Journal Pre-proofs



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)

Benjamin Levy, Fabrice Barlesi, Luis Paz-Ares, Jaafar Bennouna, Mustafa Erman, Enriqueta Felip, Dolores Isla, Hye Ryun Kim, Sang-We Kim, Jeannick Madelaine, Olivier Molinier, Mustafa Özgüroğlu, Delvys Rodríguez Abreu, Abidemi Adeniji, Robert M. Lorence, Isabelle Voccia, Michael J. Chisamore, Jonathan W. Riess

PII: S0169-5002(22)00038-1
DOI: https://doi.org/10.1016/j.lungcan.2022.01.023
Reference: LUNG 6923

To appear in: *Lung Cancer*

Received Date: 14 October 2021
Revised Date: 21 December 2021
Accepted Date: 31 January 2022

Please cite this article as: B. Levy, F. Barlesi, L. Paz-Ares, J. Bennouna, M. Erman, E. Felip, D. Isla, H. Ryun Kim, S-W. Kim, J. Madelaine, O. Molinier, M. Özgüroğlu, D. Rodríguez Abreu, A. Adeniji, R.M. Lorence, I. Voccia, M.J. Chisamore, J.W. Riess, 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), *Lung Cancer* (2022), doi: https://doi.org/10.1016/j.lungcan.2022.01.023

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2022 Published by Elsevier B.V.

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)

Benjamin Levy[a,*], Fabrice Barlesi[b], Luis Paz-Ares[c], Jaafar Bennouna[d], Mustafa Erman[e], Enriqueta Felip[f], Dolores Isla[g], Hye Ryun Kim[h], Sang-We Kim[i], Jeannick Madelaine[j], Olivier Molinier[k], Mustafa Özgüroğlu[l], Delvys Rodríguez Abreu[m], Abidemi Adeniji[n], Robert M. Lorence[n], Isabelle Voccia[o], Michael J. Chisamore[p], Jonathan W. Riess[q]

[a] *Johns Hopkins Sidney Kimmel Cancer Center at Sibley Memorial Hospital, Washington DC, USA*

[b] *Aix Marseille University, CNRS, INSERM, CRCM, Assistance Publique Hôpitaux de Marseille, Marseille, France; Gustave Roussy Cancer Campus, Villejuif, France*

[c] *Department of Medical Oncology, University Hospital 12 De Octubre, Madrid, Spain*

[d] *Department of Pneumology, Thoracic Oncology, University Hospital - Nantes, Nantes, France*

[e] *Department of Medical Oncology, Hacettepe University Cancer Institute, Ankara, Turkey*

[f] *Medical Oncology Department, Vall d'Hebron Hospital and Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain*

[g] *Department of Medical Oncology, University Hospital Lozano Blesa, Zaragoza, Spain*

[h] *Division of Medical Oncology, Department of Internal Medicine, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, South Korea*

[i] Department *of Oncology, Asan Medical Center, Seoul, South Korea*

[j] *Pulmonology Department, Caen University Hospital, Caen, France*

[k] *Pneumology Department, Hospital Center, Le Mans, France*

[l] *Department of Internal Medicine, Division of Medical Oncology, Cerrahpaşa Medical Faculty, Istanbul University-Cerrahpaşa, Istanbul, Turkey*

[m] *Department of Medical Oncology, Gran Canaria University Hospital, Las Palmas de Gran Canaria, Spain*

[n] *Boehringer Ingelheim Pharmaceuticals Inc., Ridgefield, CT, USA*

[o] *Boehringer Ingelheim Canada, Burlington, ON, Canada*

[p] *Merck & Co., Inc, Rahway, NJ, USA*

[q] *UC Davis Comprehensive Cancer Center, Sacramento, CA, USA*

***Corresponding author at:**

Benjamin Levy, MD

Medical Oncology, Sidney Kimmel Cancer Center at Sibley Memorial Hospital

5255 Loughboro Rd NW, Building B, First Floor, Washington, DC 20016.

Tel: 202-660-6500 ; Fax: 202-660-6501

Email: blevy11@jhmi.edu

Email addresses:

blevy11@jhmi.edu (B. Levy), fabrice.barlesi@gustaveroussy.fr (F. Barlesi), lpazaresr@seom.org (L. Paz-Ares), jaafar.bennouna@univ-nantes.fr (J. Bennouna), ermanm1968@gmail.com (M. Erman), efelip@vhio.net (E. Felip), lola.isla@gmail.com (D. Isla), nobelg@yuhs.ac (H.R. Kim), swkim@amc.seoul.kr (S-W. Kim), madelaine-j@chu-caen.fr (J. Madelaine), omolinier@ch-lemans.fr (O. Molinier), ozguroglu@gmail.com (M. Özgüroğlu), drodabr@gobiernodecanarias.org (D. Rodríguez Abreu), abidemi.adeniji@boehringer-ingelheim.com (A. Adeniji), robert.lorence.ext@boehringer-ingelheim.com (R.M. Lorence), isabelle.voccia@boehringer-ingelheim.com (I. Voccia), michael_chisamore@merck.com (M.J. Chisamore), jwriess@ucdavis.edu (J.W. Riess)

Highlights

- There is rationale for PD-L1 plus EGFR inhibition in patients with SqCC of the lung
- Patients with SqCC of the lung were treated with afatinib plus pembrolizumab

Journal Pre-proofs

- There were no new or unexpected safety findings, but limited efficacy was observed
- All patients discontinued treatment, and the study was discontinued early

Journal Pre-proofs

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.

Keywords: Carcinoma, Squamous Cell; Afatinib; Pembrolizumab

Clinical trial registration number: NCT03157089

Journal Pre-proofs

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 ≥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 ≥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 ≥4 weeks after an initial scan), unacceptable AEs, or other reasons for discontinuation.

All patients were aged ≥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 neo-adjuvant 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 pruritis). 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 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 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, a 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 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.

