Lung Cancer 166 (2022) 107–113

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

Phase II study of afatinib plus pembrolizumab in patients with squamous cell carcinoma of the lung following progression during or after first-line chemotherapy (LUX-Lung-IO)

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ARTICLE INFO

Keywords:
Carcinoma, Squamous Cell
Afatinib
Pembrolizumab

ABSTRACT

Introduction: Afatinib and pembrolizumab have separately shown survival benefit in patients with squamous cell carcinoma (SqCC) of the lung, and there is biological rationale for concurrent inhibition of the programmed death ligand-1 and epidermal growth factor receptor (EGFR) pathways in this patient population.
Materials and Methods: This open-label, single-arm study enrolled patients with SqCC of the lung who had progressed during/after first-line chemotherapy and comprised two parts: a safety run-in to establish the recommended phase II dose (RP2D; afatinib 40 mg or 30 mg once daily with pembrolizumab 200 mg every 3 weeks); and the main part assessing efficacy and safety of the RP2D. The primary endpoint was objective response rate (ORR); secondary endpoints included the RP2D, progression-free survival (PFS) and overall survival (OS).
Results: Twenty-four patients were treated in the safety run-in (afatinib 40 mg/30 mg cohorts: n = 12/12). Median age was 63.5 years; 79.2% of patients were male. All patients discontinued afatinib and pembrolizumab, most commonly due to disease progression (58.3% and 75.0%, respectively) or adverse events (AEs; 37.5% and 25.0%, respectively). The study was discontinued early after completion of the safety run-in, and no patients entered the main part. ORR was 12.5%; median PFS and OS were 13.1 and 29.3 weeks, respectively. All patients had ≥ 1 drug-related AE (grade ≥ 3: 45.8%).
Conclusion: While there were no new or unexpected safety findings, exploratory analysis of antitumor activity indicated limited efficacy with afatinib plus pembrolizumab in patients with SqCC of the lung who had progressed during/after first-line chemotherapy.
Clinical trial registration number: NCT03157089.

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https://doi.org/10.1016/j.lungcan.2022.01.023
Received 14 October 2021; Received in revised form 21 December 2021; Accepted 31 January 2022
Available online 3 February 2022

1. Introduction

Squamous cell carcinoma (SqCC) of the lung accounts for around 20% of lung cancers, is the second most common form of non-small-cell lung cancer (NSCLC), and is often diagnosed at an advanced stage of the disease [1]. Due to the high degree of molecular heterogeneity and lack of predominant targetable mutations in SqCCs [2,3], chemotherapy has historically been the first-line standard of care. In recent years, immunotherapy agents have also entered the SqCC treatment landscape, demonstrating robust outcomes. Immune checkpoint inhibitors (ICIs) emerged initially as second-line treatment based on overall survival (OS) improvements versus docetaxel after progression on platinum-based chemotherapy [4–11]. More recently, ICIs have also become established first-line therapies for SqCC of the lung, and options in this setting include: pembrolizumab with chemotherapy irrespective of programmed death ligand-1 (PD-L1) tumor proportion score (TPS) [7,8]; pembrolizumab monotherapy in patients with a PD-L1 TPS of $\geq$ 1% [7,8]; nivolumab monotherapy after prior chemotherapy [5,12]; nivolumab plus ipilimumab and platinum-based chemotherapy [12]; and atezolizumab or cemiplimab monotherapy (PD-L1 TPS $\geq$ 50% expression) [9,13].

While many patients with SqCC of the lung derive clinical benefit from ICI treatment, some patients show little or no benefit, underscoring the importance of additional therapeutic strategies rooted in scientific rationale. SqCC tumors are often characterized by epidermal growth factor receptor (EGFR) overexpression [14] and mutations in the ErbB family of receptors may be present in the tumors of approximately 20% of patients [15], suggesting a potential therapeutic vulnerability to ErbB inhibitors. The irreversible ErbB family blocker, afatinib, is an approved second-line treatment option for patients with SqCC of the lung after progression on platinum-based chemotherapy following results from the phase III LUX-Lung 8 trial [16–18]. Here, afatinib significantly improved OS and progression-free survival (PFS) versus erlotinib in this setting [18].

Several preclinical and early-phase clinical studies indicate potential synergy when combining EGFR tyrosine kinase inhibitors (TKIs), including afatinib, with ICIs in the treatment of SqCC of the lung. In cell-based models, afatinib enhanced T cell-mediated killing of tumor cells and demonstrated synergistic efficacy with an anti-PD-1 antibody in preclinical models independent of the activity of afatinib against the mutant EGFR [19]. One phase I study demonstrated manageable toxicity when combining an anti PD-1/PD-L1 antibody with an EGFR TKI [20]. Tolerability profiles can vary from study to study, and importantly, severe adverse events (AEs) have been witnessed, including liver function abnormalities necessitating drug discontinuation with gefitinib and durvalumab [21]. However, experiences with pembrolizumab plus afatinib in patients with head and neck SqCC suggest that such a regimen could be tolerable [22].

