Second-line Afatinib or Chemotherapy Following Immunochemotherapy for the Treatment of Metastatic, Squamous Cell Carcinoma of the Lung: Real-world Effectiveness and Safety From a Multisite Retrospective Chart Review in the USA

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Abstract

In this retrospective study, we identified 200 patients with squamous cell carcinoma of the lung who received first-line pembrolizumab plus chemotherapy, followed by afatinib (n = 99) or further chemotherapy (n = 101). Median time on treatment with afatinib (7.3 months) was encouraging with an absence of newly diagnosed immune-related adverse events, indicating that afatinib is a treatment option in this setting, following progression on immunochemotherapy.

Background: The ErbB family blocker, afatinib, is approved for patients with squamous cell carcinoma (SqCC) of the lung following platinum-doublet chemotherapy but has not been explored following immunochemotherapy. Here, we assessed the characteristics and outcomes of patients with SqCC of the lung who received second-line afatinib or chemotherapy after first-line pembrolizumab plus chemotherapy in a "real-world" setting. **Methods:** In this retrospective, multisite cohort study, community oncologists identified eligible patients and extracted data from electronic health records. Primary outcome measures were patient demographics and clinical characteristics, time on treatment, and incidence of severe immune-related adverse events (irAEs). **Results:** Two hundred patients were included: 99 received second-line afatinib and 101 received second-line chemotherapy. Median age was 68 and 66 years, respectively; 35% and 3% of patients had mixed histology tumors, and 39% and 5% of tumors were epidermal growth factor receptor (*EGFR*) mutation-positive (*EGFR*m$^+$). Median time on treatment was 7.3 months with afatinib (mixed histology/SqCC tumors: 8.1/5.8 months; *EGFR*m$^+$/*EGFR*m$^-$ tumors: 7.4/5.9 months) and 4.2 months with chemotherapy. Grade 3/4 irAEs were observed in 6 patients in the afatinib cohort (all had a prior grade 3/4 irAE during first-line therapy) and no patients in the chemotherapy cohort. The most common adverse drug reactions with afatinib were diarrhea (26%), rash (6%), stomatitis, fatigue, and nausea (5% each). **Conclusion:** Encouraging time on treatment, and absence of newly diagnosed irAEs, indicate that afatinib is a treatment option following immunochemotherapy in patients with SqCC of the lung, and is currently the only approved oral agent in this setting.

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Introduction

In recent years, the introduction of therapies that specifically target molecular drivers such as epidermal growth factor receptor (*EGFR*) mutations have revolutionized the treatment of non–small-cell lung cancer (NSCLC) with adenocarcinoma histology.[1] These therapies include first- (erlotinib, gefitinib), second- (afatinib, dacomitinib), and third-generation (osimertinib) EGFR tyrosine kinase inhibitors (TKIs), as well as agents targeting other molecular drivers such as *ALK*, *ROS1*, and *BRAF*.[2] However, progress in the treatment of squamous cell carcinoma (SqCC) of the lung has lagged behind owing to a high degree of molecular heterogeneity and a lack of predominant targetable mutations in SqCC tumors.[3,4] Currently, potential first-line options for SqCC of the lung include: pembrolizumab plus carboplatin and paclitaxel/nab-paclitaxel irrespective of programmed death ligand 1 (PD-L1) level[5-7];

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pembrolizumab monotherapy in patients with PD-L1 tumor proportion score (TPS) ≥ 1%;[5,8] nivolumab plus ipilimumab (PD-L1 TPS ≥1%)[9,10]; nivolumab plus ipilimumab and chemotherapy;[11] atezolizumab monotherapy in patients with high PD-L1 expression;[12] or combination chemotherapy.[13] Although the recent introduction of immune checkpoint inhibitors into routine clinical practice has improved outcomes in patients with SqCC of the lung, optimal second-line therapeutic strategies remain unclear, especially with immunotherapy moving into first-line in combination with chemotherapy. In patients who receive first-line immunotherapy, potential second-line options include docetaxel plus ramucirumab,[14] docetaxel monotherapy, gemcitabine monotherapy, or platinum-based chemotherapy (if not already received).[2,15]