Journal Pre-proofs

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.

Author contributions

Benjamin Levy: Conceptualization, Methodology, Formal analysis, Supervision. **Fabrice Barlesi:** Validation, Investigation, Substantial contributions to the acquisition, analysis, or interpretation of data for the work. **Luis Paz-Ares:** Investigation, Resources, Data Curation, Supervision. **Jaafar Bennouna:** Validation. **Mustafa Erman:** Investigation. **Enriqueta Felip:** Validation, Investigation, Resources. **Dolores Isla:** Validation, Investigation, Supervision. **Hye Ryun Kim:** Investigation. **Sang-We Kim:** Investigation, Resources. **Mustafa Özgüroğlu:** Formal analysis, Investigation, Resources, Data Curation, Visualization, Substantial contributions to the acquisition, analysis, or interpretation of data for the work. **Delvys Rodríguez Abreu:** Investigation. **Abidemi Adeniji:** Methodology, Software, Validation, Formal analysis, Data Curation, Visualization. **Robert M. Lorence:** Formal analysis, Project administration, Drafting the manuscript. **Isabelle Voccia:** Methodology, Investigation, 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, Methodology, Investigation, 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).

Declarations 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.

Journal Pre-proofs

References

[1] W.D. Travis, Pathology of lung cancer, Clin. Chest. Med. 32 (4) (2011) 669-692.

[2] P.S. Hammerman, et al., Comprehensive genomic characterization of squamous cell lung cancers, Nature 489 (7417) (2012) 519-525.

[3] A. Friedlaender, et al., Next generation sequencing and genetic alterations in squamous cell lung carcinoma: where are we today?, Front. Oncol. 9 (2019) 166.

[4] European Medicines Agency, Opdivo (nivolumab) summary of product characteristics. 2015. Accessed January 26, 2021, https://www.ema.europa.eu/en/documents/product-information/opdivo-epar-product-information_en.pdf.

[5] U.S. Food and Drug Administration, OPDIVO® (nivolumab). Highlights of Prescribing Information. 2014. Accessed January 26, 2021, https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/125554s070lbl.pdf.

[6] L. Horn, et al., Nivolumab versus docetaxel in previously treated patients with advanced non-small-cell lung cancer: two-year outcomes from two randomized, open-label, phase III trials (CheckMate 017 and CheckMate 057), J. Clin. Oncol. 35 (35) (2017) 3924-3933.

[7] European Medicines Agency, Keytruda (pembrolizumab) summary of product characteristics. 2015. Accessed January 26, 2021, https://www.ema.europa.eu/en/documents/product-information/keytruda-epar-product-information_en.pdf.

[8] U.S. Food and Drug Administration, KEYTRUDA® (pembrolizumab). Highlights of Prescribing Information. 2014. Accessed January 26, 2021, https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/125514s040lbl.pdf.

Journal Pre-proofs

[9] U.S. Food and Drug Administration, TECENTRIQ® (atezolizumab). Highlights of Prescribing Information. 2016. Accessed January 26, 2021, https://www.gene.com/download/pdf/tecentriq_prescribing.pdf.

[10] R.S. Herbst, et al., Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial, Lancet (London, England) 387 (10027) (2016) 1540-1550.

[11] A. Rittmeyer, et al., Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial, Lancet (London, England) 389 (10066) (2017) 255-265.

[12] European Medicines Agency, Opdivo (nivolumab) summary of product characteristics. 2020. Accessed July 19, 2021, https://www.ema.europa.eu/en/documents/product-information/opdivo-epar-product-information_en.pdf.

[13] U.S. Food and Drug Administration, LIBTAYO® (afatinib). Highlights of Prescribing Information. 2021. Accessed October 6, 2021, https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761097s007lbl.pdf.

[14] Y. Lee, et al., High EGFR gene copy number and skin rash as predictive markers for EGFR tyrosine kinase inhibitors in patients with advanced squamous cell lung carcinoma, Clin. Cancer Res. 18 (6) (2012) 1760-1768.

[15] G.D. Goss, 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 oncology 4 (9) (2018) 1189-1197.

[16] European Medicines Agency, Gilotrif (afatinib) summary of product characteristics. 2013. Accessed January 18, 2021, www.ema.europa.eu/en/documents/product-information/giotrif-epar-product-information_en.pdf.

[17] U.S. Food and Drug Administration, GILOTRIF® (afatinib). Highlights of Prescribing Information. 2013. Accessed January 18, 2021, https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/201292s014lbl.pdf.

[18] J.C. Soria, 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. 16 (8) (2015) 897-907.

[19] P.H. Lizotte, et al., A high-throughput immune-oncology screen identifies EGFR inhibitors as potent enhancers of antigen-specific cytotoxic T-lymphocyte tumor cell killing, Cancer Immunology Res. 6 (12) (2018) 1511-1523.

[20] S. Gettinger, et al., Nivolumab plus erlotinib in patients with EGFR-mutant advanced NSCLC, J. Thorac. Oncol. 13 (9) (2018) 1363-1372.

[21] B.C. Creelan, et al., A Phase 1 study of gefitinib combined with durvalumab in EGFR TKI-naive patients with EGFR mutation-positive locally advanced/metastatic non-small-cell lung cancer, Brit. J. Cancer 124 (2) (2021) 383-390.

[22] H.F. Kao, R.L. Hong, Pembrolizumab and afatinib for recurrent or metastatic head and neck squamous cell carcinoma, Ann. Oncol. 29 (2018) viii379.

[23] B. Levy, et al., Afatinib with pembrolizumab for treatment of patients with locally advanced/metastatic squamous cell carcinoma of the lung: the LUX-Lung IO/KEYNOTE 497 study protocol, Clin. Lung Cancer 20 (3) (2019) e407-e412.

[24] B. Neuenschwander, et al., Critical aspects of the Bayesian approach to phase I cancer trials, Stat. Med. 27 (13) (2008) 2420-2439.

