First-Line Afatinib versus Chemotherapy in Patients with Non-Small Cell Lung Cancer and Common Epidermal Growth Factor Receptor Gene Mutations and Brain Metastases

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ABSTRACT

Introduction: Metastatic spread to the brain is common in patients with non–small cell lung cancer (NSCLC), but these patients are generally excluded from prospective clinical trials. The studies, phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations (LUX-Lung 3) and a randomized, open-label, phase III study of BIBW 2992 versus chemotherapy as first-line treatment for patients with stage IIIB or IV adenocarcinoma of the lung harbouring an EGFR mutation, did not address the role of afatinib in this setting. We conducted the phase III Randomized Evaluation of Brain Metastases in NSCLC (RESONATE-1) trial to assess the benefit of afatinib compared with chemotherapy as first-line treatment for patients with stage IIIB or IV NSCLC with brain metastases and common EGFR mutations (exon 19 deletions or L858R or T790M mutations).

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Trial registration information located at https://clinicaltrials.gov/identifiers: NCT01121393, NCT00949650.


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activating mutation (LUX-Lung 6) investigated first-line afatinib versus platinum-based chemotherapy in epidermal growth factor receptor gene (EGFR) mutation-positive patients with NSCLC and included patients with brain metastases; prespecified subgroup analyses are assessed in this article.

**Methods:** For both LUX-Lung 3 and LUX-Lung 6, prespecified subgroup analyses of progression-free survival (PFS), overall survival, and objective response rate were undertaken in patients with asymptomatic brain metastases at baseline (n = 35 and n = 46, respectively). Post hoc analyses of clinical outcomes was undertaken in the combined data set (n = 81).

**Results:** In both studies, there was a trend toward improved PFS with afatinib versus chemotherapy in patients with brain metastases (LUX-Lung 3: 11.1 versus 5.4 months, hazard ratio [HR] = 0.54, p = 0.1378; LUX-Lung 6: 8.2 versus 4.7 months, HR = 0.47, p = 0.1060). The magnitude of PFS improvement with afatinib was similar to that observed in patients without brain metastases. In combined analysis, PFS was significantly improved with afatinib versus with chemotherapy in patients with brain metastases (8.2 versus 5.4 months; HR, 0.50; p = 0.0297). Afatinib significantly improved the objective response rate versus chemotherapy in patients with brain metastases. Safety findings were consistent with previous reports.

**Conclusions:** These findings lend support to the clinical activity of afatinib in EGFR mutation–positive patients with NSCLC and asymptomatic brain metastases.

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**Keywords:** Afatinib; NSCLC; Brain metastases; Epidermal growth factor receptor

**Introduction**

Metastatic spread to the brain is common in patients with advanced non–small cell lung cancer (NSCLC), occurring in more than 25% of patients at some point during their disease course.1 These patients have a poor prognosis with a median survival of only 1 month from diagnosis if untreated, 2 months with glucocorticoid therapy, and 2 to 5 months with whole brain radiation therapy (WBRT).1–7 Emerging evidence suggests that patients with epidermal growth factor receptor gene (EGFR) mutation–positive NSCLC are particularly prone to the development of brain metastases, with the frequency of such lesions in this patient subgroup ranging from 44% to 63%.8,9 In the era of EGFR tyrosine kinase inhibitors (TKIs), it is of high clinical relevance to determine the efficacy and safety of these agents in patients with EGFR mutation–positive NSCLC who present with brain metastases. As most prospective clinical trials of systemic therapy have excluded such patients because of their poor prognosis;10 however, there is currently a paucity of prospective data on EGFR TKIs in patients with brain metastases. Some retrospective data and small phase II studies have indicated that these agents display intracranial activity11–15; however, the data vary widely and have not yet been formally validated.