The aim of this phase II study was to assess the efficacy and safety of afatinib in combination with pembrolizumab in patients with SqCC of the lung who had previously progressed during or after first-line chemotherapy [23]. This trial was designed prior to the approval of front-line immunotherapy strategies as either single agent or in combination with chemotherapy in patients with advanced SqCC of the lung.

2. Material and methods

2.1. Study design and patients

The design of the LUX-Lung-IO/KEYNOTE 497 study has previously been described in detail [23]. LUX-Lung-IO was a phase II, non-randomized, open-label, single-arm study (NCT03157089) conducted at 13 sites in five countries (France, Korea, Spain, Turkey, and the USA). The trial design comprised two parts. The first was a 'safety run-in', during which a planned 12 patients would receive afatinib 40 mg once daily (QD) plus pembrolizumab 200 mg every 3 weeks (Q3W). On completion of the first 21-day cycle, the safety monitoring committee (SMC) would assess the overall safety profile and determine whether afatinib 40 mg plus pembrolizumab 200 mg could be considered as the recommended phase II dose (RP2D), to be assessed in the second 'main study part' of the trial. In the event of toxicities from the first safety run-in being deemed unacceptable by the SMC (defined as: dose-limiting toxicities [DLTs] during the first cycle of the safety run-in; the total safety profile during the safety run-in, with a particular focus on the permanent discontinuation rates due to AEs; and the recommendation of the Bayesian Logistic Regression Model [BLRM] analysis), a second run-in was planned. This would comprise patients from the first run-in who were still on treatment, and 12 additional patients who would receive a starting afatinib dose of 30 mg QD. Following completion of one cycle of treatment in at least 12 patients, the SMC would again assess the overall safety profile and determine whether a decision on the RP2D could be made.

The daily dose of afatinib could be adjusted following careful monitoring of patients' AEs, with dose reduction to 30 mg or 20 mg permitted for patients experiencing certain AEs as described in Supplemental Table 1. Treatment could continue for up to 35 cycles or until disease progression (radiological progression confirmed by another subsequent scan $\geq$ 4 weeks after an initial scan), unacceptable AEs, or other reasons for discontinuation.

All patients were aged $\geq$ 18 years with locally advanced or metastatic SqCC of the lung that had progressed during or after first-line platinum-based treatment. Patients had Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1, measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 and adequate organ function. Patients were not permitted to have any prior therapy with ICI or EGFR targeted therapy (except neoadjuvant therapy completed at least 12 months prior), or have had chemotherapy, non-EGFR targeted therapy or anticancer hormonal treatment within 2 weeks prior to study initiation (further key patient inclusion and exclusion criteria are detailed in Supplemental Table 2).

2.2. Study endpoints and assessments

The primary endpoint was objective response rate (ORR; complete response [CR] + partial response [PR]), determined by investigator assessment according to RECIST version 1.1. Secondary endpoints were the RP2D, disease control rate ([DCR] CR + PR + stable disease [SD]), PFS, OS, and tumor shrinkage.

The toxicities listed in Supplemental Table 3 were considered DLTs if judged by the investigator to be related to study drug administration. Safety was assessed based on the incidence and severity of AEs, graded according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. Assessment of efficacy by PD-L1 expression status and exploratory assessment of biomarkers related to immune status in tumor tissue (in relation to the emergence of treatment resistance) were also conducted. Safety and efficacy analyses were performed on the treated set.

2.3. Statistical analyses

This was an exploratory study, and no formal hypotheses were tested. Efficacy endpoints were summarized using descriptive statistics, and Kaplan–Meier estimates were calculated for PFS, OS, and duration of objective response (OR).

A BLRM with overdose control was applied to guide the dose confirmation part of the study and to assess the risk for excessive toxicity [24,25]. The distributions originally selected for each of the parameters of the BLRM were updated as DLT data were accumulated from the first treatment cycle of each safety run-in. The BLRM-recommended dose combination was the combination of afatinib with pembrolizumab (among those that fulfilled the overdose control) that had the highest posterior probability of the DLT rate falling in the target interval of

0.16–0.33. The toxicity probability calculated at each dose level guided the SMC's decision on the RP2D, alongside their review of other safety data from the study.

2.4. Ethical conduct of research

The trial was performed in accordance with the Declaration of Helsinki, the International Conference on Harmonisation Guideline for Good Clinical Practice, and applicable region-specific requirements, and was initiated only after approval by the respective institutional review boards/independent ethics committees at each center. All patients provided written informed consent.