[25] J. Babb, et al., Cancer phase I clinical trials: efficient dose escalation with overdose control, Stat. Med. 17 (10) (1998) 1103-1120.

[26] T.S.K. Mok, et al., Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial, Lancet (London, England) 393 (10183) (2019) 1819-1830.

[27] G.R. Oxnard, et al., TATTON: a multi-arm, phase Ib trial of osimertinib combined with selumetinib, savolitinib, or durvalumab in EGFR-mutant lung cancer, Ann. Oncol. 31 (4) (2020) 507-516.

[28] J.C. Yang, et al., Pembrolizumab in combination with erlotinib or gefitinib as first-line therapy for advanced NSCLC with sensitizing EGFR mutation, J. Thorac. Oncol. 14 (3) (2019) 553-559.

[29] Y. Oshima, et al., EGFR-TKI-associated interstitial pneumonitis in nivolumab-treated patients with non-small cell lung cancer, JAMA Oncol. 4 (8) (2018) 1112-1115.

[30] J.Y. Zhou, et al., Safety of EGFR-TKIs for EGFR mutation-positive non-small cell lung cancer, Expert Opin. Drug Saf. 19 (5) (2020) 589-599.

[31] F. Martins, et al., Adverse effects of immune-checkpoint inhibitors: epidemiology, management and surveillance, Nat. Rev. Clin. Oncol. 16 (9) (2019) 563-580.

[32] M. Reck, et al., Pembrolizumab versus chemotherapy for PD-L1–positive non–small-cell lung cancer, N. Engl. J. Med. 375 (19) (2016) 1823-1833.

[33] L. Paz-Ares, et al., Pembrolizumab plus chemotherapy for squamous non-small-cell lung cancer, N. Engl. J. Med. 379 (21) (2018) 2040-2051.

[34] J. De Grève, et al., Phase II study of afatinib, an irreversible ErbB family blocker, in demographically and genotypically defined lung adenocarcinoma, Lung cancer (Amsterdam, Netherlands) 88 (1) (2015) 63-69.

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 (%)			

Journal Pre-proofs

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.

Journal Pre-proofs

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.

Journal Pre-proofs

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)

Journal Pre-proofs

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.

Journal Pre-proofs

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

Journal Pre-proofs

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.

Highlights

- There is rationale for PD-L1 plus EGFR inhibition in patients with SqCC of the lung
- Patients with SqCC of the lung were treated with afatinib plus pembrolizumab
- There were no new or unexpected safety findings, but limited efficacy was observed
- All patients discontinued treatment, and the study was discontinued early

ICMJE DISCLOSURE FORM

Date: 4 June 2021

Your Name: Abidemi Adeniji

Manuscript Title: 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)

Manuscript number (if known): N/A

In the interest of transparency, we ask you to disclose all relationships/activities/interests listed below that are related to the content of your manuscript. "Related" means any relation with for-profit or not-for-profit third parties whose interests may be affected by the content of the manuscript. Disclosure represents a commitment to transparency and does not necessarily indicate a bias. If you are in doubt about whether to list a relationship/activity/interest, it is preferable that you do so.

The following questions apply to the author's relationships/activities/interests as they relate to the current manuscript only.

The author's relationships/activities/interests should be defined broadly. For example, if your manuscript pertains to the epidemiology of hypertension, you should declare all relationships with manufacturers of antihypertensive medication, even if that medication is not mentioned in the manuscript.

Journal Pre-proofs

In item #1 below, report all support for the work reported in this manuscript without time limit. For all other items, the time frame for disclosure is the past 36 months.

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
Time frame: Since the initial planning of the work			
1	All support for the present manuscript (e.g., funding, provision of study materials, medical writing, article processing charges, etc.) No time limit for this item.	_X_ None	
Time frame: past 36 months			
2	Grants or contracts from any entity (if not indicated in item #1 above).	_X_ None	
3	Royalties or licenses	_X_ None	
4	Consulting fees	Boehringer Ingelheim	Consultant
5	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	_X_ None	
6	Payment for expert testimony	_X_ None	
7	Support for attending meetings and/or travel	_X_ None	
8	Patents planned, issued or pending	_X_ None	
9	Participation on a Data Safety Monitoring Board or Advisory Board	_X_ None	
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	_X_ None	
11	Stock or stock options	_X_ None	

12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	_X_ None	
13	Other financial or non-financial interests	M-Estimator LLC	Employment

Please place an "X" next to the following statement to indicate your agreement:

_X_ I certify that I have answered every question and have not altered the wording of any of the questions on this form.

ICMJE DISCLOSURE FORM

Date: 3 June 2021

Your Name: Fabrice Barlesi

Manuscript Title: 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)

Manuscript number (if known): N/A

In the interest of transparency, we ask you to disclose all relationships/activities/interests listed below that are related to the content of your manuscript. "Related" means any relation with for-profit or not-for-profit third parties whose interests may be affected by the content of the manuscript. Disclosure represents a commitment to transparency and does not necessarily indicate a bias. If you are in doubt about whether to list a relationship/activity/interest, it is preferable that you do so.

The following questions apply to the author's relationships/activities/interests as they relate to the current manuscript only.

The author's relationships/activities/interests should be defined broadly. For example, if your manuscript pertains

to the epidemiology of hypertension, you should declare all relationships with manufacturers of antihypertensive medication, even if that medication is not mentioned in the manuscript.

In item #1 below, report all support for the work reported in this manuscript without time limit. For all other items, the time frame for disclosure is the past 36 months.

