Bevacizumab in Patients with Nonsquamous Non–Small Cell Lung Cancer and Asymptomatic, Untreated Brain Metastases (BRAIN): A Nonrandomized, Phase II Study

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Abstract

Purpose: The phase II prospective, noncomparative BRAIN study (NCT00800202) investigated efficacy and safety of bevacizumab in chemotherapy-naïve or pretreated patients with nonsquamous non–small cell lung cancer (NSCLC) and asymptomatic untreated brain metastases to provide data in this previously unexplored subgroup.

Experimental Design: Patients with stage IV nonsquamous NSCLC, Eastern Cooperative Oncology Group performance status 0–1, and untreated, asymptomatic brain metastases received first-line bevacizumab (15 mg/kg) plus carboplatin (area under the curve ×6) and paclitaxel (200 mg/m²) every 3 weeks (B + CP), or second-line bevacizumab plus erlotinib (150 mg/d; B + E). Six-month progression-free survival (PFS) was the primary endpoint. The trial could be stopped if there were more than three (B + CP) or more than two (B + E) intracranial hemorrhages.

Results: In first-line B + CP cohort (n = 67), 6-month PFS rate was 56.5% with a median PFS of 6.7 months (95% confidence interval [CI], 5.7–7.1) and median overall survival (OS) of 16.0 months. Investigator-assessed overall response rate (ORR) was 62.7%: 61.2% in intracranial lesions and 64.2% in extracranial lesions. Because of low enrolment (n = 24), efficacy results for the second-line B + E cohort were exploratory only; 6-month PFS rate was 57.2%, median PFS was 6.3 months (95% CI, 3.0–8.4), median OS was 12.0 months, and ORR was 12.5%. Adverse events were comparable with previous trials of bevacizumab. One grade 1 intracranial hemorrhage occurred and resolved without sequelae.

Conclusions: The BRAIN study demonstrates encouraging efficacy and acceptable safety of bevacizumab with first-line paclitaxel and carboplatin in patients with NSCLC and asymptomatic, untreated brain metastases.

Introduction

The development of brain metastases is common in patients with advanced nons–small cell lung cancer (NSCLC), occurring in 24% to 44% of patients (1–3), more frequently in patients with adenocarcinoma histology. Brain metastases often lead to deterioration in neurologic and neurocognitive function (1) and are associated with significant morbidity (4), including a risk of spontaneous hemorrhage at a rate of 1.4% to 10% (average of 2% to 3%; ref. 5). The primary score used to predict prognosis of patients with brain metastases remains the recursive partitioning analysis (RPA) score, which splits patients into 3 classes (class 1: patients with Karnofsky performance status <70% and age <65 years with controlled primary and no extracranial metastases; class 2: KPS <70%; class 2: all others; refs. 6–9). Most patients are RPA class 3 with a prognosis of 2 months or RPA class 2 with a prognosis of 6 months (10). Recently, a new prognostic index was reported—the graded prognostic assessment—which takes into account the number of metastases to give a score from 0 to 4 (4 representing the best prognosis; ref. 11).
Translational Relevance

The development of brain metastases is common in patients with advanced non–small cell lung cancer (NSCLC). Systemic treatments have often not been considered for brain metastases due to the complexities of crossing the blood–brain barrier. To our knowledge, BRAIN is the first prospective study to investigate bevacizumab-based regimens in both a first-line and second-line setting in patients with NSCLC and asymptomatic brain metastases. The results suggested that a bevacizumab-based regimen is capable of eliciting an intracranial response and might offer an alternative treatment option for patients with NSCLC and asymptomatic brain metastases, instead of the current option of whole brain radiotherapy. Further prospective research is needed in this subgroup to validate the initial findings presented in this exploratory phase II trial.