Afatinib is an orally available, irreversible ErbB family blocker that, in contrast to the first-generation EGFR TKIs, selectively and irreversibly blocks signaling from all homodimers and heterodimers formed by the EGFR, erb-b2 receptor tyrosine kinase 2 (HER2/ERBB2), HER3/ERBB3, and HER4/ERBB4 receptors.16,17 In two large phase III studies (LUX-Lung 3, which was conducted globally, and LUX-Lung 6, which was conducted in China, the Republic of Korea, and Thailand), afatinib demonstrated significantly improved progression-free survival (PFS) rates, objective response rates (ORRs), and patient-reported outcomes compared with platinum-based chemotherapy (pemetrexed/cisplatin in LUX-Lung 3 and gemcitabine/cisplatin in LUX-Lung 6) as first-line treatment of patients with EGFR-mutated, advanced NSCLC.18–20 Moreover, both studies showed afatinib to be the only TKI to confer improved overall survival (OS) versus standard-of-care platinum doublet chemotherapy in patients harboring EGFR Del19 mutations, the most common EGFR aberration in patients with NSCLC.21 Earlier studies of afatinib suggest that it is effective in patients with NSCLC and brain metastases. Subgroup analysis of LUX-Lung 2, a phase II trial of afatinib in patients with NSCLC and activating EGFR mutations, showed that response rates were similar in patients with or without brain metastases (65% and 60%, respectively).22 Furthermore, in a recent compassionate use program, 35% of patients with brain metastases and a documented EGFR mutation had an intracranial response when treated with afatinib.4 These data substantiate preclinical and clinical observations that afatinib can penetrate the blood-brain barrier at concentrations sufficient to elicit antitumor activity.4,23

Together, the phase III LUX-Lung 3 and LUX-Lung 6 trials represent the largest prospective data set on EGFR mutation–positive patients with NSCLC treated with a TKI. Owing to their nearly identical design, combined analysis of the trials is feasible and facilitates robust subanalyses in clinically relevant patient subgroups. Both trials permitted the enrollment of patients with clinically asymptomatic and controlled brain metastases. In this study, we performed subgroup analyses of the efficacy of first-line treatment with afatinib or platinum-based chemotherapy in these patients. Analysis was undertaken in both the individual trials and in a
combined data set. As patients harboring uncommon EGFR mutations represent a heterogeneous population with variable responses to treatment,24 efficacy analyses focused on patients with common sensitizing EGFR mutations. Given the observation that afatinib confers an OS benefit in patients with Del19,21 we also undertook an analysis in patients with Del19 and L858R mutations separately.

Materials and Methods

Detailed study designs, patient inclusion and exclusion criteria, and methods of the primary analyses of LUX-Lung 3 and LUX-Lung 6 have been published18,19 and are outlined only briefly in the following sections.

Study Design and Patients

LUX-Lung 3 and LUX-Lung 6 were randomized, open-label, phase III studies. Eligible patients had previously untreated stage IIIb/IV lung adenocarcinoma harboring EGFR mutations centrally confirmed on the basis of analysis of biopsy tissue with a validated test kit (Therascreen EGFR 29, Qiagen, Manchester, United Kingdom). Patients were required to have an Eastern Cooperative Oncology Group performance status of 0 or 1 and measurable disease according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. Patients with clinically asymptomatic and controlled brain metastases (defined as stable for at least 4 weeks and/or asymptomatic and/or not requiring treatment with anticonvulsants or steroids and/or no leptomeningeal disease) were included in both studies.

Each study was conducted in accordance with the Declaration of Helsinki and International Conference on Harmonization Guidelines on Good Clinical Practice, and the protocols were approved by local ethics committees at each participating center. All patients provided written informed consent for trial participation.

Study Treatment

Eligible patients were randomized 2:1 to receive afatinib, 40 mg orally once daily, or up to 6 cycles of intravenous platinum-based chemotherapy (LUX-Lung 3: cisplatin, 75 mg/m², and pemetrexed, 500 mg/m², once every 21 days; LUX-Lung 6: gemcitabine, 1000 mg/m² on days 1 and 8, plus cisplatin, 75 mg/m² on day 1 of a 21-day cycle). Randomization was stratified by EGFR mutation type (Del19, L858R, or other) and race (Asian or non-Asian in LUX-Lung 3 only). Several prespecified subgroup analyses, including presence of brain metastases (yes/no), were defined.

Treatment with afatinib continued until investigator-assessed disease progression or intolerable adverse events (AEs). A well-defined dose optimization protocol for afatinib was utilized by investigators to maximize efficacy while managing tolerability. All patients had to be initiated at the protocol-defined and approved starting dose of 40 mg.25-26 Dose escalation to 50 mg after the first 21-day cycle was allowed if a patient did not experience treatment-related AEs with a grade higher than 1. If a patient experienced any treatment-related grade 3 or higher AE or selected prolonged grade 2 AEs, the dose of afatinib was reduced in 10-mg decrements to a minimum of 20 mg. Afatinib was discontinued if a patient experienced intolerable AEs at the dose of 20 mg. Dose reductions for patients receiving chemotherapy were in accordance with guidance provided in the summary of product characteristics and institutional guidelines.