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
Time frame: Since the initial planning of the work			
1	All support for the present manuscript (e.g., funding, provision of study materials, medical writing, article processing charges, etc.) No time limit for this item.	_X___None	
Time frame: past 36 months			
2	Grants or contracts from any entity (if not indicated in item #1 above).	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: my institution
3	Royalties or licenses	_X___None	
4	Consulting fees	Roche/Genentech, Pfizer, Novartis, Pierre Fabre, Bristol-Myers Squibb, AstraZeneca/MedImmune, Boehringer Ingelheim, Lilly, Merck Serono, MSD Oncology, Takeda, Bayer, Mirati Therapeutics	Recipient: me
5	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	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: me
6	Payment for expert testimony	_X___None	
7	Support for attending meetings and/or travel	_X___None	

Journal Pre-proofs

8	Patents planned, issued or pending	_X___None	
9	Participation on a Data Safety Monitoring Board or Advisory Board	_X___None	
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	_X___None	
11	Stock or stock options	_X___None	
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	_X___None	
13	Other financial or non-financial interests	Roche/Genentech, Bristol-Myers Squibb, AstraZeneca/MedImmune, MSD Oncology	Travel, Accommodations, Expenses; Recipient: me

Please place an "X" next to the following statement to indicate your agreement:

_X_ I certify that I have answered every question and have not altered the wording of any of the questions on this form.

ICMJE DISCLOSURE FORM

Date: 4 June 2021

Your Name: Jaafar Bennouna

Manuscript Title: 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)

Manuscript number (if known): N/A

In the interest of transparency, we ask you to disclose all relationships/activities/interests listed below that are related to the content of your manuscript. "Related" means any relation with for-profit or not-for-profit third parties whose interests may be affected by the content of the manuscript. Disclosure represents a commitment

to transparency and does not necessarily indicate a bias. If you are in doubt about whether to list a relationship/activity/interest, it is preferable that you do so.

The following questions apply to the author's relationships/activities/interests as they relate to the current manuscript only.

The author's relationships/activities/interests should be defined broadly. For example, if your manuscript pertains to the epidemiology of hypertension, you should declare all relationships with manufacturers of antihypertensive medication, even if that medication is not mentioned in the manuscript.

In item #1 below, report all support for the work reported in this manuscript without time limit. For all other items, the time frame for disclosure is the past 36 months.

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
Time frame: Since the initial planning of the work			
1	All support for the present manuscript (e.g., funding, provision of study materials, medical writing, article processing charges, etc.) **No time limit for this item.**	None	
Time frame: past 36 months			
2	Grants or contracts from any entity (if not indicated in item #1 above).	AstraZeneca	Recipient: my institution
3	Royalties or licenses	None	
4	Consulting fees	Bristol Myers Squibb, MSD, AstraZeneca, Roche	Recipient: me
5	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	Bristol Myers Squibb, MSD, AstraZeneca, Roche, Servier, Bayer AMGEN	Recipient: me
6	Payment for expert testimony	None	

7	Support for attending meetings and/or travel	None	
8	Patents planned, issued or pending	None	
9	Participation on a Data Safety Monitoring Board or Advisory Board	None	
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	None	
11	Stock or stock options	None	
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	None	
13	Other financial or non-financial interests	None	

Please place an "X" next to the following statement to indicate your agreement:

_X_ I certify that I have answered every question and have not altered the wording of any of the questions on this form.

ICMJE DISCLOSURE FORM

Date: 3 June 2021

Your Name: Michael J. Chisamore

Manuscript Title: 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)

Manuscript number (if known): N/A

In the interest of transparency, we ask you to disclose all relationships/activities/interests listed below that are related to the content of your manuscript. "Related" means any relation with for-profit or not-for-profit third

Journal Pre-proofs

parties whose interests may be affected by the content of the manuscript. Disclosure represents a commitment to transparency and does not necessarily indicate a bias. If you are in doubt about whether to list a relationship/activity/interest, it is preferable that you do so.

The following questions apply to the author's relationships/activities/interests as they relate to the current manuscript only.

The author's relationships/activities/interests should be defined broadly. For example, if your manuscript pertains to the epidemiology of hypertension, you should declare all relationships with manufacturers of antihypertensive medication, even if that medication is not mentioned in the manuscript.

In item #1 below, report all support for the work reported in this manuscript without time limit. For all other items, the time frame for disclosure is the past 36 months.

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
Time frame: Since the initial planning of the work			
1	All support for the present manuscript (e.g., funding, provision of study materials, medical writing, article processing charges, etc.) **No time limit for this item.**	_X___None	
Time frame: past 36 months			
2	Grants or contracts from any entity (if not indicated in item #1 above).	__X__None	
3	Royalties or licenses	__X__None	
4	Consulting fees	_X___None	
5	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	__X__None	
6	Payment for expert testimony	__X__None	

7	Support for attending meetings and/or travel	_X___None	
8	Patents planned, issued or pending	_X___None	
9	Participation on a Data Safety Monitoring Board or Advisory Board	___X_None	
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	__X__None	
11	Stock or stock options	_Y__	Merck & Co. Inc
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	__X__None	
13	Other financial or non-financial interests	____Y__	Employee of Merck & Co. Inc

Please place an "X" next to the following statement to indicate your agreement:

_X_ I certify that I have answered every question and have not altered the wording of any of the questions on this form.

ICMJE DISCLOSURE FORM

Date: 3 June 2021

Your Name: Enriqueta Felip

Manuscript Title: 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)

Manuscript number (if known): N/A

In the interest of transparency, we ask you to disclose all relationships/activities/interests listed below that are related to the content of your manuscript. "Related" means any relation with for-profit or not-for-profit third

Journal Pre-proofs

parties whose interests may be affected by the content of the manuscript. Disclosure represents a commitment to transparency and does not necessarily indicate a bias. If you are in doubt about whether to list a relationship/activity/interest, it is preferable that you do so.

The following questions apply to the author's relationships/activities/interests as they relate to the current manuscript only.

The author's relationships/activities/interests should be defined broadly. For example, if your manuscript pertains to the epidemiology of hypertension, you should declare all relationships with manufacturers of antihypertensive medication, even if that medication is not mentioned in the manuscript.