At present, the only chemotherapy-free second-line option is the ErbB family blocker, afatinib, which was approved for the treatment of patients with metastatic SqCC of the lung progressing after platinum-based chemotherapy on the basis of the phase III LUX-Lung 8 trial.[16-18] In LUX-Lung 8, afatinib significantly improved progression-free survival (PFS) (median 2.4 vs. 1.9 months; hazard ratio [HR], 0.82 [95% confidence interval {CI}, 0.68-1.00]; $P = .0427$), and overall survival (OS) (median 7.9 vs. 6.8 months; HR, 0.81 [95% CI, 0.69-0.95]; $P = .0077$) versus the first-generation EGFR TKI, erlotinib, and was associated with a predictable and manageable tolerability profile and improved health-related quality of life. Despite the fact that *EGFR* mutations are considered rare (~5% of cases) in SqCC of the lung,[3] and a lack of prospective head-to-head data versus contemporary second-line treatment options, there is a biological rationale for considering total ErbB blockade with afatinib, at least for some patients. Mutations in the ErbB family of receptors may be present in approximately one-fifth of patients with SqCC of the lung.[19] Also, overexpression of EGFR (up to 80% of cases)[20] and other ErbB proteins has been observed.[21-24] Furthermore, ad hoc biomarker analysis of LUX-Lung 8 demonstrated encouraging outcomes in patients with *ErbB* mutations (median PFS: 4.9 months; median OS: 10.6 months).[19] These observations suggest that afatinib could be considered as a second-line treatment option, especially for patients with SqCC of the lung whose tumors have an ErbB family aberration, and it warrants investigation as a potential oral therapy following immunochemotherapy. Afatinib in the second- or third-line therapy setting is currently recognized in the European Society of Medical Oncology (ESMO),[2] but is not recommended as a treatment option for patients with relapsed/refractory SqCC NSCLC in the US NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)[25] and requires clinical validation.

In this study, we have undertaken a retrospective "real-world" analysis of the characteristics and clinical outcomes of 200 patients with advanced/metastatic SqCC of the lung who received first-line pembrolizumab plus chemotherapy, followed by afatinib or further chemotherapy. The aims were to assess (1) the demographics and clinical characteristics of these patients; (2) time on treatment; and (3) the incidence of severe immune-related adverse events (irAEs).

Methods

Study Design

This retrospective, noninterventional, multisite cohort study utilized existing data from the electronic medical records of patients with advanced or metastatic SqCC of the lung treated with first-line pembrolizumab in combination with platinum-doublet chemotherapy, followed by second-line afatinib or chemotherapy. Eligible patients were selected by US-based community oncologists/hematologists from the Cardinal Health Oncology Provider Extended Network (OPEN), who were invited to participate following a feasibility assessment. All providers were board-certified and had treated at least 2 patients with SqCC of the lung with first-line immunochemotherapy followed by afatinib since 2016. Each provider identified up to 10 consecutive patients. Providers abstracted data from existing electronic medical records completed during routine care into electronic case report forms (eCRFs). The eCRF was pretested for functionality and conformed to the rules and regulations of the Health Insurance Portability and Accountability Act (HIPAA) of 1996 governing the abstraction and storage of protected health information. The eCRFs were subsequently reviewed by Cardinal Health.

The study was conducted in accordance with the Guidelines for Good Pharmacoepidemiology Practices of the International Society for Pharmacoepidemiology (ISPE 2008), the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines, and with the ethical principles laid down in the Declaration of Helsinki. All data were de-identified; the study was approved and monitored by a central institutional review board, which provided exemption from obtaining informed consent.

All patients were aged ≥ 18 years, initiated first-line pembrolizumab and platinum-based combination chemotherapy after June 1, 2018, and subsequently discontinued first-line therapy. In addition, all patients had started second-line treatment with either afatinib or any chemotherapy at least 3 months prior to the date of data collection. Consequently, the maximum follow-up period for any patient was approximately 15 months. Patients were excluded if they had received pembrolizumab in combination with platinum-based chemotherapy as part of an interventional clinical trial.

Data Collection and Outcomes

Data extracted from patients' electronic medical records and captured by the study eCRF included demographic and clinical characteristics including tumor genetics where available (details of specific *EGFR* mutations were not collected), first- and second-line treatment, clinical outcomes (discontinuations, disease progression, death), and severe (grade ≥ 3) irAEs of special interest (pneumonitis, colitis, hepatitis, interstitial lung disease, indeterminate pulmonary event, or death). If prespecified severe irAEs were reported, providers were asked whether they occurred during treatment. These events had to have been documented as immune-mediated in real time by the primary oncologist and supported by radiologic and/or pathologic evidence. Adverse events (AEs) considered to be possibly immune-mediated but with alternative or mixed etiologies were termed "indeterminate irAEs."

Key outcome measures included patient demographic and clinical characteristics, time on second-line treatment, and incidence of irAEs of specific interest during second-line treatment. Adverse drug reactions (ADRs) experienced by patients receiving second-line afatinib, but not chemotherapy, were also captured. Subgroup analyses were conducted to evaluate outcomes in patients according

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to *EGFR* mutation status (positive or negative; both cohorts) and histology (squamous only or mixed; afatinib cohort only).