End Points and Assessments

For both LUX-Lung 3 and LUX-Lung 6, the primary efficacy end point was PFS, as assessed by independent review. Key secondary end points in both studies were OS, ORR (complete response and partial response), and disease control (complete response/partial response or stable disease). Other secondary end points included patient-reported outcomes and safety.

In both studies, tumor assessments were performed by computed tomography or magnetic resonance imaging every 6 weeks for the first 48 weeks, and then every 12 weeks until disease progression or start of new anticancer therapy. Scans were subjected to independent central radiologic review. Tumor response was determined according to assessment of target lesions, nontarget lesions, and the occurrence of new lesions, as per RECIST, version 1.1.27 Evaluation of intracranial lesions was performed as part of standard RECIST imaging, but intracranial response was not assessed as a separate end point. Safety of study treatments was assessed according to the incidence and intensity of AEs graded using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0, and changes in laboratory parameters.

Statistical Analysis

Each study was powered (90%) at a two-sided 5% significance level to detect an improvement in median PFS from 7 months for chemotherapy to 11 months for afatinib. A minimum of 217 progression or death events were required with estimated sample sizes of at least 330 patients for each study. The primary analysis of PFS was performed approximately 30 months after study initiation, when an initial analysis of OS was also
performed. A subsequent analysis of OS was planned after approximately 209 deaths in LUX-Lung 3 and 237 deaths in LUX-Lung 6, when it was estimated that the data would be mature. The data presented herein are from the time point of the mature OS analysis.

Analysis of study end points was undertaken in patients with common EGFR mutations. Data from LUX-Lung 3 and LUX-Lung 6 were assessed independently. Also, because the number of patients with brain metastases in each study was relatively small, a post hoc exploratory analysis of combined individual patient data from LUX-Lung 3 and LUX-Lung 6 was performed. Heterogeneity was evaluated by testing the study-by-treatment interaction for this subgroup of patients.

The main comparisons of PFS and OS between treatment arms were performed using a log-rank test; combined analyses were stratified by study (LUX-Lung 3 or LUX-Lung 6). Cox proportional hazard models were used to derive hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) for the comparison between the two treatment arms. Kaplan-Meier estimates were used to construct survival curves and calculate median PFS and OS values. Logistic regression models were used to compare ORRs and rates of disease control between treatment groups.

**Results**

**Patients**

A total of 42 of 345 randomized patients (12.2%) in LUX-Lung 3 and 49 of 364 randomized patients (13.5%) in LUX-Lung 6 had brain metastases present at baseline (Fig. 1). Most of these patients (35 [83.3%] and 46 [93.9%] in LUX-Lung 3 and LUX-Lung 6, respectively) harbored common (Del19 and L858R) EGFR mutations. In both studies, baseline characteristics were generally well balanced between patients who did or did not have brain metastases and across treatment groups (Table 1). In patients with brain metastases, the proportion who received prior WBRT was similar across trials and treatment groups. In LUX-Lung 3, the frequency of prior WBRT was 35.0% in the afatinib group and 33.3% in the cisplatin-pemetrexed group. In LUX-Lung 6, 21.4% and 33.3% of patients in the afatinib and cisplatin-gemcitabine groups received prior WBRT for brain lesions.

In addition to the 81 patients described herein, a further 10 patients with brain metastases (seven in LUX-Lung 3 and three in LUX-Lung 6) (see Fig. 1) were found to have uncommon EGFR mutations. Nine of these patients were treated with afatinib.