3. Results

3.1. Patients, disposition and treatment exposure

Of 28 patients enrolled, 24 received at least one dose of study medication (afatinib plus pembrolizumab; Fig. 1). Twelve patients received an afatinib starting dose of 40 mg ('afatinib 40 mg' cohort) in the first run-in, and 12 patients received an afatinib starting dose of 30 mg ('afatinib 30 mg' cohort) in the second run-in. Baseline demographics overall and by dose cohort are shown in Table 1. Overall, median age was 63.5 years and most patients were male (79.2%, n = 19). Most patients were white (58.3%, n = 14) or Asian (20.8%, n = 5), five (20.8%) patients had ECOG PS 0, and 19 (79.2%) patients had ECOG PS 1. Baseline characteristics between dose cohorts were generally similar. All patients discontinued study medication. Reasons for discontinuation of afatinib and pembrolizumab were disease progression (58.3%, n = 14; and 75.0%, n = 18), AEs (37.5%, n = 9; and 25.0%, n = 6), and other (4.2%, n = 1; and 0%, n = 0), respectively (Fig. 1).

For the 12 patients in the afatinib 40 mg cohort, five patients (41.7%) permanently discontinued trial medication due to AEs (each reported once: pneumonitis, diarrhea, pneumonia, dermatitis acneiform, and pruritus). For the 12 patients in the afatinib 30 mg cohort, four patients (33.3%) permanently discontinued trial medication due to AEs (each reported once: pneumonitis, diarrhea, immune-mediated pneumonitis, vomiting, immune-mediated hepatitis, and asthenia).

After completion of the safety run-ins, and on the recommendation of the SMC, the study was terminated due to low response rates and high discontinuation rates; thus, no patients were entered into the main part of the trial. The median duration of treatment was 63 days (range: 21–402) and 107.5 days (range: 13–528) for patients treated with afatinib 40 mg and 30 mg, respectively. The proportion of patients who had at least one dose reduction of afatinib was 50.0% (n = 6) in the afatinib 40 mg cohort and 33.3% (n = 4) in the afatinib 30 mg cohort.

3.2. Anti-tumor activity

Overall, the ORR was 12.5% (n = 3; all PRs; duration of OR: 18.1, 26.4 and 58.3 weeks) and the DCR was 54.2% (n = 13; median duration: 26.3 weeks, 95% confidence interval [CI]: 15.7–45.3) across both dose levels. Median PFS was 13.1 weeks (95% CI: 6.0–21.7) and median OS was 29.3 weeks (95% CI: 20.6–46.3). In patients with PD-L1-negative tumors (TPS < 1%), median PFS (95% CI) was 8.6 weeks (4.9–17.9) and median OS was 26.0 weeks (15.0–30.4). In patients with PD-L1-positive tumors (TPS ≥ 1%), median PFS (95% CI) was 27.1 weeks (95% CI: 5.0–53.9), and median OS was 37.2 weeks (95% CI: 8.6–81.3). Of the 23 patients with evaluable post-baseline tumor assessments, 11 (45.8%) had reductions in tumor size (median change in tumor lesion size: 0%; range: –70.3–207.7%; Fig. 2).

3.3. Dose-limiting toxicities

During the first safety run-in (afatinib 40 mg), three patients (25.0%) had DLTs (Table 2). Of these, two patients had grade 3 DLTs that occurred during cycle 1 and were therefore considered for the BLRM analysis (pneumonitis [n = 1]; dermatitis acneiform and pruritus [n = 1]). Following review by the SMC, the second safety run-in was initiated (afatinib 30 mg), during which three patients had DLTs (Table 2). One patient had a DLT (grade 3 immune-mediated hepatitis) that occurred