Statistical Analysis

The planned sample size of 200 patients (100 per cohort) was based on the number of potentially eligible patients identified during a feasibility assessment. A consideration when determining sample size was the ability of the study to measure time on second-line treatment and the precision of that point estimate, estimated from the findings of the LUX-Lung 8 trial. Based on the planned data collection period, it was anticipated that there would be sufficient patients for this measurement. As the study had no formal hypothesis tests or comparisons, no formal sample size/power analysis was conducted. No statistical comparisons were made between the 2 cohorts of patients.

Time on treatment (defined as the interval from the start of second-line treatment until discontinuation of second-line treatment for any reason, eg, toxicity, progression, death, patient choice) was determined using the Kaplan–Meier method, as was the median and 2-sided 95% CIs. Patients were censored on their last clinic visit date if reported as alive and still receiving therapy at the time of data collection. All other data were described using standard descriptive statistics.

Results

Patient and Disease Characteristics

Data collection occurred between May 8 and May 18, 2020, by 32 community oncologists in the United States (see Supplemental Table 1 in the online version at doi:10.1016/j.cllc.2021.02.006). In total, 200 patients were included: 99 patients who received second-line afatinib and 101 who received second-line chemotherapy (Table 1).

At initial diagnosis, most patients had stage IV disease (afatinib/chemotherapy: 80%/89%). The percentage of never, current, and former smokers was 12%, 16%, and 72%, respectively, in patients who subsequently received afatinib. The percentages were 0%, 19%, and 81%, respectively, in patients who subsequently received chemotherapy. All patients were diagnosed with SqCC of the lung. Approximately one-third of patients in the afatinib cohort had mixed histology. Only 3% of patients in the chemotherapy cohort had mixed histology. The distribution of ethnic backgrounds was similar across the 2 cohorts. The percentage of patients included from the Northeast was higher in the afatinib cohort than the chemotherapy cohort (46% and 12%, respectively). Conversely, the percentage of patients from the South was higher in the chemotherapy cohort than the afatinib cohort (53% and 14%, respectively).

First-line therapy for all patients consisted of pembrolizumab plus platinum-doublet chemotherapy. Almost all patients (99%) received pembrolizumab 200 mg every 3 weeks. Two patients, both of whom were treated with subsequent afatinib, received 400 mg pembrolizumab every 6 weeks. Median duration of first-line pembrolizumab therapy was 7.8 (interquartile range [IQR], 4.6-12.7) months in the afatinib cohort and 8.2 (IQR, 4.8-11.2) months in the chemotherapy cohort. The median number of cycles of first-line therapy received was 5 (range, 2-19) and 4 (range, 2-27), respectively.

Median age at initiation of second-line therapy was 68 years (IQR, 61-73) in the afatinib cohort and 66 years (IQR, 61-70) in the chemotherapy cohort (Table 1). The liver was the most common site of metastatic disease (66% and 68% in the afatinib and chemotherapy cohorts, respectively). Fourteen (14%) and 10 (10%) patients had brain metastases at the initiation of afatinib and chemotherapy, respectively. Ninety percent of patients in the afatinib cohort received the approved starting dose of 40 mg/day; 9% received < 40 mg/day. In the chemotherapy cohort, 34% of patients received docetaxel plus ramucirumab, 21% received docetaxel monotherapy, 33% received gemcitabine or gemcitabine-based regimens, 7% received paclitaxel or nab-paclitaxel, and 6% received other regimens (Table 2). Median time from discontinuation of first-line therapy to initiation of second-line therapy was 0.8 months (IQR, 0.6-1.5) in the afatinib cohort and 0.7 months (IQR, 0.5-1.0) in the chemotherapy cohort.

More patients in the afatinib cohort (69%) than the chemotherapy cohort (38%) were tested for *EGFR* mutations (Table 3). In the afatinib cohort, 71% of patients with mixed histology tumors and 22% with SqCC tumors were *EGFR* mutation-positive (*EGFR*m$^+$; Table 3). Forty-two percent of patients in the afatinib cohort were also tested for *HER2* (*ErbB2*) and/or *HER3* (*ErbB3*) and/or *HER4* (*ErbB4*) mutations. Four patients were positive (one each for *HER2, HER3,* and *HER4;* one patient had a *HER2* and a *HER3* mutation). All 4 of these patients were *EGFR* mutation-negative (*EGFR*m$^-$). Among patients who received second-line chemotherapy, 5 (5%) were found to have an *EGFR* mutation, and all 5 patients had squamous histology only. Twenty-eight percent of the chemotherapy cohort were tested for *HER2/3/4* mutations. One patient had a *HER2* mutation (who was *EGFR*m$^+$).