In item #1 below, report all support for the work reported in this manuscript without time limit. For all other items, the time frame for disclosure is the past 36 months.

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
Time frame: Since the initial planning of the work			
1	All support for the present manuscript (e.g., funding, provision of study materials, medical writing, article processing charges, etc.) No time limit for this item.	_X_ None	
Time frame: past 36 months			
2	Grants or contracts from any entity (if not indicated in item #1 above).	_X_ None	
3	Royalties or licenses	_X_ None	
4	Consulting fees	_X_ None	
5	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	AMGEN, ASTRA ZENECA, BRISTOL-MYERS SQUIBB, ELI LILLY, F. HOFFMANN-LA ROCHE, JANSSEN MEDSCAPE, MERCK SHARP & DOHME, MERCK SERONO, PEERVOICE, PFIZER, SPRINGER,	Recipient: me

		TOUCH MEDICAL	
6	Payment for expert testimony	_X_ None	
7	Support for attending meetings and/or travel	_X_ None	
8	Patents planned, issued or pending	_X_ None	
9	Participation on a Data Safety Monitoring Board or Advisory Board	AMGEN, ASTRA ZENECA, 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: me
		GRÍFOLS	Independent Member of the Board
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	_X_ None	
11	Stock or stock options	_X_ None	
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	_X_ None	
13	Other financial or non-financial interests	_X_ None	

Please place an "X" next to the following statement to indicate your agreement:

_X_ I certify that I have answered every question and have not altered the wording of any of the questions on this form.

ICMJE DISCLOSURE FORM

Journal Pre-proofs

Journal Pre-proofs

Date: 7 June 2021

Your Name: Hye Ryun Kim

Manuscript Title: 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)

Manuscript number (if known): N/A

In the interest of transparency, we ask you to disclose all relationships/activities/interests listed below that are related to the content of your manuscript. "Related" means any relation with for-profit or not-for-profit third parties whose interests may be affected by the content of the manuscript. Disclosure represents a commitment to transparency and does not necessarily indicate a bias. If you are in doubt about whether to list a relationship/activity/interest, it is preferable that you do so.

The following questions apply to the author's relationships/activities/interests as they relate to the current manuscript only.

The author's relationships/activities/interests should be defined broadly. For example, if your manuscript pertains to the epidemiology of hypertension, you should declare all relationships with manufacturers of antihypertensive medication, even if that medication is not mentioned in the manuscript.

In item #1 below, report all support for the work reported in this manuscript without time limit. For all other items, the time frame for disclosure is the past 36 months.

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
Time frame: Since the initial planning of the work			
1	All support for the present manuscript (e.g., funding, provision of study materials, medical writing, article processing charges, etc.) **No time limit for this item.**	_X_ None	
Time frame: past 36 months			
2	Grants or contracts from any entity (if not indicated in item #1 above).	_X_ None	

3	Royalties or licenses	_X_ None	
4	Consulting fees	_X_ None	
5	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	_X_ None	
6	Payment for expert testimony	_X_ None	
7	Support for attending meetings and/or travel	_X_ None	
8	Patents planned, issued or pending	_X_ None	
9	Participation on a Data Safety Monitoring Board or Advisory Board	_X_ None	
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	_X_ None	
11	Stock or stock options	_X_ None	
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	_X_ None	
13	Other financial or non-financial interests	_X_ None	

Please place an "X" next to the following statement to indicate your agreement:

_X_ I certify that I have answered every question and have not altered the wording of any of the questions on this form.

ICMJE DISCLOSURE FORM

Journal Pre-proofs

Date: 3 June 2021

Your Name: Dolores Isla

Manuscript Title: 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)

Manuscript number (if known): N/A

In the interest of transparency, we ask you to disclose all relationships/activities/interests listed below that are related to the content of your manuscript. "Related" means any relation with for-profit or not-for-profit third parties whose interests may be affected by the content of the manuscript. Disclosure represents a commitment to transparency and does not necessarily indicate a bias. If you are in doubt about whether to list a relationship/activity/interest, it is preferable that you do so.

The following questions apply to the author's relationships/activities/interests as they relate to the current manuscript only.

The author's relationships/activities/interests should be defined broadly. For example, if your manuscript pertains to the epidemiology of hypertension, you should declare all relationships with manufacturers of antihypertensive medication, even if that medication is not mentioned in the manuscript.

In item #1 below, report all support for the work reported in this manuscript without time limit. For all other items, the time frame for disclosure is the past 36 months.

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
Time frame: Since the initial planning of the work			
1	All support for the present manuscript (e.g., funding, provision of study materials, medical writing, article processing charges, etc.) No time limit for this item.	_X___None	
Time frame: past 36 months			

2	Grants or contracts from any entity (if not indicated in item #1 above).	__X__None	
3	Royalties or licenses	__X__None	
4	Consulting fees	_X___None	
5	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	__X__None	
6	Payment for expert testimony	__X__None	
7	Support for attending meetings and/or travel	_X___None	
8	Patents planned, issued or pending	_X___None	
9	Participation on a Data Safety Monitoring Board or Advisory Board	___X_None	
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	__X__None	
11	Stock or stock options	_X___None	
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	__X__None	
13	Other financial or non-financial interests	_X___None	

Please place an "X" next to the following statement to indicate your agreement:

_X_ I certify that I have answered every question and have not altered the wording of any of the questions on this form.

Journal Pre-proofs

Journal Pre-proofs

ICMJE DISCLOSURE FORM

Date: 8 June 2021

Your Name: Madelaine Jeannick

Manuscript Title: 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)

Manuscript number (if known): N/A

In the interest of transparency, we ask you to disclose all relationships/activities/interests listed below that are related to the content of your manuscript. "Related" means any relation with for-profit or not-for-profit third parties whose interests may be affected by the content of the manuscript. Disclosure represents a commitment to transparency and does not necessarily indicate a bias. If you are in doubt about whether to list a relationship/activity/interest, it is preferable that you do so.