Whole-brain radiotherapy (WBRT) represents the standard treatment for NSCLC brain metastases (12), based on improvements in survival (13). Because the blood–brain barrier is disrupted in the presence of brain metastases (14, 15), systemic treatments could potentially offer an alternative to WBRT. In a phase II study, the response rate of brain metastases to pemetrexed–cisplatin before WBRT was numerically superior to that of extracranial metastases: 41.9% versus 34.9%, respectively (16). It has been demonstrated that WBRT can be delayed until the end of initial cisplatin-based chemotherapy without impacting overall survival (OS; ref. 17). Furthermore, a retrospective analysis of a phase III study of 175 patients with NSCLC and brain metastases suggested that use of multiple systemic treatments allows the delay of WBRT and its associated morbidity until the appearance of neurologic symptoms, without decreasing OS (18).

Bevacizumab is a recombinant monoclonal antibody targeting VEGF. First-line treatment of nonsquamous NSCLC in the phase III Eastern Cooperative Oncology Group (ECOG) 4599 trial reported a longer median OS for bevacizumab plus paclitaxel and carboplatin compared with paclitaxel and carboplatin alone (19). Bevacizumab in combination with erlotinib [an EGF receptor (EGFR) tyrosine kinase inhibitor (TKI)] as a second-line treatment in untreated patients with nonsquamous NSCLC (20) significantly prolonged progression-free survival (PFS) but not OS compared with erlotinib alone (21). Patients with central nervous system (CNS) metastases were initially excluded from bevacizumab clinical trials after the occurrence of a fatal cerebral hemorrhage in the phase I study (22). However, the brain metastasis contraindication was removed from the EU Summary of Product Characteristics in 2009 after the submission of comprehensive safety data (23). Retrospective analysis of clinical trial data demonstrated that 3 (3.3%) of 91 bevacizumab-treated patients with brain metastases experienced CNS bleeding (grade 4), compared with one (1%, grade 5) of 96 patients who were not exposed to bevacizumab (24).

Although brain metastases are a very common and clinically challenging progression of NSCLC, there are few prospective studies addressing the management of asymptomatic patients with NSCLC brain metastases. In the BRAIN study (ML21823, NCT00800202), the BRAIN investigators sought to prospectively explore the safety and efficacy of bevacizumab either in combination with chemotherapy or with erlotinib in chemotherapy-naïve or pretreated patients with NSCLC, respectively.

Materials and Methods

Study design and patients

BRAIN was an open-label, noncomparative, nonrandomized, multicenter, phase II study assessing bevacizumab in 2 separate arms of patients with metastatic nonsquamous NSCLC and asymptomatic brain metastases. In one arm, bevacizumab was assessed in combination with chemotherapy in the first-line setting, and in the other noncomparative arm (all efficacy and safety data are detailed in the Appendix), bevacizumab plus erlotinib was assessed in the second-line setting after failure of platinum-based chemotherapy. The 2 arms were assessed independently of one another and were not compared. Having 2 independent arms approved in one protocol allowed investigators the freedom to enroll patients into either arm depending on the line of therapy required by their patient.

The main inclusion criteria were: patients ≥18 years of age with an ECOG performance status (PS) of 0 to 1, with asymptomatic, untreated brain metastases, at least one measurable lesion (not exclusively applying to brain metastases) according to Response Evaluation Criteria in Solid Tumors (RECIST), and adequate hematologic, hepatic, and renal function. Exclusion criteria included symptomatic, treated, or hemorrhagic brain metastases, brain metastases only amenable to surgical treatment or radiosurgery (according to the investigators’ institutional guidelines), previous antiangiogenic treatment or neoadjuvant or adjuvant chemotherapy ≤6 months before enrollment to the first-line arm or a history of hemoptysis or poorly controlled arterial hypertension. No maximum number of lesions was specified and steroid treatment was not allowed.

Patients were not selected on the basis of EGFR mutation status in either arm because EGFR testing was not widely performed at the time of study initiation. EGFR mutation analysis was optional and was performed at the discretion of the investigator, if part of their routine practice. EGFR mutation status was retrospectively collected from patient notes where available. All EGFR assays were performed at investigational sites by either high-resolution melting or sequencing. All patients were required to provide written informed consent. The trial was approved by local independent ethics committees, including an independent review board, and complied with the Declaration of Helsinki and Good Clinical Practice principles.