Treatment Outcomes

After a median follow-up of 4.1 months (IQR, 3.3-6.4) from the initiation of afatinib, 53 (54%) patients were still on treatment and 46 (46%) had discontinued. Of these patients, 9 (9%) had discontinued afatinib without further lines of therapy, 4 (4%) had initiated third-line therapy, and 33 (33%) were deceased at data cut-off. The reasons for discontinuation of afatinib were disease progression (n = 41), death during treatment (n = 2), AE (n = 2), and patient preference (n = 1).

In the chemotherapy cohort, after a median follow-up of 3.9 months from the initiation of second-line treatment (IQR, 2.9-4.9), 41 (41%) patients were still on treatment and 60 (59%) patients had discontinued. Of these patients, 9 (9%) had discontinued chemotherapy without further lines of therapy, 5 (5%) had initiated third-line therapy, and 46 (46%) were deceased at data cut-off. The reasons for discontinuation of chemotherapy were disease progression (n = 55), patient preference (n = 3), death during treatment (n = 1), and completion of scheduled duration of therapy (n = 1). The discontinuation rate was 38%, 73%, and 57% among patients who received docetaxel/ramucirumab, gemcitabine-based regimens, and docetaxel monotherapy, respectively.

Median time on treatment from initiation of second-line therapy was 7.3 months (95% CI, 5.2-8.1) in the afatinib cohort (Figure 1A). Median time on treatment was longer for patients with mixed histology (8.1 months [95% CI, 5.5-9.9]) compared

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Table 1 Baseline Demographic and Clinical Characteristics

	Second-Line Treatment	
	Afatinib (n = 99)	Chemotherapy (n = 101)
Age at initiation of second-line therapy median (IQR)	68 (61-73)	66 (61-70)
Male, n (%)	56 (57)	67 (66)
Smoking history, n		
Never	12 (12)	0
Current	16 (16)	19 (19)
Former	71 (72)	82 (81)
Ethnicity, n (%)		
White	59 (60)	73 (72)
Asian	6 (6)	1 (1)
Black/African American	30 (30)	23 (23)
Other	4 (4)	4 (4)
US region of residence		
Northeast	46 (46)	12 (12)
Midwest	8 (8)	12 (12)
South	14 (14)	54 (53)
West	31 (31)	23 (23)
ECOG PS at initiation of second-line therapy, n (%)		
0/1	45 (45)	50 (50)
≥ 2	54 (55)	51 (50)
Histology, n (%)		
Squamous cell only	64 (65)	98 (97)
Mixed histology	35 (35)	3 (3)
*EGFR*m$^+$, n (%)	39 (39)	5 (5)
Stage at initial diagnosis, n (%)		
I-IIIA	13 (13)	8 (8)
IIIB	7 (7)	3 (3)
IV	79 (80)	90 (89)
Sites of metastatic disease at initiation of second-line therapy, n (%)		
Liver	65 (66)	69 (68)
Contralateral lung nodule	51 (52)	43 (43)
Blood and bone marrow	41 (41)	47 (47)
Adrenal gland	26 (26)	48 (48)
Pleura (nodules, effusion)	24 (24)	21 (21)
Intra-abdominal lymph nodes	19 (19)	14 (14)
Brain	14 (14)	10 (10)
Most common comorbidities at initiation of second-line treatment, n (%)		
Any comorbidity	98 (99)	88 (87)
Hypertension	62 (63)	56 (55)
Chronic pulmonary disease	35 (35)	49 (49)
Cardiovascular disease	23 (23)	33 (33)
Depression	27 (27)	14 (14)
Diabetes without chronic complications	21 (21)	16 (16)
Patients with prior surgical resection, n (%)	8 (8)	4 (4)

(*continued on next page*)

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Table 1 (*continued*)

	Second-Line Treatment	
	Afatinib (n = 99)	Chemotherapy (n = 101)
Radiation therapy, n (%)		
First-line or prior	14 (14)	10 (10)
Second-line	12 (12)	9 (9)
PD-L1 expression level, n (%)		
< 1%	26 (26)	30 (30)
1% to 49%	55 (56)	54 (53)
> 50%	15 (15)	6 (6)
Not tested	3 (3)	11 (11)

Abbreviations: ECOG PS = Eastern Cooperative Oncology Group Performance Status; *EGFR* = epidermal growth factor receptor; *EGFR*m+ = *EGFR* mutation-positive; IQR = interquartile range; PD-L1 = programmed death ligand 1.