The following questions apply to the author's relationships/activities/interests as they relate to the current manuscript only.

The author's relationships/activities/interests should be defined broadly. For example, if your manuscript pertains to the epidemiology of hypertension, you should declare all relationships with manufacturers of antihypertensive medication, even if that medication is not mentioned in the manuscript.

In item #1 below, report all support for the work reported in this manuscript without time limit. For all other items, the time frame for disclosure is the past 36 months.

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
Time frame: Since the initial planning of the work			
1	All support for the present manuscript (e.g., funding, provision of study materials, medical writing, article processing charges, etc.) **No time limit for this item.**	_X_ None	
Time frame: past 36 months			

2	Grants or contracts from any entity (if not indicated in item #1 above).	_X_ None	
3	Royalties or licenses	_X_ None	
4	Consulting fees	_X_ None	
5	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	_X_ None	
6	Payment for expert testimony	_X_ None	
7	Support for attending meetings and/or travel	_X_ None	
8	Patents planned, issued or pending	_X_ None	
9	Participation on a Data Safety Monitoring Board or Advisory Board	_X_ None	
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	_X_ None	
11	Stock or stock options	_X_ None	
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	_X_ None	
13	Other financial or non-financial interests	_X_ None	

Please place an "X" next to the following statement to indicate your agreement:

_X_ I certify that I have answered every question and have not altered the wording of any of the questions on this form.

Journal Pre-proofs

ICMJE DISCLOSURE FORM

Date: 3 June 2021

Your Name: Benjamin Levy

Manuscript Title: 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)

Manuscript number (if known): N/A

In the interest of transparency, we ask you to disclose all relationships/activities/interests listed below that are related to the content of your manuscript. "Related" means any relation with for-profit or not-for-profit third parties whose interests may be affected by the content of the manuscript. Disclosure represents a commitment to transparency and does not necessarily indicate a bias. If you are in doubt about whether to list a relationship/activity/interest, it is preferable that you do so.

The following questions apply to the author's relationships/activities/interests as they relate to the current manuscript only.

The author's relationships/activities/interests should be defined broadly. For example, if your manuscript pertains to the epidemiology of hypertension, you should declare all relationships with manufacturers of antihypertensive medication, even if that medication is not mentioned in the manuscript.

In item #1 below, report all support for the work reported in this manuscript without time limit. For all other items, the time frame for disclosure is the past 36 months.

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
Time frame: Since the initial planning of the work			
1	All support for the present manuscript (e.g., funding, provision of study materials, medical writing, article processing charges, etc.) **No time limit for this item.**	Boehringer	Manuscript Writing
Time frame: past 36 months			

2	Grants or contracts from any entity (if not indicated in item #1 above).	_X_ None	
3	Royalties or licenses	_X_ None	
4	Consulting fees	AstraZeneca, Daiichi Sankyo, _Takeda, Janssen, Genentech, Eli Lilly, Merck, Pfizer, Guardant ,BMS	Consulting
5	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	_X_ None	
6	Payment for expert testimony	_X_ None	
7	Support for attending meetings and/or travel	_X_ None	
8	Patents planned, issued or pending	_X_ None	
9	Participation on a Data Safety Monitoring Board or Advisory Board	_X_ None	
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	_X_ None	
11	Stock or stock options	_X_ None	
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	_X_ None	
13	Other financial or non-financial interests	_X_ None	

Please place an "X" next to the following statement to indicate your agreement:

_X_ I certify that I have answered every question and have not altered the wording of any of the questions on this form.

Journal Pre-proofs

ICMJE DISCLOSURE FORM

Date: 4 June 2021

Your Name: Robert M. Lorence

Manuscript Title: 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)

Manuscript number (if known): N/A

In the interest of transparency, we ask you to disclose all relationships/activities/interests listed below that are related to the content of your manuscript. "Related" means any relation with for-profit or not-for-profit third parties whose interests may be affected by the content of the manuscript. Disclosure represents a commitment to transparency and does not necessarily indicate a bias. If you are in doubt about whether to list a relationship/activity/interest, it is preferable that you do so.

The following questions apply to the author's relationships/activities/interests as they relate to the current manuscript only.

The author's relationships/activities/interests should be defined broadly. For example, if your manuscript pertains to the epidemiology of hypertension, you should declare all relationships with manufacturers of antihypertensive medication, even if that medication is not mentioned in the manuscript.

In item #1 below, report all support for the work reported in this manuscript without time limit. For all other items, the time frame for disclosure is the past 36 months.

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
Time frame: Since the initial planning of the work			
1	All support for the present manuscript (e.g., funding, provision of study materials, medical writing, article processing charges, etc.) **No time limit for this item.**	_X_ None	
Time frame: past 36 months			

2	Grants or contracts from any entity (if not indicated in item #1 above).	_X_ None	
3	Royalties or licenses	_X_ None	
4	Consulting fees	_X_ None	
5	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	_X_ None	
6	Payment for expert testimony	_X_ None	
7	Support for attending meetings and/or travel	_X_ None	
8	Patents planned, issued or pending	_X_ None	
9	Participation on a Data Safety Monitoring Board or Advisory Board	_X_ None	
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	_X_ None	
11	Stock or stock options	_X_ None	
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	_X_ None	
13	Other financial or non-financial interests	Boehringer Ingelheim	Employment

Please place an "X" next to the following statement to indicate your agreement:

_X_ I certify that I have answered every question and have not altered the wording of any of the questions on this form.

Journal Pre-proofs

ICMJE DISCLOSURE FORM

Date: 4 June 2021

Your Name: Luis Paz-Ares

Manuscript Title: 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)

Manuscript number (if known): N/A

In the interest of transparency, we ask you to disclose all relationships/activities/interests listed below that are related to the content of your manuscript. "Related" means any relation with for-profit or not-for-profit third parties whose interests may be affected by the content of the manuscript. Disclosure represents a commitment to transparency and does not necessarily indicate a bias. If you are in doubt about whether to list a relationship/activity/interest, it is preferable that you do so.