Study treatment

Patients received paclitaxel 200 mg/m² and carboplatin AUC 6 every 3 weeks for a maximum of 6 cycles, plus concomitant maintenance bevacizumab (15 mg/kg every 3 weeks) until disease progression or unacceptable toxicity (B + CP first-line arm). Second-line bevacizumab plus erlotinib (B + E) treatment is detailed in the Appendix.

Assessments

Assessments were performed every 2 cycles, including chest–abdomen CT-scans and mandatory MRI for assessment of brain metastases. The occurrence of brain hemorrhage was monitored by the sponsor and the independent Data Safety Monitoring Board. If more than 3 patients in the first line had a clinically significant intracranial hemorrhage [symptomatic, with National
Cancer Institute Common Terminology Criteria for Adverse Events (AE) grading ≥2] occurring between first administration of bevacizumab and up to 60 days after bevacizumab discontinuation, the study arm would be stopped.

**Study endpoints**

The primary endpoint was investigator-assessed 6-month PFS rate, a frequently used and clinically meaningful endpoint in trials of brain tumors, as it gives an early window of opportunity to assess efficacy and reduces time-dependent assessment bias introduced by visit or image frequency (25, 26). Secondary endpoints were investigator-assessed overall response rate (ORR) according to RECIST 1.0, median PFS, median OS, and safety. Exploratory endpoints included response rates of brain metastases assessed by the investigator and by independent radiologic review, investigator-assessed response rates of extracranial lesions, duration of response of brain metastases in patients with measurable brain disease, and benefit of treatment in patients with known EGFR mutation–positive NSCLC. Further exploratory biomarker data will be presented in a separate publication.

**Statistical methods**

A single-step Fleming method was used to calculate the sample size, using an alpha risk of 2.5% and a beta risk of 10%. The predefined criteria for first-line B + CP 6-month PFS rate were ≤30% (H0) and ≥50% (H1). This required 66 patients to demonstrate the efficacy of first-line B + CP. Treatment efficacy would be proven if the lower limit of the confidence interval (CI) was above the predefined minimum threshold of efficacy, with the point estimate above the predefined threshold of interest. The statistical assumptions were based on previous trial data (19, 21). PFS at 6 months and median PFS and OS were analyzed using Kaplan–Meier methodology with 95% CIs; for response rates, 95% CIs were estimated using the Pearson–Clopper method.

The intention-to-treat (ITT) population included all patients enrolled; patients who did not undergo any postenrollment evaluations were not included in the ITT population. The safety population included all patients who received at least one dose of study treatment.

**Results**

Between April 2009 and April 2011, a total of 91 patients (all RPA class 2) were enrolled into the BRAIN trial in 22 centers in France. All 91 patients enrolled and treated in this study were included in the ITT and safety populations: 67 patients in B + CP and 24 patients in B + E. The data cutoff date was December 13, 2012. Results of the B + CP cohort only are given here. For results from the second-line B + E cohort, see the Appendix.

**Patient characteristics**

A total of 67 patients were enrolled into the first-line B + CP cohort. Patient disposition is shown in Fig. 1 and baseline characteristics are given in Table 1. A total of 24 patients prematurely withdrew or discontinued any study treatment (16 due to AEs, one due to death, 7 due to patient or investigator decision). EGFR mutation status testing was optional and was collected from 42 patients; 6 patients were positive for EGFR mutations (4 exon 19 deletions, 2 exon 21 mutations). Median follow-up was 16.3 months. Median duration of exposure to bevacizumab was 8 cycles.

**Efficacy outcomes**

Investigator-assessed ORR in the ITT population was 62.7% (95% CI, 50.0–74.2; Fig. 2 and Supplementary Table S1); the response rate of brain metastases by independent radiological review was 61.2% (48.5–72.9; n = 41; individual patient responses are shown in Fig. 2). The response rate of extracranial lesions was 64.2% (95% CI, 51.5–75.5). The median duration of brain metastases response in patients with measurable brain disease (n = 29) was 8.1 months (95% CI, 5.5–11.3). Progression was the most frequent cause for bevacizumab withdrawal (89.6%): intracranial progression in 20.9%, extracranial progression in 50.7% of patients, and progression at both sites in 9% of patients.