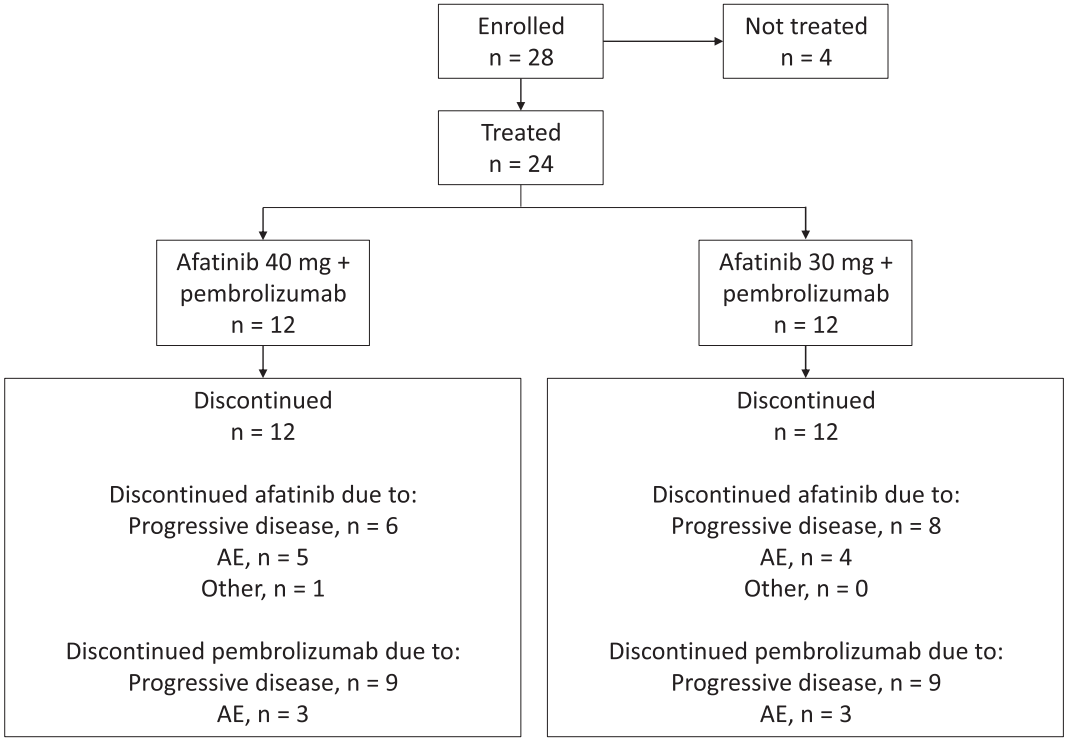

Fig. 1. Disposition of patients in the study. AE, adverse event.

Table 1
Patient baseline demographics.

	Afatinib 40 mg + pembrolizumab cohort (n = 12)	Afatinib 30 mg + pembrolizumab cohort (n = 12)	Total (N = 24)
Sex, n (%)			
Male	8 (66.7)	11 (91.7)	19 (79.2)
Female	4 (33.3)	1 (8.3)	5 (20.8)
Age, years (min, max)			
Median	62.0 (47.0, 81.0)	64.5 (52.0, 75.0)	63.5 (47.0, 81.0)
Race, n (%)			
Asian	5 (41.7)	0 (0.0)	5 (20.8)
White	6 (50.0)	8 (66.7)	14 (58.3)
Unknown	1 (8.3)	4 (33.3)	5 (20.8)
ECOG PS, n (%)			
0	3 (25.0)	2 (16.7)	5 (20.8)
1	9 (75.0)	10 (83.3)	19 (79.2)
Clinical stage at screening, n (%)			
IIIB	1 (8.3)	1 (8.3)	2 (8.3)
IV	0 (0.0)	2 (16.7)	2 (8.3)
IVA	6 (50.0)	1 (8.3)	7 (29.2)
IVB	5 (41.7)	4 (33.3)	9 (37.5)
IVC	0 (0.0)	4 (33.3)	4 (16.7)
Smoking status, n (%)			
Never	1 (8.3)	1 (8.3)	2 (8.3)
Current	5 (41.7)	2 (16.7)	7 (29.2)
Former	6 (50.0)	9 (75.0)	15 (62.5)
Number of previous chemotherapy lines, n (%)			
1	8 (66.7)	10 (83.3)	18 (75.0)
2	3 (25.0)	2 (16.7)	5 (20.8)
3	1 (8.3)	0 (0.0)	1 (4.2)

Abbreviation: ECOG PS, Eastern Cooperative Oncology Group performance status.

during cycle 1 and was considered for the BLRM analysis. BLRM analysis satisfied the overdose control criterion and the highest probability that the true DLT rate was within the toxicity interval of 0.16–0.33 occurred at the afatinib 40 mg dose level (p = 0.246; Supplemental Table 4).

3.4. Adverse events

All patients (100.0% [n = 24]) experienced at least one AE of any causality (grade ≥ 3: 70.8%, n = 17) and all patients also had at least one AE that was considered to be drug-related by the investigator (DRAE; grade ≥ 3: 45.8%, n = 11) (Table 3). In the afatinib 40 mg cohort, the most common grade ≥ 3 DRAE was increased amylase (16.7%, n = 2). In the afatinib 30 mg cohort the most common grade ≥ 3 DRAEs were diarrhea and vomiting (both 16.7%, n = 2).