**Progression-Free Survival**

In both studies, PFS was longer with afatinib than with chemotherapy in patients with brain metastases and common EGFR mutations but did not achieve statistical significance, most likely because of small sample size. In LUX-Lung 3, median PFS was 11.1 months with afatinib and 5.4 months with cisplatin-pemetrexed (HR = 0.54, 95% CI: 0.23–1.25, p = 0.1378) (Fig. 2A). The magnitude of PFS improvement with afatinib over chemotherapy was similar to that observed in patients without brain metastases (13.8 versus 8.1 months, HR = 0.48, 95% CI: 0.34–0.69, p < 0.0001) (see Fig. 2A).
**Table 1. Baseline Demographics and Clinical Characteristics of Patients with Common EGFR Mutations and with or without Brain Metastases (Randomized Set)**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>LUX-Lung 3</th>
<th>LUX-Lung 6</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Afatinib</td>
<td>Cisplatin-Pemetrexed</td>
</tr>
<tr>
<td></td>
<td>Without BM (n = 166)</td>
<td>With BM (n = 20)</td>
</tr>
<tr>
<td><strong>Median age (range), y</strong></td>
<td>63.0 (35–86)</td>
<td>60.5 (37–71)</td>
</tr>
<tr>
<td><strong>Gender, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>56 (33.7)</td>
<td>6 (30.0)</td>
</tr>
<tr>
<td>Female</td>
<td>110 (66.3)</td>
<td>14 (70.0)</td>
</tr>
<tr>
<td><strong>Race, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>47 (28.3)</td>
<td>3 (15.0)</td>
</tr>
<tr>
<td>Asian</td>
<td>117 (70.5)</td>
<td>17 (85.0)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (1.2)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Smoking status, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smoked</td>
<td>113 (68.1)</td>
<td>14 (70.0)</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>50 (30.1)</td>
<td>6 (30.0)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>3 (1.8)</td>
<td>0</td>
</tr>
<tr>
<td><strong>ECOG PS, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>72 (43.4)</td>
<td>4 (20.0)</td>
</tr>
<tr>
<td>1</td>
<td>94 (56.6)</td>
<td>16 (80.0)</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Adenocarcinoma stage, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIIB</td>
<td>18 (10.8)</td>
<td>0</td>
</tr>
<tr>
<td>IV</td>
<td>148 (89.2)</td>
<td>20 (100.0)</td>
</tr>
<tr>
<td><strong>EGFR mutation, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L858R alone</td>
<td>77 (46.4)</td>
<td>9 (45.0)</td>
</tr>
<tr>
<td>L858R + Del19&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Del19 alone</td>
<td>89 (53.6)</td>
<td>11 (55.0)</td>
</tr>
<tr>
<td><strong>Prior whole brain radiotherapy, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2 (1.2)</td>
<td>7 (35.0)</td>
</tr>
<tr>
<td>No</td>
<td>164 (98.8)</td>
<td>13 (65.0)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Included in the L858R group for analysis.

BM, brain metastases; ECOG, European Cooperative Oncology Group; EGFR, epidermal growth factor receptor gene; LUX-Lung 3, phase III study of Afatinib or Cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations; LUX-Lung 6, a randomized, open-label, phase III study of BIBW 2992 versus chemotherapy as first-line treatment for patients with stage IIIB or IV adenocarcinoma of the lung harbouring an EGFR activating mutation; PS, performance status.
LUX-Lung 6, median PFS of patients with brain metastases treated with afatinib was 8.2 months versus 4.7 months in patients receiving cisplatin-gemcitabine (HR = 0.47, 95% CI: 0.18–1.21, p = 0.1060) (Fig. 2B). In patients without brain metastases, median PFS was 11.1 with afatinib and 5.6 months with chemotherapy (HR = 0.22, 95% CI: 0.15–0.33, p < 0.0001) (see Fig. 2B).

To increase the sample size of patients with brain metastases, we undertook a combined analysis of LUX-Lung 3 and LUX-Lung 6. Given the caveat that the two trials used different chemotherapy regimens as comparators, this analysis was exploratory only. Nevertheless, compared with chemotherapy, afatinib significantly improved PFS in patients with NSCLC plus brain metastases and common EGFR mutations (median PFS 8.2 versus 5.4 months, HR = 0.50, 95% CI: 0.27–0.95, p = 0.0297) (Fig. 3). Interestingly, the PFS benefit conferred by afatinib in patients with brain metastases was higher in those who received prior WBRT (n = 24, 13.8 versus 4.7 months, HR = 0.37, 95% CI: 0.12–1.17, p = 0.0767) than in those who did not (n = 57, 6.9 versus 5.4 months, HR = 0.62, 95% CI: 0.28–1.36, p = 0.2222).

Further analysis of a combined patient data set was undertaken in patients with brain metastases and specific EGFR mutations (see Fig. Supplemental Digital Content 1, which demonstrates PFS and best response with respect to mutation type in individual patients). In patients with a Del19 mutation, afatinib significantly improved PFS versus chemotherapy (n = 43, 9.5 versus 4.7 months, HR = 0.24, 95% CI: 0.09–0.62, p = 0.0012) (see Fig. Supplemental Digital Content 2, which shows Kaplan-Meier PFS curves according to mutation type). In
In patients with baseline brain metastases and common EGFR mutations treated with afatinib, rates of central nervous system (CNS) progression were similar in patients treated with afatinib (nine [45.0%] in LUX-Lung 3 and six [21.4%] in LUX-Lung 6) or chemotherapy (five [33.3%] in LUX-Lung 3 and five [27.8%] in LUX-Lung 6). The rates of CNS progression in patients without baseline brain metastases were also similar in patients treated with afatinib (12 [7.2%] in LUX-Lung 3 and 10 [5.4%] in LUX-Lung 6) or chemotherapy (three [3.7%] in LUX-Lung 3 and four [4.7%] in LUX-Lung 6). Interestingly, the median time to CNS progression was longer with afatinib versus with chemotherapy (LUX-Lung 3: 15.2 months [95% CI: 7.7–29.0] and 5.7 months [95% CI: 2.6–8.2]; LUX-Lung 6: 15.2 months [95% CI: 3.8–23.7] and 7.3 months [95% CI: 3.7–10.9] with afatinib and chemotherapy, respectively). However, the patient numbers in this analysis were small and preclude definitive conclusions.