Median PFS was 6.7 months (95% CI, 5.7–7.1; Fig. 3A) and the median OS was 16.0 months (12.0–21.0; Fig. 3B). The 6-month PFS and 12-month OS rates were 56.3% (95% CI, 43.8–67.4) and 64.2% (51.5–74.4), respectively. As the lower 95% CI for 6-
month PFS was above the predefined threshold (30% for this arm), the primary endpoint was met.

Efficacy results according to EGFR mutation status are shown in Table 2. The 6-month PFS rate for patients with EGFR mutation–positive disease was 50.0%, with those testing as EGFR wild-type having a 6-month PFS rate of 58.5%.

Post-study therapy
Among the B + CP patients, 85.1% received post-study therapy: 82.1% received at least one systemic cancer treatment (most common treatments were pemetrexed 64.2% and erlotinib 47.8%); 13.4% received radiotherapy for NSCLC; and 3.0% underwent surgery. All 6 patients with confirmed EGFR mutation–positive NSCLC went on to receive EGFR TKI therapy after disease progression. A total of 33 patients received WBRT for their metastases, and the median time to WBRT was 12.7 months (range, 2.8–34.7 months).

Safety
One intracranial hemorrhage (ICH) event (grade 1) occurred, which resolved. This patient received their last dose of bevacizumab 21 days before that event, and disease progression was
determined to have occurred simultaneously with the event. The investigator considered this event related to progression and bevacizumab. A total of 27 (40.3%) patients experienced serious AEs, the most common being neutropenia (23.9%). There was one serious AE, a case of epilepsy not considered to be related to treatment, that led to death in this group. Grade 3 AEs occurred in 83.6% of patients in the first-line cohort, and grade 3 AEs of special interest occurred in 19.4% of patients (Table 3). The most common grade 3 AEs (>10%) were neutropenia (43.3%) and thrombocytopenia (11.8%).

Discussion
To our knowledge, the phase II BRAIN study represents the first prospective study of bevacizumab in patients with nonsquamous NSCLC and untreated brain metastases. The primary endpoint of 6-month PFS rate met the protocol-defined criteria for first-line treatment (B + CP). The overall safety profile was consistent with that of patients with NSCLC without brain metastases (19–21). In the ECOG 4599 study, the treatment scheme was similar (first-line bevacizumab plus paclitaxel and carboplatin) and resulted in a median OS of 12.3 months and a

Table 2. PFS, OS, and response rates according to EGFR mutation status in 67 patients treated with bevacizumab plus paclitaxel and carboplatin

<table>
<thead>
<tr>
<th>EGFR mutation-positive (n = 6)</th>
<th>EGFR wild-type (n = 34)</th>
<th>Nonevaluable (n = 27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-mo PFS (95% CI), mo</td>
<td>60.0 (39.9–102.0)</td>
<td>6.7 (5.4–7.5)</td>
</tr>
<tr>
<td>Median OS (95% CI), mo</td>
<td>29.5 (16.0–53.7)</td>
<td>13.1 (8.1–21.3)</td>
</tr>
<tr>
<td>12-mo survival rate (95% CI)</td>
<td>100.0 (100)</td>
<td>59.0 (40.6–73.2)</td>
</tr>
<tr>
<td>18-mo survival rate (95% CI)</td>
<td>83.0 (27.3–97.5)</td>
<td>41.0 (24.8–56.9)</td>
</tr>
<tr>
<td>Responders</td>
<td>6 (100%)</td>
<td>21 (62%)</td>
</tr>
<tr>
<td>Complete response</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Partial response</td>
<td>6 (100%)</td>
<td>21 (62%)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>0</td>
<td>7 (21%)</td>
</tr>
<tr>
<td>Progressive disease, n (%)</td>
<td>0</td>
<td>5 (15%)</td>
</tr>
<tr>
<td>Missing, n (%)</td>
<td>0</td>
<td>1 (3%)</td>
</tr>
</tbody>
</table>
Bevacizumab in NSCLC Patients with Asymptomatic Brain Metastases