Table 2 Second-line Chemotherapy Regimens in the Chemotherapy Cohort (n = 101)

Second-Line Therapy Received, n (%)	
Bevacizumab/carboplatin/paclitaxel	1 (1)
Carboplatin/docetaxel	1 (1)
Carboplatin/gemcitabine	2 (2)
Cisplatin/gemcitabine	1 (1)
Docetaxel	21 (21)
Docetaxel/ramucirumab	34 (34)
Gemcitabine	24 (24)
Gemcitabine/docetaxel	3 (3)
Gemcitabine/vinorelbine	3 (3)
Nab-paclitaxel	6 (6)
Paclitaxel	1 (1)
Cisplatin/nab-paclitaxel	3 (3)
Necitumumab/cisplatin/gemcitabine	1 (1)

with those with squamous histology only (5.8 months [95% CI, 4.4-8.0]; Figure 1B). *EGFR*m$^+$ patients remained on afatinib longer than *EGFR*m$^-$ or *EGFR* status unknown patients (median 7.4 [95% CI, 5.6-8.6]; 5.9 [95% CI, 4.4-not reached {NR}] [Figure 1C]; and 4.3 months [95% CI, 3.1-8.0], respectively). All 4 patients in the *EGFR*m$^-$ group with one or more ErbB mutations remained on treatment at data cutoff. Time on treatment was < 4 months in each case. In the chemotherapy cohort, median time on treatment was 4.2 months (95% CI, 3.9-4.9; Figure 1D). Median time on docetaxel, docetaxel/ramucirumab, and gemcitabine-based regimens was 3.9 (95% CI, 2.9-NR), 5.2 (95% CI, 3.4-NR), and 4.8 months (95% CI, 3.2-5.6), respectively. Median time on treatment among the 33 patients known to be *EGFR*m$^-$ was 5.1 months (95% CI, 3.5-5.6). In patients with unknown *EGFR* status median time on treatment was 4.2 months (95% CI, 3.5-4.5).

Safety

In the afatinib group there were 18 grade 3/4 irAEs during first-line treatment with immunochemotherapy. However, only 6 (6%) patients went on to experience a grade 3/4 irAE while receiving

Table 3 Tumor Histology and Epidermal Growth Factor Receptor Mutation Status

	Histology		Total
	Squamous Cell	Mixed Histology	
Second-line afatinib, n (%)	64 (65)	35 (35)	99 (100)
EGFR testing status, n (%)			
Positive	14 (22)	25 (71)	39 (39)
Negative [a]	21 (33)	7 (20)	28 (28)
Not tested	28 (44)	3 (9)	31 (31)
Results not available	1 (2)	0	1 (1)
Second-line chemotherapy, n (%)	98 (97)	3 (3)	101 (100)
EGFR testing status, n (%)			
Positive [b]	5 (5)	0	5 (5)
Negative	32 (33)	1 (33)	33 (33)
Not tested	61 (62)	2 (67)	63 (62)

Abbreviations: *EGFR* = epidermal growth factor receptor.
[a] Three patients in the afatinib *EGFR* mutation-negative group had *HER2, HER3,* or *HER4* mutation-positive disease, and one patient had *HER2* and *HER3* mutation-positive disease.
[b] One patient in the chemotherapy *EGFR* mutation-positive group was also *HER2* mutation-positive.