**OS**

There was no significant difference in OS in patients with brain metastases who were treated with afatinib or chemotherapy (LUX-Lung 3: median OS 19.8 versus 33.2 months, HR = 1.15, 95% CI: 0.49–2.67, p = 0.7517; LUX-Lung 6: 22.4 versus 24.7 months, HR = 1.13, 95% CI: 0.56–2.26, p = 0.7315; and combined data set: 22.4 versus 25.0 months, HR = 1.14, 95% CI: 0.66–1.94, p = 0.6412) (Figs. 3 and 4).

OS was also assessed according to type of EGFR mutation. There was no significant difference in OS between afatinib and chemotherapy in patients with brain metastases and a Del19 mutation (22.4 versus 20.6 months; HR = 0.78, 95% CI: 0.37–1.66, p = 0.5229) nor in patients with brain metastases and an L858R mutation (22.6 versus 26.2 months, HR = 1.53, 95% CI: 0.69–3.41, p = 0.2897) (see Fig. Supplemental Digital Content 2, which shows Kaplan-Meier OS curves according to mutation type).

**Tumor Response Rate**

In both LUX-Lung 3 and 6, ORR was significantly greater with afatinib than with chemotherapy in patients with brain metastases and common EGFR mutations (Table 2). Across both studies, the ORR in patients with brain metastases who were treated with afatinib was 23 of 28 (82.1%) and 12 of 20 (60.0%) in those with Del19 or L858R mutations, respectively (see Fig. Supplemental Digital Content 1, which demonstrates PFS and best response with respect to mutation type in individual patients). Disease control rates were also higher with afatinib than with chemotherapy but did not reach statistical significance. Additionally, in patients with uncommon EGFR mutations and brain metastases, ORR was observed in three of nine patients (33.3%)
across both studies (see Fig. Supplemental Digital Content 3, which shows PFS and best response in individual patients with uncommon \textit{EGFR} mutations).

**Safety and Tolerability**

In both studies, the AE profile of patients with brain metastases was similar to that of those without brain metastases for both treatment groups, with no unexpected safety findings (see Supplemental Digital Content 4, which shows treatment-related grade $\geq 3$ AEs). The incidence of grade 3 or 4 AEs in patients without brain metastases treated with afatinib was 49.5% in LUX-Lung 3 versus 36.4% in LUX-Lung 6. In patients with brain metastases, 46.2% and 33% of patients experienced grade 3 or 4 AEs in LUX-Lung 3 and LUX-Lung 6, respectively.

**Discussion**

In this study, we utilized the phase III LUX-Lung 3 and LUX-Lung 6 data sets to assess the activity of afatinib in the prespecified subset of patients with \textit{EGFR} mutation–positive NSCLC who presented with baseline brain metastases. Of the 91 individuals identified as belonging to this subset, 81 harbored common \textit{EGFR} mutations; they constituted the largest prospective cohort of such patients to be analyzed for response to a TKI. Several observations in this analysis suggest that patients with
NSCLC and asymptomatic brain metastases can benefit from treatment with afatinib. First, in both studies, afatinib conferred longer PFS versus chemotherapy in patients with brain metastases who harbored common EGFR mutations. The outcomes were particularly promising in patients with a Del19 mutation, a subgroup for whom afatinib is the only TKI to demonstrate superior OS from treatment with afatinib. First, in both studies, afatinib/afatinib can improve outcomes in patients with metastatic lung adenocarcinoma with EGFR mutations; LUX-Lung 6, a randomized, open-label, phase III study of BIBW 2992 versus chemotherapy as first-line treatment for patients with stage IIIb or IV adenocarcinoma of the lung harbouring an EGFR activating mutation; ORR, objective response rate; CI, confidence interval; DCR, disease control rate.