All measures of efficacy were promising compared with historical data for both cohorts as demonstrated above. It is acknowledged that these historical comparisons are with patients who were not known to have brain metastases at baseline. OS of 16.0 and 12.0 months for the first- and second-line arms, respectively, are favorable outcomes for patients with asymptomatic brain metastases, a poorly investigated group to date. As a comparison, the expected median OS would have been 6 months as all patients included in the current study cohorts were RPA class 2. The historical dataset however included patients regardless of neurologic symptoms (9). It is important to note that the BRAIN study enrolled only patients with asymptomatic brain metastases; therefore, comparisons of this selected population with outcomes and data derived from patients presenting with symptomatic brain metastases cannot be reliably made. However, the most appropriate historical controls available have been discussed. With regard to ORR, tumor burden was assessed on a 6-weekly scanning schedule in both study cohorts. It is unlikely that we overestimated the response assessments because the independent radiological review, which was done only on the brain MRI, resulted in a similar assessment of ORR (Table 2 and Appendix Table 2).

Response rates were similar for brain metastases compared with other metastatic sites. Optimizing the intracranial control with systemic treatment could have delayed the neurologic symptoms indicative of recurrence, theoretically leading to the safe postponement of WBRT to the time of CNS disease progression. Although there were previous safety concerns regarding the use of bevacizumab in patients with brain metastases, the incidence of ICH in this study was low and similar to historical controls in NSCLC without brain metastases, although direct cross-trial comparisons should be viewed with caution (30–32). One could hypothesize that the small lesions described in the study (mean size, 13 mm) might be less likely to bleed or perhaps have less intracranial edema. In this study, one ICH event (grade 1) was reported in the B + CP arm, whereas no ICH events were reported in the B + E cohort. A retrospective analysis identified 3 patients with grade 4 cerebral hemorrhage of 91 bevacizumab-treated patients with NSCLC and brain metastases in randomized controlled trials (24). Retrospective analyses of patients with NSCLC and treated brain metastases in the ATLAS and PASSPORT studies reported no grade >2 hemorrhages (n = 85; ref. 32). A recent evidence-based review was carried out on the risk of CNS hemorrhage in patients with NSCLC receiving anti-VEGF therapy, which concluded that there was no significantly increased risk of CNS hemorrhage associated with anti-VEGF therapy (33). The most common grade $\geq 3$ AEs reported in BRAIN (neutropenia and thrombocytopenia) were as expected for a B + CP regimen.

These findings are interesting when considered in the light of expected outcomes for patients with brain metastases secondary to primary NSCLC where the median prognoses are poor. The favorable outcomes in BRAIN for both treatment groups might be explained by numerous factors, such as the highly selected population and the absence of patients with ECOG PS 2. Of note, patients were screened and enrolled in this study and treated before they became symptomatic and required steroids. In a real-life setting, while brain computed tomography scans may be included in initial diagnosis and subsequent follow-up visits, some patients may present with neurologic symptoms before screening and therefore before treatment for intracranial disease can begin. Therefore, it is possible that the BRAIN results may

### Table 3. Overview of AEs in 67 patients treated with bevacizumab plus paclitaxel and carboplatin

<table>
<thead>
<tr>
<th>Event</th>
<th>Bevacizumab plus paclitaxel and carboplatin (n = 67)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>67 (100%)</td>
</tr>
<tr>
<td>Serious AEs</td>
<td>27 (40%)</td>
</tr>
<tr>
<td>Grade 3–5 AEs</td>
<td>56 (84%)</td>
</tr>
<tr>
<td>Grade 5 AEs (leading to death)</td>
<td>1 (2%)a</td>
</tr>
<tr>
<td>Patients who discontinued bevacizumab treatment due to AE</td>
<td>8 (12%)</td>
</tr>
<tr>
<td>Grade 3–5 AESIs</td>
<td>13 (19%)</td>
</tr>
<tr>
<td>Bevacizumab-related AESIs</td>
<td></td>
</tr>
<tr>
<td>Thromboembolic events (venous)</td>
<td>7 (10%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>3 (4%)</td>
</tr>
<tr>
<td>Thromboembolic events (arterial)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Bleeding event (post-procedural hematoma)</td>
<td>0</td>
</tr>
<tr>
<td>Erlotinib-related AESIs</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0</td>
</tr>
<tr>
<td>Rash</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviation: AESI, AEs of special interest.