The following questions apply to the author's relationships/activities/interests as they relate to the current manuscript only.

The author's relationships/activities/interests should be defined broadly. For example, if your manuscript pertains to the epidemiology of hypertension, you should declare all relationships with manufacturers of antihypertensive medication, even if that medication is not mentioned in the manuscript.

In item #1 below, report all support for the work reported in this manuscript without time limit. For all other items, the time frame for disclosure is the past 36 months.

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
Time frame: Since the initial planning of the work			
1	All support for the present manuscript (e.g., funding, provision of study materials, medical writing, article processing charges, etc.) **No time limit for this item.**	_X_ None	
Time frame: past 36 months			

2	Grants or contracts from any entity (if not indicated in item #1 above).	Merck Sharp & Dohme, AstraZeneca, Pfizer, Bristol-Myers Squibb	
3	Royalties or licenses	_X_ None	
4	Consulting fees	Lilly, Merck Sharp & Dohme, Roche, Pharmamar, Merck, AstraZeneca, Novartis, Servier, Amgen, Pfizer, Ipsen, Sanofi, Bayer, Blueprint, Bristol-Myers Squibb, Mirati	
5	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	AstraZeneca, Janssen, Merck, Mirati, Sanofi	
6	Payment for expert testimony	_X_ None	
7	Support for attending meetings and/or travel	_X_ None	
8	Patents planned, issued or pending	_X_ None	
9	Participation on a Data Safety Monitoring Board or Advisory Board	_X_ None	
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	Genomica	
		Altum sequency	
11	Stock or stock options	_X_ None	
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	_X_ None	
13	Other financial or non-financial interests	_X_ None	

Please place an "X" next to the following statement to indicate your agreement:

_X_ I certify that I have answered every question and have not altered the wording of any of the questions on this form.

Journal Pre-proofs

ICMJE DISCLOSURE FORM

Date: 8 June 2021

Your Name: Jonathan W. Riess

Manuscript Title: 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)

Manuscript number (if known): N/A

In the interest of transparency, we ask you to disclose all relationships/activities/interests listed below that are related to the content of your manuscript. "Related" means any relation with for-profit or not-for-profit third parties whose interests may be affected by the content of the manuscript. Disclosure represents a commitment to transparency and does not necessarily indicate a bias. If you are in doubt about whether to list a relationship/activity/interest, it is preferable that you do so.

The following questions apply to the author's relationships/activities/interests as they relate to the current manuscript only.

The author's relationships/activities/interests should be defined broadly. For example, if your manuscript pertains to the epidemiology of hypertension, you should declare all relationships with manufacturers of antihypertensive medication, even if that medication is not mentioned in the manuscript.

In item #1 below, report all support for the work reported in this manuscript without time limit. For all other items, the time frame for disclosure is the past 36 months.

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
Time frame: Since the initial planning of the work			
1	All support for the present manuscript (e.g., funding, provision of study materials, medical writing, article processing charges, etc.) **No time limit for this item.**	_X_ None	
Time frame: past 36 months			

2	Grants or contracts from any entity (if not indicated in item #1 above).	Boehringer Ingelheim	To institution
3	Royalties or licenses	_X_ None	
4	Consulting fees	Boehringer Ingelheim	Unrelated to manuscript but listing since sponsor of study
5	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	_X_ None	
6	Payment for expert testimony	_X_ None	
7	Support for attending meetings and/or travel	_X_ None	
8	Patents planned, issued or pending	_X_ None	
9	Participation on a Data Safety Monitoring Board or Advisory Board	Boehringer Ingelheim	
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	_X_ None	
11	Stock or stock options	_X_ None	
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	_X_ None	
13	Other financial or non-financial interests	_X_ None	

Please place an "X" next to the following statement to indicate your agreement:

_X_ I certify that I have answered every question and have not altered the wording of any of the questions on this form.

Journal Pre-proofs

ICMJE DISCLOSURE FORM

Date: 4 June 2021

Your Name: Sang-We Kim

Manuscript Title: 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)

Manuscript number (if known): N/A

In the interest of transparency, we ask you to disclose all relationships/activities/interests listed below that are related to the content of your manuscript. "Related" means any relation with for-profit or not-for-profit third parties whose interests may be affected by the content of the manuscript. Disclosure represents a commitment to transparency and does not necessarily indicate a bias. If you are in doubt about whether to list a relationship/activity/interest, it is preferable that you do so.

The following questions apply to the author's relationships/activities/interests as they relate to the current manuscript only.

The author's relationships/activities/interests should be defined broadly. For example, if your manuscript pertains to the epidemiology of hypertension, you should declare all relationships with manufacturers of antihypertensive medication, even if that medication is not mentioned in the manuscript.

In item #1 below, report all support for the work reported in this manuscript without time limit. For all other items, the time frame for disclosure is the past 36 months.

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
Time frame: Since the initial planning of the work			
1	All support for the present manuscript (e.g., funding, provision of study materials, medical writing, article processing charges, etc.) **No time limit for this item.**	_X_ None	
Time frame: past 36 months			

2	Grants or contracts from any entity (if not indicated in item #1 above).	_X_ None	
3	Royalties or licenses	_X_ None	
4	Consulting fees	_X_ None	
5	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	_X_ None	
6	Payment for expert testimony	_X_ None	
7	Support for attending meetings and/or travel	_X_ None	
8	Patents planned, issued or pending	_X_ None	
9	Participation on a Data Safety Monitoring Board or Advisory Board	_X_ None	
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	_X_ None	
11	Stock or stock options	_X_ None	
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	_X_ None	
13	Other financial or non-financial interests	_X_ None	

Please place an "X" next to the following statement to indicate your agreement:

_X_ I certify that I have answered every question and have not altered the wording of any of the questions on this form.

