**Appendix: Methods and Results in Patients Treated with Second-Line Bevacizumab Plus Erlotinib**

**Methods**

**Study design**

Inclusion criteria specific to the bevacizumab plus erlotinib (B+E) second-line cohort were that patients had not been previously treated with bevacizumab or erlotinib. Exclusion criteria specific to the B+E second-line cohort were: clinically significant, inflammatory, or infectious ocular disease; clinically significant gastrointestinal disease; patients unable to take oral medication or requiring parenteral feeding; hypersensitivity to erlotinib or any of its excipients (including lactose); previous first-line treatment with erlotinib; previous treatment with a drug targeting the epidermal growth factor receptor (EGFR; HER1) pathway: gefitinib, cetuximab, vandetanib, lapatinib, panitumumab, or others; or any known significant ophthalmological abnormalities of the surface of the eye.

**Study treatment**

Patients received bevacizumab plus erlotinib (150 mg/day orally) until disease progression or unacceptable toxicity.

**Assessments**

Assessments were performed every two cycles, including chest–abdomen scans and mandatory MRI scans 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 two patients in the second-line arm had a clinically significant intracranial hemorrhage (symptomatic, with National Cancer Institute Common Terminology Criteria for AEs 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 endpoints were investigator-assessed 6-month PFS rate. Secondary endpoints were investigator-assessed ORR according to RECIST, median PFS, median OS, and safety. Exploratory endpoints included response rates of brain metastases assessed by 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.

**Statistical analysis**

The predefined criteria for B+E second-line 6-month PFS rate was ≤15% (H0) and ≥35% (H1); this required 44 patients to be enrolled to demonstrate the efficacy of second-line B+E.

**Results**

**Patient characteristics**

24 patients were enrolled into the second-line B+E cohort (this cohort was capped at 24 patients as opposed to the originally specified 44 because of slow recruitment). Six patients (25.0%) withdrew or discontinued bevacizumab treatment due to AEs.None of the 12 patients tested had *EGFR* mutation-positive disease (Appendix Table 1). Median follow-up in the B+E cohort was 11.8 months; median duration of exposure to bevacizumab was five cycles.

**Efficacy outcomes**

Investigator-assessed ORRwas12.5% (95% CI, 2.7–32.4) (Appendix Figure 1 and Appendix Table 2). Responserate of brain metastases was20.8% (95% CI, 7.1–42.2);response rate of extracranial lesionswas12.5% (2.7–32.4) (Appendix Figure 2). The median duration of brain metastases response in patients with measurable brain disease (*n = 3*) was 8.6 months (95% CI, 6.1–not reached). Bevacizumab withdrawal due to intracranial progression occurred in 16.7% and extracranial progression in 54.2% of patients, with both reported in 4.2%.

The 6-month PFS rate was57.2% (95% CI, 37.0–76.3), with median PFS of6.3 months (3.0–8.4) (Appendix Figure 3). Because of the low number of patients enrolled, the primary efficacy analysis was of a descriptive nature only for the second-line cohort. Median OS was 12.0 months (95% CI, 8.9–20.2) (Appendix Figure 3),the 12-month survival rate was 50.0% (30.5–69.5), and the 18-month survival rate was 41.7% (23.1–61.5).Results by *EGFR* mutation are shown in Appendix Table 3.

**Post-study therapy**

Post-study therapy was given in 79.2% of B+E patients: 75.0% received at least one systemic cancer treatment (most common treatments were pemetrexed 50.0% and docetaxel 25.0%); 29.2% received radiotherapy for NSCLC; 8.3% underwent surgery. A total of eight patients received WBRT for their brain metastases, and the median time to WBRT was 6.6 months (range: 2.5 to 21.9 months).

**Safety**

No intracranial hemorrhage events were reported.There was one grade ≥3 bleeding event (grade 3 post-procedural hematoma, extracranial site). There were two serious AEs leading to death (one case of possible hypertensive encephalopathy and one case of ischaemic stroke, both considered related to bevacizumab). Grade ≥3 AEs occurred in 54.2% of patients (Appendix Table 4) andgrade ≥3 AEs of special interest occurred in 25.5% of patients.

**Appendix Tables**

**Appendix Table 1:** Characteristics of patients at baseline

|  |  |
| --- | --- |
|  | **Bevacizumab plus erlotinib (*n = 24*)a** |
| Sex |  |
| Male | 11 (46%) |
| Female | 13 (54%) |
| Age, years | 54.0 (34–70) |
| ECOG performance status |  |
| 0 | 13 (54%) |
| 1 | 11 (46%) |
| Histology |  |
| Adenocarcinoma | 23 (96%) |
| Large cell carcinoma | 1 (4%) |
| Recurrence of previous lung cancer |  |
| No | NA |
| Yes | NA |
| Additional metastatic sites |  |
| Lymph nodes | 13 (54%) |
| Liver | 5 (21%) |
| Adrenal | 9 (38%) |
| Pleura | 0 |
| Bone | 8 (33%) |
| Other | 4 (17%) |
| Median diameter per lesion, mm | 13.00 |
| Median number of target brain lesions at baseline\* |  |
| 0 | 5 (21%) |
| 1 | 13 (54%) |
| 2 | 6 (25%) |
| Smoking status |  |
| Past smoker | 17 (71%) |
| Current smoker | 4 (17%) |
| Never smoker | 3 (12%) |
| Recursive partitioning analysis class |  |
| 2 | 24 (100%) |
| *EGFR* mutation status |  |
| Tested | 12 (50%) |
| Positive | 0 |
| Exon 19 mutations | 0 |
| Exon 21 mutations | 0 |
| Negative | 10 (8%) |
| Sample not evaluable | 2 (17%) |
| No data available | 3 |