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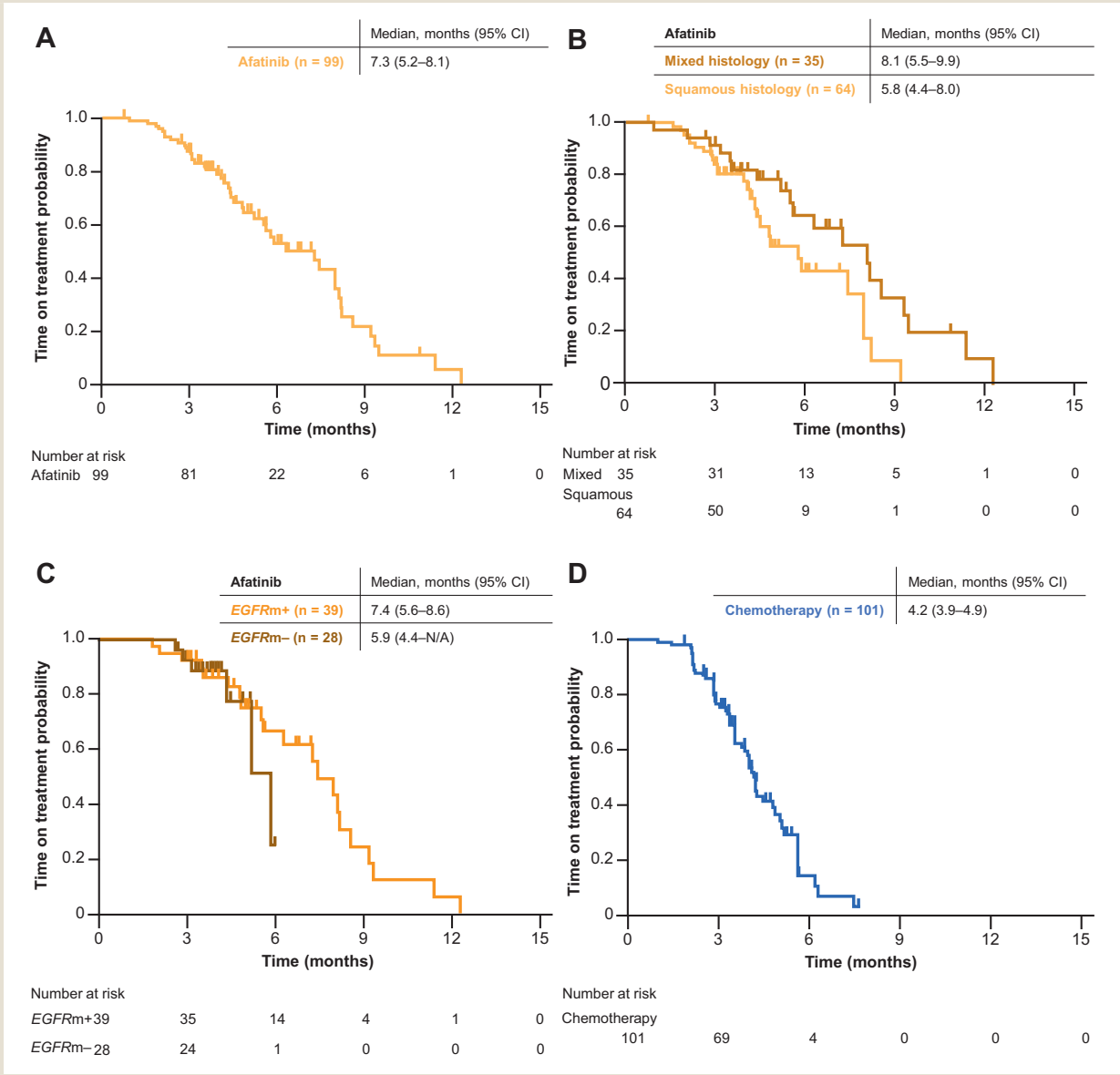
Figure 1 Time on treatment from initiation of second-line therapy in (A) afatinib cohort, (B) afatinib cohort: squamous and mixed histology, (C) afatinib cohort: *EGFR*m$^+$ and *EGFR*m$^-$, and (D) chemotherapy cohort. Abbreviations: CI = confidence interval; EGFR = epidermal growth factor receptor; *EGFR*m$^+$ = *EGFR* mutation-positive; *EGFR*m− = *EGFR* mutation-negative.



second-line afatinib. All of these patients experienced a grade 3/4 irAE during first-line therapy (Table 4). Only one of the 6 patients experienced a grade 4 irAE (a case of pneumonitis). This patient was *EGFR*m$^+$. Patients with irAEs were treated with steroids and none were hospitalized. One of the patients with an irAE was *EGFR*m$^+$ and the other 5 were *EGFR*m$^-$; all patients had squamous histology only. No irAEs were reported in patients who received second-line chemotherapy.

In total, 37 (37%) patients in the afatinib cohort reported an ADR (any grade). The most common were diarrhea (26%), skin rash (6%), fatigue, nausea, and stomatitis (5% each). Single cases of bloating/nausea, cheilitis, increased alanine aminotransferase, nausea/vomiting, neuropathy, and pruritis were also reported. Two on-treatment fatal events were reported in the afatinib cohort: cancer-related death and suicide.