Four patients in each cohort had serious drug-related AEs (40 mg cohort [33.3%, n = 4]: pneumonia, pneumonitis, vomiting, and pruritus, each reported once; 30 mg cohort [33.3%, n = 4]: immune-mediated pneumonitis, pneumonitis, diarrhea, vomiting, and immune-mediated hepatitis, each reported once, with the diarrhea and vomiting occurring in the same patient). In the 40 mg and 30 mg cohorts, five (41.7%) and four (33.3%) patients, respectively, had AEs leading to dose reduction; five (41.7%) and four (33.3%) patients, respectively, had AEs

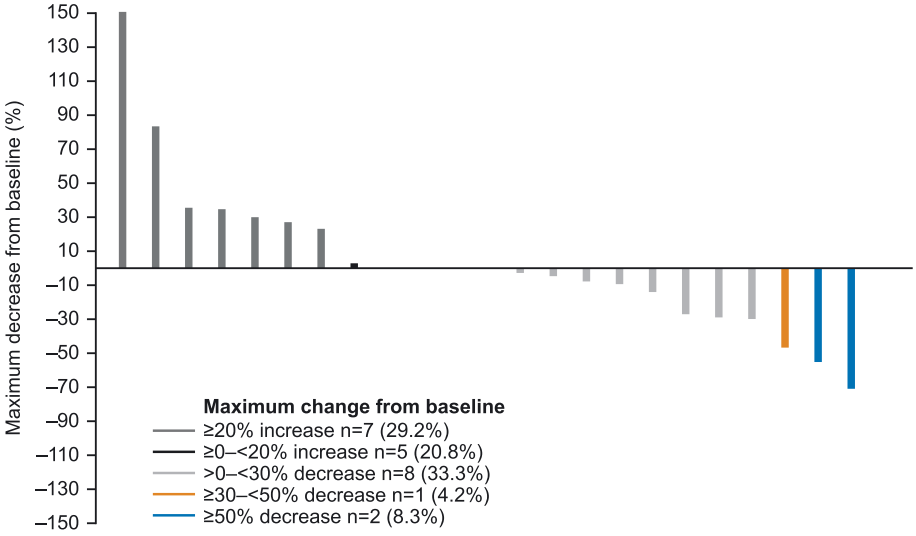

Fig. 2. Waterfall plot showing the maximum decrease in tumor size from baseline in evaluable patients (n = 23). Patients were categorized by increments of maximum tumor size change.

Table 2
DLTs during the safety run-ins.

Patient cohort	Preferred term	CTCAE grade	Onset in cycle 1
Afatinib 40 mg	Transaminases increased	4	No
Afatinib 40 mg	Pneumonitis	3	Yes
Afatinib 40 mg	Dermatitis acneiform	3	Yes
	Pruritus	3	Yes
Afatinib 30 mg	Immune-mediated pneumonitis	3	No
Afatinib 30 mg	Vomiting	3	No
Afatinib 30 mg	Immune-mediated hepatitis	3	Yes

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; DLT, dose-limiting toxicity.

leading to treatment discontinuation. Two patients had AEs leading to death: pneumonia that was considered to be drug-related (n = 1; 40 mg cohort) and acute coronary syndrome that was not considered to be drug-related (n = 1; 30 mg cohort).

4. Discussion

This phase II trial was the first clinical investigation of afatinib plus pembrolizumab in patients with locally advanced/metastatic SqCC of the lung following progression during or after platinum-based chemotherapy. Although the BLRM analysis of afatinib in combination with pembrolizumab that guided the dose confirmation part of the study satisfied the overdose control criterion, owing to the low response rates and also high treatment discontinuation rates among patients treated in the safety run-in stages, an RP2D was not established and the trial was discontinued early. Exploratory analysis indicated only limited efficacy with this treatment combination.

A key aim of this study was to assess whether the combination of afatinib and pembrolizumab could yield better efficacy outcomes compared with either agent alone in patients with SqCC of the lung who had progressed on prior chemotherapy. The primary endpoint in this study was ORR; the rate of 12.5% reported among all patients is higher than has previously been reported in patients who had progressed after platinum-based chemotherapy and received subsequent afatinib monotherapy (6% in LUX-Lung 8) [18], but lower than that reported for patients who received subsequent pembrolizumab monotherapy (18% for TPS ≥ 1% and ~ 30% for TPS ≥ 50% in KEYNOTE-010) [10]. However, differences in the trial populations, including NSCLC histologies, prevent any direct comparison. As expected, median PFS (27.1 and 8.6 weeks) and OS (37.2 and 26.0 weeks) were notably higher for patients with PD-L1-positive tumors versus PD-L1-negative tumors, in line with existing data supporting the use of pembrolizumab in patients with a PD-L1 TPS ≥ 1% [26].