Table 2. Tumor Response Rates in Patients with and without Brain Metastases and Common EGFR Mutations in LUX-Lung 3 and 6

<table>
<thead>
<tr>
<th>Outcome</th>
<th>With Brain Metastases</th>
<th>No Brain Metastases</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LUX-Lung 3</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORR, n (%)</td>
<td>Afatinib n = 20</td>
<td>Cisplatin-pemetrexed n = 15</td>
<td>0.0058</td>
</tr>
<tr>
<td></td>
<td>14 (70.0, 45.7-88.1)</td>
<td>3 (20.0, 4.3-48.1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cisplatin-gemcitabine</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>19 (95.0, 75.1-99.9)</td>
<td>12 (80.0, 51.9-95.7)</td>
<td>0.1986</td>
</tr>
<tr>
<td><strong>LUX-Lung 6</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORR, n (%)</td>
<td>Afatinib n = 28</td>
<td>Cisplatin-gemcitabine n = 18</td>
<td>0.0027</td>
</tr>
<tr>
<td></td>
<td>21 (75.0, 55.1-89.3)</td>
<td>5 (27.8, 9.7-53.5)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cisplatin-pemetrexed</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>124 (67.0, 59.7-73.7)</td>
<td>19 (22.1, 13.9-32.3)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

EGFR, epidermal growth factor receptor gene; LUX-Lung 3, phase III study of Afatinib or Cisplatin plus Pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations; LUX-Lung 6, a randomized, open-label, phase III study of BIBW 2992 versus chemotherapy as first-line treatment for patients with stage IIIb or IV adenocarcinoma of the lung harbouring an EGFR activating mutation; ORR, objective response rate; CI, confidence interval; DCR, disease control rate.

In the present study, intracranial response rates were not assessed. Therefore, no direct conclusions can be made regarding afatinib’s ability to cross the blood-brain barrier in concentrations sufficient to elicit CNS responses; however, previous studies indicate that this may be the case. In a recent report on a compassionate use program, 100 patients with brain metastases and/or leptomeningeal disease were treated with afatinib following progression after chemotherapy and EGFR-TKI treatment.4 The median time to treatment failure was 3.6 months, which did not differ from that in a matched group of 100 patients without CNS metastases. Therefore, it seems that afatinib may be able to attain clinical activity in the brain. Interestingly, in our study, the magnitude of PFS benefit from afatinib favored those patients who had received WBRT before study entry, although statistical significance was not reached. As WBRT is reported to increase the permeability of the blood-brain barrier,28 this observation might indirectly point to a dose effect of afatinib in the brain. Case study data with first-generation EGFR inhibitors indicate that the level of CNS penetration can be improved with pulsatile high-dose administration regimens.29-33 It will be interesting, therefore, to assess the efficacy of pulsed-dose afatinib in patients with brain metastases. Another area that requires further study is the ability of afatinib to control active brain metastases (an exclusion criterion in both LUX-Lung 3 and LUX-Lung 6).

In addition to the current study with afatinib, several retrospective or small phase II studies have shown that gefitinib/afatinib can improve outcomes in patients with EGFR-mutated NSCLC that has metastasized to the brain. Response rates (per RECIST criteria, not intracranial responses) between 58% and 83% have been reported, and median PFS and OS were in the range of 7 to 15 months and 13 to 18 months, respectively.13-15 Given the apparent efficacy of these agents, it is interesting to speculate how TKIs could potentially become incorporated into current standard treatment regimens for patients with brain metastases. It is possible, for example, that in patients with asymptomatic brain metastases treatment with a first-line TKI could delay the requirement for WBRT, thereby delaying or preventing exposure to the side effects of cranial irradiation. Indeed, in
some studies, tumor responses achieved by EGFR TKIs have successfully delayed the requirement for WBRT.\textsuperscript{12,13} In this study, however, disease control appeared to be better in patients who had previously received WBRT, suggesting that sequential approaches warrant careful investigation.

In summary, the findings of the current analysis lend further support to the efficacy of afatinib in asymptomatic brain metastases secondary to NSCLC harboring common \textit{EGFR} mutations, and they add valuable insights into a clinically unmet need. Further studies exploring the effects of afatinib in patients with NSCLC and \textit{EGFR} mutations and brain metastases are warranted.

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\section*{Supplementary Data}
Note: To access the supplementary material accompanying this article, visit the online version of the \textit{Journal of Thoracic Oncology} at www.jto.org and at http://dx.doi.org/10.1016/j.jtho.2015.11.014.

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