*a All data are n (%).

*bEpilepsy.

*cPatients may have had more than one AESI.
indicate a degree of lead-time bias. In addition, the use of frequent brain MRIs may have resulted in inclusion of patients with very small brain metastases that would prove more responsive to larger metastases. It must be noted, however, that although these practices are a real-life issue in the authors’ institutions, this may not be consistent in a global setting. The high proportion of patients with adenocarcinoma histology (88.1% of the B + CP group) might also help to explain the results because this subgroup has been observed to derive a greater benefit from bevacizumab-based therapy (34). High post-study treatment rates (85.1%) might also have influenced OS. Activating mutations of the EGFR are also known to influence patient outcomes, especially when such patients receive EGFR TKIs as part of their treatment regimen. EGFR mutation testing was not mandated by this study; however, the protocol was amended to allow the collection of pre-existing test results from the patients’ records where available. Definitive results were not available for all patients. Six patients in the B + CP arm were found to have EGFR mutation–positive disease, all of whom received EGFR TKIs as part of their post-progression therapy. None of the 10 samples evaluated for EGFR mutations of the 24 patients who received B + E was positive, and efficacy was not better in patients with unknown or un evaluable EGFR mutation status. This could argue against an enrichment of EGFR-mutated tumors; however, it is difficult to draw firm conclusions from this small patient group.

Overall, the BRAIN data appear to be favorable and consistent with the E4599 and BeTa Lung results. However, this interpretation should be placed in the context of small cohort sizes and the absence of control arms. There are also potential issues with cross-trial comparisons, where patients with brain metastases were included from trial to trial. No clinical trials are planned or ongoing in this particular patient population; however, further investigation to confirm these phase II findings would be helpful.

Conclusion

The BRAIN study indicated that B + CP demonstrated promising activity in the first-line treatment of patients with NSCLC and asymptomatic, untreated brain metastases according to prespecified criteria. The B + E combination showed a potential efficacy signal in second-line therapy; however, owing to the low number of patients enrolled, analysis of the B + E cohort was of a descriptive nature only. The incidence and intensity of ICH was low and comparable with that expected in bevacizumab-treated historical controls without brain metastases, as was the overall safety profile. BRAIN is the first study in patients with NSCLC and asymptomatic, untreated brain metastases. Although the data have not yet been validated in a larger trial, they suggest that bevacizumab-based systemic treatment may be an alternative approach to WBRT followed by chemotherapy in this highly selected population.

Disclosure of Potential Conflicts of Interest

B. Besse reports receiving a research grant from Roche. F. Barlesi and P.J. Souquet report receiving speakers bureau honoraria from and are consultant/advisory board members for Roche. C. Chouaid, X. Quantin, and J.-C. Soria are consultant/advisory board members for Roche. D. Moro-Sibilot is a consultant/advisory board member for Eli Lilly and Roche. M. Pérol reports receiving speakers bureau honoraria from and is a consultant/advisory board member for Eli Lilly and Roche. No potential conflicts of interest were disclosed by the other authors.

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Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): B. Besse, S. Le Moulec, J. Mazières, H. Senellart, F. Barlesi, C. Chouaid, E. Dansin, H. Bézard, R. Gervais, G. Robinet, A.-M. Ruppert, R. Schott, H. Léna, X. Quantin, P.J. Souquet, J. Trédaniel, D. Moro-Sibilot, M. Pérol


Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): A.-C. Madroszyk

Study supervision: I. Falchero, G. Robinet

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