Discussion

To the best of our knowledge this retrospective study provides the first available insight into the real-world use of afatinib or chemotherapy following first-line immunochemotherapy in patients with SqCC of the lung. The median time on treatment observed with second-line afatinib (7.3 months) was promis-

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Table 4 Immune-related Adverse Events of Special Interest in Patients Treated with Second-line Afatinib

Patient	Treatment Line	
	First-line Pembrolizumab Plus Platinum-based Chemotherapy	Second-line Afatinib
1	Grade 3 pneumonitis	Grade 4 pneumonitis
2	Grade 3 hepatitis	Grade 3 hepatitis
3	Grade 3 colitis	Grade 3 pneumonitis
4	Grade 3 pneumonitis	Grade 3 colitis
5	Grade 3 indeterminant pulmonary event	Grade 3 pneumonitis
6	Grade 3 pneumonitis	Grade 3 colitis

ing. In the chemotherapy cohort, median time on treatment was 4.2 months, ranging from 5.2 months in patients receiving docetaxel/ramucirumab and 3.9 months in patients receiving docetaxel monotherapy. Although the study was not powered to formally compare outcomes between cohorts, the time on treatment with afatinib appears to be encouraging in the context of other studies.[14] In the phase III REVEL trial, median time on treatment with second-line ramucirumab plus docetaxel and docetaxel was 15 and 12 weeks, respectively, in patients with NSCLC.[14] Although rigorous safety monitoring was not undertaken, available data suggest that the tolerability profile of afatinib was in keeping with previous studies, with diarrhea and rash the most common ADRs. Thirty-seven percent of patients reported an ADR and no serious newly diagnosed irAEs were observed with afatinib in this study. Few patients discontinued afatinib because of AEs. Overall, our findings suggest that afatinib could be a possible second-line chemotherapy-free treatment option in patients with SqCC of the lung regardless of histology following first-line immunochemotherapy, with the convenience of oral dosing. This is a particularly relevant finding with immune checkpoint inhibitors now being routinely incorporated into first-line treatment regimens.

A key objective of this study was to assess differences in the characteristics of patients who received second-line afatinib and those who received second-line chemotherapy. Notably, more patients had mixed histology and were *EGFR*m$^+$ in the afatinib cohort. Also, the afatinib cohort included 12 never smokers, whereas there were no never smokers in the chemotherapy cohort. There were also geographic differences; more patients from the Northeast United States received afatinib, and the majority from the South United States received chemotherapy. It is likely that these factors influenced the outcomes seen in each cohort. For example, treatment protocols, financial or insurance incentives, and/or molecular testing procedures may have differed across regions, thus impacting on clinical decisions. Other patient characteristics, including stage at diagnosis, Eastern Cooperative Oncology Group Performance Status (ECOG PS), PD-L1 expression levels, and median age were similar in both cohorts.

One particularly interesting observation in this study was that over one-third of patients in the afatinib cohort were reported to be *EGFR*m$^+$ yet did not receive an EGFR TKI as first-line therapy. *EGFR* mutations were especially common in patients with mixed histology tumors. Information on the subclassification of the mixed histology tumors was not collected in this study, so it is unknown how many patients had adenosquamous histology (which accounts for approximately 3% of all lung cancers) or other rarer variants such as sarcomatoid, mucoepidermoid, pleomorphic, blastoma, or carcinosarcoma characteristics.[26] Nevertheless, our findings seem to be consistent with previous studies that have demonstrated relatively high *EGFR* mutation rates in mixed histology lung tumors.[27] Such tumors can respond well to EGFR TKIs.[28] Accordingly, the results from this study indicate that patients with SqCC tumors with a mixed histology component should be tested for *EGFR* mutations at diagnosis, so that first-line EGFR TKIs could be considered when appropriate.

All patients with a grade 3/4 irAE during treatment with afatinib had previously had an irAE on first-line immunochemotherapy. This observation is encouraging, given previous findings in patients receiving PD-L1 blockade and an EGFR TKI, either concurrently or consecutively.[29-31] The study by Schoenfeld et al.,[31] in particular, indicated that severe irAEs were more common among patients treated with PD-L1 blockade followed by osimertinib than in those who received other treatment sequences. However, no irAEs were observed in patients who received afatinib or erlotinib following PD-L1 blockade, indicating that risk of irAEs varies with different EGFR TKIs and is not class related. In the current study, every patient who experienced a severe irAE on afatinib treatment also experienced an irAE during first-line treatment. Given the short amount of time between discontinuing immunochemotherapy and initiating afatinib, some patients may not have had time to fully recover from the initial occurrence. Nevertheless, our findings suggest that patients with a prior history of irAEs during first-line therapy may be at elevated risk of subsequent events, and would benefit from early, close monitoring or, potentially, alternative treatment. Conversely, patients without a prior history of severe irAEs could be at low risk of such events during second-line treatment with afatinib.