The combination of afatinib with pembrolizumab in this study did not reveal new or unexpected safety signals. AEs that have previously been associated with afatinib and pembrolizumab monotherapy, including diarrhea, rash, stomatitis, fatigue, and nausea [10,16,18], were among the most frequently observed AEs in this study of combined treatment. While no new safety signals were witnessed, the combination of afatinib and pembrolizumab was not well tolerated, underscoring the potentiation of AEs when adding an EGFR TKI to an ICI; common immune-related AEs, including dermatitis, rash, and pneumonitis were observed in this study. Indeed, the SMC decision to terminate this study early was primarily based on the high rate of treatment discontinuation due to AEs (37.5% overall) and the high proportion of patients with grade ≥ 3 AEs (70.8%).

Despite promising preclinical data on EGFR TKI and ICI combination treatment [19] and the clear scientific rationale for their use, other clinical trials assessing this treatment combination in advanced NSCLC populations have also been discontinued early due to AEs. One arm of a phase Ib study investigating the combination of the third-generation EGFR TKI, osimertinib, with the anti-PD-L1 antibody, durvalumab, was halted due to the emergence of high rates of interstitial lung disease [27]. A study investigating pembrolizumab plus gefitinib as first-line therapy was discontinued early due to the observation of grade 3/4 liver toxicity in five of seven patients, and grade 3 immune-mediated hepatitis was observed in one patient treated with pembrolizumab plus erlotinib [28]. An increased risk of interstitial pneumonitis was observed in a database study of patients receiving nivolumab plus an EGFR TKI [29]. While these studies were conducted in patients with *EGFR* mutation-positive NSCLC, it is important to note that these AEs are considered class effects of EGFR TKI and ICI treatment [30,31], and may therefore also be expected in SqCC populations. Importantly, these studies were published after the current study was initiated (the first

Table 3
Summary of AEs.

	Afatinib 40 mg + pembrolizumab 200 mg (n = 12)		Afatinib 30 mg + pembrolizumab 200 mg (n = 12)		Total (N = 24)	
	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3
Any AE	12 (100.0)	8 (66.6)	12 (100.0)	9 (75.0)	24 (100.0)	17 (70.8)
SAEs	4 (33.3)	4 (33.3)	9 (75.0)	8 (66.6)	13 (54.2)	12 (50.0)
AEs leading to permanent discontinuation of trial medication[a]	5 (41.7)	3 (25.0)	4 (33.3)	3 (25.0)	9 (37.5)	6 (25.0)
AEs leading to dose reduction	5 (41.7)	0 (0.0)	4 (33.3)	2 (16.7)	9 (37.5)	2 (8.3)
Any DRAE[b]	12 (100.0)	6 (50.0)	12 (100.0)	5 (41.7)	24 (100.0)	11 (45.8)
Diarrhea	11 (91.7)	0 (0.0)	7 (58.3)	2 (16.7)	18 (75.0)	2 (8.3)
Vomiting	3 (25.0)	0 (0.0)	4 (33.3)	2 (16.7)	7 (29.2)	2 (8.3)
Dermatitis acneiform	2 (16.7)	1 (8.3)	5 (41.7)	0 (0.0)	7 (29.2)	1 (4.2)
Fatigue	3 (25.0)	0 (0.0)	3 (25.0)	0 (0.0)	6 (25.0)	0 (0.0)
Rash	5 (41.7)	0 (0.0)	1 (8.3)	0 (0.0)	6 (25.0)	0 (0.0)
Nausea	1 (8.3)	0 (0.0)	4 (33.3)	1 (8.3)	5 (20.8)	1 (4.2)
Stomatitis	4 (33.3)	0 (0.0)	1 (8.3)	0 (0.0)	5 (20.8)	1 (4.2)
Asthenia	2 (16.7)	0 (0.0)	2 (16.7)	0 (0.0)	5 (20.8)	0 (0.0)
Amylase increased	3 (25.0)	2 (16.7)	1 (8.3)	0 (0.0)	4 (16.7)	2 (8.3)
Decreased appetite	3 (25.0)	0 (0.0)	1 (8.3)	0 (0.0)	4 (16.7)	0 (0.0)
Hyperthyroidism	2 (16.7)	0 (0.0)	2 (16.7)	0 (0.0)	4 (16.7)	0 (0.0)
Anemia	1 (8.3)	0 (0.0)	2 (16.7)	1 (8.3)	3 (12.5)	1 (4.2)
Pruritus	2 (16.7)	1 (8.3)	1 (8.3)	0 (0.0)	3 (12.5)	1 (4.2)
Mucosal inflammation	1 (8.3)	0 (0.0)	2 (16.7)	0 (0.0)	3 (12.5)	0 (0.0)
Cheilitis	2 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	2 (8.3)	0 (0.0)
Hypothyroidism	0 (0.0)	0 (0.0)	2 (16.7)	0 (0.0)	2 (8.3)	0 (0.0)

[a] Defined as afatinib, pembrolizumab, or the combination of both;
[b] Investigator-assessed. *Note*: Two patients died during the on-treatment period of the study: pneumonia (afatinib 40 mg cohort; drug-related) and acute coronary syndrome (afatinib 30 mg; not drug-related). Abbreviations: AE, adverse event; DRAE, drug-related AE; SAE, serious AE.

patient was enrolled in November 2017) and as such, these safety signals were not as well characterized or anticipated at the time patients began to enroll in our study.

