatment cannot influence the latter two challenges, access to health care may be partly improved by the use of convenient anticancer therapies. As afatinib is available as oral tablets and in multiple strengths, it can be self-administered in an outpatient setting, with uncomplicated and effective tolerability-guided dose adjustments.<sup>14,84,85</sup> These attributes may help simplify cancer treatment for patients with limited access to medical infrastructure, such as those living in remote areas, and help overcome one of the many challenges to effective cancer care in China.<sup>83</sup>

None of the clinical trials leading to the global approval of nivolumab, pembrolizumab, atezolizumab, and ramucirumab for second-line treatment of SqCC of the lung included the analysis of data from Chinese patients, meaning that there is a paucity of data to guide treatment decisions in this patient group. By contrast, data are available on outcomes of Chinese patients from the LUX-Lung 8 trial, which led to the global approval of afatinib, including approval in China, in this setting. The manageable efficacy, safety, ease of administration, and QoL data with afatinib indicate that it is a valid treatment option for Chinese patients with advanced SqCC of the lung who have progressed on or after platinum-based chemotherapy. In addition, the findings of the biomarker analyses conducted on LUX-Lung 8 data indicate that clinicians should consider testing all patients, including Chinese patients, for ErbB family mutations and VS-G profile, as these may be useful as predictive biomarkers for afatinib in SqCC of the lung.

Expanding second-line treatment options necessitates the selection of the optimal treatment choice and sequence, and the data reported from the ongoing trials with novel targeted therapies and potential biomarkers that include Chinese patients will aid such management decisions.

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