NA = not applicable

aData are *n* (%) or median (range).

bAll patients in the study had brain lesions [target (i.e. measurable) or non-target].

**Appendix Table 2:** Best response rates for primary tumors and metastases in 24 patients treated with second-line bevacizumab plus erlotinib

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Best overall responsea** | **Intracranial metastases responsea** | **Extracranial metastases responsea** |
| Responders (95% CI) | 12% (2.7–32.4) | 21% (7.1–42.2) | 12% (2.7–32.4) |
| Complete response (95% CI) | 0 | 4% (0.1–21.1) | 0 |
| Partial response (95% CI) | 12% (2.7–32.4) | 17% (4.7–37.4) | 12% (2.7–32.4) |
| Stable disease (95% CI) | 62% (40.6–81.2) | 50% (29.1–70.9) | 67 (44.7–84.4) |
| Progressive disease (95% CI) | 17% (4.7–37.4) | 17% (4.7–37.4) | 12% (2.7–32.4) |
| Missing | 8.3 | 12.5 | 8.3 |

aData are % (95% CI) or *n* (%).

**Appendix Table 3:**PFS, OS, and response rates according to *EGFR* mutation status in 24 patients treated with second-line bevacizumab plus erlotinib

|  |  |  |  |
| --- | --- | --- | --- |
|  | ***EGFR* mutation positive (*n = 0*)a** | ***EGFR* wild type (*n = 10*)a** | **Non-evaluable (*n = 14*)a** |
| 6-month PFS (95% CI) | – | 60% (25.3–82.7) | 55% (25.8–76.8) |
| Median PFS (95% CI), months | – | 8.4 (1.2–16.8) | 6.3 (2.5–7.5) |
| Median OS (95% CI), months | – | 20.1 (16.1–28.1) | 9.2 (6.3–13.6) |
| 12-month survival rate (95% CI) | – | 80% (51.2–97.7) | 29% (8.8–54.0) |
| 18-month survival rate (95% CI) | – | 70% (39.7–92.9) | 21% (4.7–45.8) |
| Responders | – | 1 (10%) | 2 (14%) |
| Complete response | – | 0 | 0 |
| Partial response | – | 1 (10%) | 2 (14%) |
| Stable disease | – | 6 (60%) | 9 (64%) |
| Progressive disease | – | 3 (30%) | 1 (7%) |
| Missing | – | 0 | 2 (14%) |

aData are % (95% CI) or *n* (%).

**Appendix Table 4:** Overview of AEs in 24 patients treated with second-line bevacizumab plus erlotinib

|  |  |
| --- | --- |
|  | **Bevacizumab plus erlotinib**  **(*n = 24*)a** |
| Any AE | 24 (100%) |
| Serious AEs | 7 (29%) |
| Grade 3–5 AEs | 13 (54%) |
| Grade 5 AEs (leading to death) | 2 (8%)b |
| Patients who discontinued bevacizumab treatment due to AE | 5 (21%) |
| Grade 3–5 AESIs |  |
| Total patients with at least one grade 3–5 AESIc | 6 (26%) |
| Bevacizumab-related AESIs |  |
| Thromboembolic events (venous) | 1 (4%) |
| Hypertension | 2 (8%) |
| Proteinuria | 2 (8%) |
| Thromboembolic events (arterial) | 1 (4%) |
| Bleeding event (post-procedural hematoma) | 1 (4%) |
| Erlotinib-related AESIs |  |
| Diarrhea | 1 (4%) |
| Rash | - |

aAll data are *n* (%).

bOne case of possible hypertensive encephalopathy and one case of ischemic stroke.

cPatients may have had more than one AESI.

**Appendix Figures**



**Appendix Figure 1.** Response rates for patients treated with second-line bevacizumab plus erlotinib. (A) Response rates for primary tumors and metastases, (B) best overall response for primary tumors in individual patients.

\*This patient had new lesions despite having a reduction in the primary lesion so was classed as having a best overall response of progressive disease.



**Appendix Figure 2.** Waterfall plots of best overall response for patients treated with second-line bevacizumab plus erlotinib.(A) For brain lesions, (B) for extracranial lesions

\*This patient had new lesions despite having a reduction in the primary lesion so was classed as having a best overall response of progressive disease.



**Appendix Figure 3.** Kaplan–Meier curves for second-line treatment with bevacizumab plus erlotinib. (A) Progression-free survival, (B) overall survival.