The study was halted given the toxicities described, combined with the changing landscape of first-line treatment of NSCLC [32,33]. SqCC of the lung is associated with a high degree of molecular heterogeneity, and ErbB mutations, found in over 20% of these tumors, may be biomarkers of interest [15]. In the LUX-Lung 8 study, pronounced activity was seen in patients with ErbB mutation-positive SqCC of the lung treated with afatinib, particularly in those with *HER2* or *HER4* mutations, rather than in those with *EGFR* mutations [15]. Indeed, activity has also been observed in pretreated patients with adenocarcinoma NSCLC harboring *HER2* mutations subsequently treated with afatinib [34].

5. Conclusion

Although there were no new or unexpected safety findings with afatinib plus pembrolizumab in this population of patients with SqCC of the lung, the exploratory and descriptive evaluation of antitumor activity indicated limited efficacy, as well as concern for potentiation of immune-related AEs with addition of an EGFR TKI. As the results did not support the continuation of the combination treatment in this clinical setting, the SMC recommended that the trial was terminated early. In the context of SqCC of the lung, afatinib remains an approved treatment option for patients with metastatic squamous NSCLC progressing after platinum-based chemotherapy, and pembrolizumab with/without chemotherapy (dependent on TPS) remains an important immunotherapy option in the first- or second-line setting. Future novel combination strategies will hopefully improve outcomes for patients with advanced SqCC of the lung.

Funding

This work was supported by Boehringer Ingelheim International GmbH and Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. Both study sponsors participated in the design of the study, the collection, analysis, and interpretation of the data, writing this article, and the decision to submit the article for publication.

CRediT authorship contribution statement

Benjamin Levy: Conceptualization, Formal analysis, Methodology, Supervision. **Fabrice Barlesi:** Investigation, Substantial contributions to the acquisition, analysis, or interpretation of data for the work, Validation. **Luis Paz-Ares:** Data curation, Investigation, Resources, Supervision. **Jaafar Bennouna:** Validation. **Mustafa Erman:** Investigation. **Enriqueta Felip:** Investigation, Resources, Validation. **Dolores Isla:** Investigation, Supervision, Validation. **Hye Ryun Kim:** Investigation. **Sang-We Kim:** Investigation, Resources. **Mustafa Özgüroğlu:** Data curation, Formal analysis, Investigation, Resources, Substantial contributions to the acquisition, analysis, or interpretation of data for the work, Visualization. **Delvys Rodríguez Abreu:** Investigation. **Abidemi Adeniji:** Data curation, Formal analysis, Methodology, Software, Validation, Visualization. **Robert M. Lorence:** Drafting the manuscript, Formal analysis, Project administration. **Isabelle Voccia:** Investigation, Methodology, Supervision. **Michael J. Chisamore:** Conceptualization, Formal analysis, Investigation, Resources, Substantial contributions to the acquisition, analysis, or interpretation of data for the work. **Jonathan W. Riess:** Conceptualization, Investigation, Methodology, Supervision. All authors contributed towards drafting and/or writing of the manuscript, provided final approval of the manuscript and agree to be accountable for all aspects of the work, which includes ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The author(s) meet criteria for authorship as recommended by the International Committee of Medical Journal Editors (ICMJE).