This study had several limitations. The narrow provider, patient, and treatment selection criteria resulted in a highly selected patient population that provided insight into only a small proportion of patient types and treatment approaches in NSCLC. Also, the study was likely influenced by recall bias and significant patient selection bias. However, to limit this possibility, providers were asked to select a maximum of 10 consecutive patients. Because participation was voluntary among the OPEN provider network, provider selection bias was also possible. It cannot be confirmed whether participating physicians accurately represent all oncologists across the United States. However, the 32 providers represented 32 unique sites of care, representing a reasonable cross-section of practice settings across the country. As with any retrospective analysis of eCRFs, confounding factors that could influence prescribing behavior/treatment decisions, such as income, were not captured. Moreover, source eCRF data were not independently verified. However, rigorous quality control and assessment procedures were implemented, including random duplicate data entry, to mitigate potential misclassification of exposures and outcomes.

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Another potential limitation, given the real-world nature of the study, was the risk that AE data were underreported or underdocumented, and that all severe irAEs were not verified. Furthermore, detailed histological information, and details of how histological diagnosis was made (ie, fine-needle aspirate, core biopsy, or surgical specimen), were unavailable and therefore confound interpretation of results in the mixed histology subgroup. Likewise, specific information on the type of *EGFR* mutation detected was not available. It is unknown what proportion were common mutations (Del19 or L858R), which are highly sensitive to EGFR TKIs, and what proportion were uncommon mutations (eg, exon 20 insertions), which are generally less sensitive to EGFR TKIs.[32] Ultimately, this information would be important when considering treatment options. Also, the censoring of 54% of afatinib-treated and 41% of chemotherapy-treated patients who were still receiving second-line treatment at data collection may have biased the results. With further follow-up, additional irAEs may have been detected, and median time on treatment may have been extended. Finally, it is likely that the underlying biology and nature of progression in individual patients could have influenced treatment decisions and may serve as greater predictors of outcome than the treatment itself. For example, patients with more indolent or slow progression may be more likely to be offered afatinib, whereas those with more fulminant progression will be treated with chemotherapy.

Conclusion

Despite the limitations of this retrospective cohort study, the data provide evidence of the effectiveness and safety of afatinib when given as second-line treatment following immunochemotherapy in routine clinical practice. These data support the use of afatinib in this setting as a valid, oral alternative to chemotherapy.

Clinical Practice Points

- What is already known about this subject?
  - First-line immunochemotherapy is standard-of-care for the treatment of SqCC of the lung.
  - Nonimmunotherapy options are required following progression on immunochemotherapy.
  - Currently, the only second-line nonimmunotherapy treatment options for SqCC of the lung are docetaxel ± ramucirumab, gemcitabine, platinum-based chemotherapy (if not already received), or afatinib.
  - Very little clinical data exist to inform choice of treatment following immunochemotherapy.
- What are the new findings?
  - To the best of our knowledge this is the only study, to date, to assess second-line treatment options following immunochemotherapy in SqCC of the lung.
  - We identified 200 patients who received first-line pembrolizumab plus chemotherapy, followed by afatinib (n = 99) or further chemotherapy (n = 101) in a 'real-world' clinical setting.
  - Median time on treatment in the afatinib cohort was encouraging (7.3 months).
  - Median time on treatment in the chemotherapy cohort was 4.2 months. The tolerability profile of afatinib was predictable; the most frequent ADRs were diarrhea, rash, stomatitis, fatigue, and nausea.
  - Importantly, no new irAEs were reported in patients treated with afatinib.
- How might it impact on clinical practice in the foreseeable future?
  - In an area of unmet clinical need, afatinib appears to be an effective and tolerable treatment option following immunochemotherapy in patients with SqCC of the lung.
  - As afatinib is the only approved oral agent following chemotherapy in patients with SqCC, physicians may consider it as an option after failure of immunochemotherapy.

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Credit Authorship Contribution Statement

Edward S. Kim: conceptualization, methodology, investigation, supervision, visualization, project administration, drafting the manuscript, final approval of manuscript; **Jonathan K. Kish:** conceptualization, data curation, formal analysis, methodology, drafting the manuscript, final approval of manuscript; **Agnieszka Cseh:** conceptualization, data curation, funding acquisition, methodology, supervision, visualization, drafting the manuscript, final approval of manuscript; **Barbara Moehring:** conceptualization, methodology, project administration, resources, drafting the manuscript, final approval of manuscript; **Wenbo Tang:** formal analysis, methodology, manuscript writing, final approval of manuscript; **Elizabeth Terlizzi:** conceptualization, methodology, project administration, supervision, validation, visualization, drafting of manuscript, manuscript writing, final approval the manuscript; **Janakiraman Subramanian:** conceptualization, investigation, methodology, supervision, validation, drafting the manuscript, manuscript writing, final approval of manuscript.

Disclosure

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Data sharing

The datasets generated and analyzed during the study are available on reasonable request.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cllc.2021.02.006.

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