Journal Pre-proofs

ICMJE DISCLOSURE FORM

Date: 4 June 2021

Your Name: Isabelle Voccia

Manuscript Title: 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)

Manuscript number (if known): N/A

In the interest of transparency, we ask you to disclose all relationships/activities/interests listed below that are related to the content of your manuscript. "Related" means any relation with for-profit or not-for-profit third parties whose interests may be affected by the content of the manuscript. Disclosure represents a commitment to transparency and does not necessarily indicate a bias. If you are in doubt about whether to list a relationship/activity/interest, it is preferable that you do so.

The following questions apply to the author's relationships/activities/interests as they relate to the current manuscript only.

The author's relationships/activities/interests should be defined broadly. For example, if your manuscript pertains to the epidemiology of hypertension, you should declare all relationships with manufacturers of antihypertensive medication, even if that medication is not mentioned in the manuscript.

In item #1 below, report all support for the work reported in this manuscript without time limit. For all other items, the time frame for disclosure is the past 36 months.

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
Time frame: Since the initial planning of the work			
1	All support for the present manuscript (e.g., funding, provision of study materials, medical writing, article processing charges, etc.) **No time limit for this item.**	_X_ None	
Time frame: past 36 months			

2	Grants or contracts from any entity (if not indicated in item #1 above).	_X_ None	
3	Royalties or licenses	_X_ None	
4	Consulting fees	_X_ None	
5	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	_X_ None	
6	Payment for expert testimony	_X_ None	
7	Support for attending meetings and/or travel	_X_ None	
8	Patents planned, issued or pending	_X_ None	
9	Participation on a Data Safety Monitoring Board or Advisory Board	_X_ None	
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	_X_ None	
11	Stock or stock options	_X_ None	
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	_X_ None	
13	Other financial or non-financial interests	Boehringer Ingelheim	Employment

Please place an "X" next to the following statement to indicate your agreement:

_X_ I certify that I have answered every question and have not altered the wording of any of the questions on this form.

Journal Pre-proofs

Journal Pre-proofs

ICMJE DISCLOSURE FORM

Date: 3 June 2021

Your Name: Delvys Rodríguez Abreu

Manuscript Title: 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)

Manuscript number (if known): N/A

In the interest of transparency, we ask you to disclose all relationships/activities/interests listed below that are related to the content of your manuscript. "Related" means any relation with for-profit or not-for-profit third parties whose interests may be affected by the content of the manuscript. Disclosure represents a commitment to transparency and does not necessarily indicate a bias. If you are in doubt about whether to list a relationship/activity/interest, it is preferable that you do so.

The following questions apply to the author's relationships/activities/interests as they relate to the current manuscript only.

The author's relationships/activities/interests should be defined broadly. For example, if your manuscript pertains to the epidemiology of hypertension, you should declare all relationships with manufacturers of antihypertensive medication, even if that medication is not mentioned in the manuscript.

In item #1 below, report all support for the work reported in this manuscript without time limit. For all other items, the time frame for disclosure is the past 36 months.

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
Time frame: Since the initial planning of the work			
1	All support for the present manuscript (e.g., funding, provision of study materials, medical writing, article processing charges, etc.) **No time limit for this item.**	_X_ None	
Time frame: past 36 months			

2	Grants or contracts from any entity (if not indicated in item #1 above).	_X_ None	
3	Royalties or licenses	_X_ None	
4	Consulting fees	_X_ None	
5	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	_X_ None	
6	Payment for expert testimony	_X_ None	
7	Support for attending meetings and/or travel	_X_ None	
8	Patents planned, issued or pending	_X_ None	
9	Participation on a Data Safety Monitoring Board or Advisory Board	_X_ None	
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	_X_ None	
11	Stock or stock options	_X_ None	
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	_X_ None	
13	Other financial or non-financial interests	_X_ None	

Please place an "X" next to the following statement to indicate your agreement:

_X_ I certify that I have answered every question and have not altered the wording of any of the questions on this form.

Journal Pre-proofs

Journal Pre-proofs

ICMJE DISCLOSURE FORM

Date: 3 June 2021

Your Name: Mustafa Özgüroğlu

Manuscript Title: 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)

Manuscript number (if known): N/A

In the interest of transparency, we ask you to disclose all relationships/activities/interests listed below that are related to the content of your manuscript. "Related" means any relation with for-profit or not-for-profit third parties whose interests may be affected by the content of the manuscript. Disclosure represents a commitment to transparency and does not necessarily indicate a bias. If you are in doubt about whether to list a relationship/activity/interest, it is preferable that you do so.

The following questions apply to the author's relationships/activities/interests as they relate to the current manuscript only.

The author's relationships/activities/interests should be defined broadly. For example, if your manuscript pertains to the epidemiology of hypertension, you should declare all relationships with manufacturers of antihypertensive medication, even if that medication is not mentioned in the manuscript.

In item #1 below, report all support for the work reported in this manuscript without time limit. For all other items, the time frame for disclosure is the past 36 months.

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
Time frame: Since the initial planning of the work			
1	All support for the present manuscript (e.g., funding, provision of study materials, medical writing, article processing charges, etc.) **No time limit for this item.**	_X___None	

		Time frame: past 36 months	
2	Grants or contracts from any entity (if not indicated in item #1 above).	_X___None	
3	Royalties or licenses	_X___None	
4	Consulting fees	_X___None	
5	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	__X__None	
6	Payment for expert testimony	_X___None	
7	Support for attending meetings and/or travel	__X__None	
8	Patents planned, issued or pending	_X___None	
9	Participation on a Data Safety Monitoring Board or Advisory Board	_X___None	
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	_X___None	
11	Stock or stock options	_X___None	
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	__X__None	
13	Other financial or non-financial interests	__X__None	

Please place an "X" next to the following statement to indicate your agreement:

_X_ I certify that I have answered every question and have not altered the wording of any of the questions on this form.

Journal Pre-proofs