Declaration of Competing Interest

Dr Levy reports support for the present manuscript from Boehringer Ingelheim (manuscript writing); consulting fees from AstraZeneca, Daiichi Sankyo, Takeda, Janssen, Genentech, Eli Lilly, Merck, Pfizer, Guardant, Bristol Myers Squibb. **Prof. Dr Barlesi** reports grants or contracts from Roche/Genentech, AstraZeneca/MedImmune, Bristol Myers Squibb, Pierre Fabre, Abbvie, Amgen, Bayer, Boehringer Ingelheim, Eisai, Lilly, Ipsen, Innate Pharma, Novartis, Merck Serono, MSD Oncology, Pfizer, Sanofi/Aventis, Takeda (recipient: institution); consulting fees from Roche/Genentech, Pfizer, Novartis, Pierre Fabre, Bristol Myers Squibb, AstraZeneca/MedImmune, Boehringer Ingelheim, Lilly, Merck Serono, MSD Oncology, Takeda, Bayer, Mirati Therapeutics (recipient: Prof. Dr Barlesi); payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Genentech/Roche, Pfizer, Pierre Fabre, AstraZeneca, Bristol Myers Squibb, Boehringer Ingelheim, Lilly, Novartis, Pierre Fabre, Merck Serono, MSD Oncology, Takeda, Bayer, Seattle Genetics, Mirati Therapeutics (recipient: Prof. Dr Barlesi); other financial or non-financial interests (travel, accommodations, expenses; recipient: Prof. Dr Barlesi) from Roche/Genentech, Bristol Myers Squibb, AstraZeneca/MedImmune, Merck Sharp & Dohme Oncology. **Dr Paz-Ares** reports grants or contracts from Merck Sharp & Dohme, AstraZeneca, Pfizer, Bristol Myers Squibb; consulting fees from Lilly, Merck Sharp & Dohme, Roche, Pharmamar, Merck, AstraZeneca, Novartis, Servier, Amgen, Pfizer, Ipsen, Sanofi, Bayer, Blueprint, Bristol Myers Squibb, Mirati; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from AstraZeneca, Janssen, Merck, Mirati, Sanofi; leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid, for Genomica and Altum sequency. **Prof. Bennouna** reports grants or contracts from AstraZeneca (recipient: institution); consulting fees from Bristol Myers Squibb, Merck Sharp & Dohme, AstraZeneca, Roche (recipient: Prof. Bennouna); payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Bristol Myers Squibb, Merck Sharp & Dohme, AstraZeneca, Roche, Servier, Bayer Amgen (recipient: Prof. Bennouna). **Prof. Dr Erman** reports grants or contracts from Pfizer, Merck Sharp & Dohme, Roche, Janssen, Novartis, Bristol Myers Squibb, Beigene, AstraZeneca, Merck, Abbvie, Lilly (recipient: institution); payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Pfizer, Merck Sharp & Dohme, Roche, Astellas, Janssen, Novartis, Gen Ilac, Nobel Ilac, DEVA, Bristol Myers Squibb, Takeda, AstraZeneca (recipient: institution); payment for expert testimony from DEVA, Abdi Ibrahim (recipient: institution); support for attending meetings and/or travel from Merck Sharp & Dohme, Astellas. **Dr Felip** reports payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Amgen, AstraZeneca, Bristol Myers Squibb, Eli Lilly, F. Hoffmann-La Roche, Janssen, Medscape, Merck Sharp & Dohme, Merck Serono, Peervoice, Pfizer, Springer, Touch Medical (recipient: Dr Felip); participation on a data safety monitoring board or advisory board for Amgen, AstraZeneca, Bayer, Beigene, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly, F. Hoffman-La Roche, Glaxo Smith Kline, Janssen, Medical Trends, Merck Sharp & Dohme, Merck Serono, Peptomyc, Pfizer, Puma, Regeneron, Sanofi, Syneos Health, Takeda (recipient: Dr Felip) and for Grífols as an independent member of the board. **Dr Isla** reports no potential conflict of interest. **Prof. Kim** reports no potential conflict of interest. **Dr Kim** reports no potential conflict of interest. **Dr Madelaine** reports no potential conflict of interest. **Dr Molinier** reports consulting fees for Merck Sharp & Dohme, AstraZeneca, Takeda, Novartis, Amgen. **Prof. Dr Özgüroğlu** reports no potential conflict of interest. **Dr Rodríguez Abreu** reports no potential conflict of interest. **Dr Adeniji** reports employment with M-Estimator LLC and consultancy for Boehringer Ingelheim. **Dr Lorence** reports employment with Boehringer Ingelheim. **Dr Voccia** reports employment with Boehringer Ingelheim. **Dr Chisamore** reports stock or stock options

from Merck & Co. Inc and being an employee of Merck & Co. Inc. **Dr Riess** reports grants or contracts from Boehringer Ingelheim (recipient: institution); consulting fees from Boehringer Ingelheim (unrelated to the manuscript but listed since sponsor of the study); and participation on a Data Safety Monitoring Board or Advisory Board for Boehringer Ingelheim.

Acknowledgements

The authors received no direct compensation related to the development of the manuscript. BI was given the opportunity to review the manuscript for medical and scientific accuracy as well as intellectual property considerations. Medical writing support for the development of this manuscript, under the direction of the authors, was provided by Steven Kirkham, PhD, of Ashfield MedComms, an Ashfield Health company, and funded by Boehringer Ingelheim.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.lungcan.2022.01.023.

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