BRIDGE: An Open-Label Phase II Trial Evaluating the Safety of Bevacizumab + Carboplatin/Paclitaxel as First-Line Treatment for Patients with Advanced, Previously Untreated, Squamous Non-small Cell Lung Cancer

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Background: Patients with predominantly squamous non-small cell lung cancer (NSCLC) have been generally excluded from studies of bevacizumab treatment, because squamous histology was identified as a possible risk factor for severe (grade ≥3) pulmonary hemorrhage (PH) in a phase II study. BRIDGE was designed to determine whether delaying initiation of bevacizumab treatment and selecting patients without baseline risk factors for PH would lower the incidence of severe PH among patients with squamous NSCLC.

Methods: Patients in this open-label, single-arm study were treated with carboplatin/paclitaxel for two cycles, followed by carboplatin/paclitaxel and bevacizumab in cycles 3 to 6, followed by bevacizumab until progression or unacceptable toxicity. Eligible patients had stage IIIb, stage IV, or recurrent squamous NSCLC. The primary end point was incidence of grade ≥3 PH.

Results: Grade ≥3 PH occurred in 1 of 31 patients who received ≥1 dose of bevacizumab: estimated incidence was 3.2% (90% confidence interval 0.3–13.5%). The patient experienced grade 3 PH, discontinued from the study, then experienced grade 4 PH 10 days later, and died of progressive disease. No other serious bleeding events occurred. Nine patients (29.0%) experienced grade 3 adverse events, including five with hypertension; five patients experienced grade 4 adverse events (dyspnea, PH, basal ganglia infarction, cerebral ischemia, and pain). Median progression-free survival was 6.2 months (95% confidence interval 5.32–7.62 months).

Conclusions: The incidence of grade ≥3 PH was 3.2% (one patient). No new safety signals were identified. Although the rate of PH was low, the number of patients in this study was also low. Treatment of squamous NSCLC with bevacizumab should be considered experimental.

Key Words: Squamous, Non-small cell lung cancer, Bevacizumab, Pulmonary hemorrhage, Delayed initiation.

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Lung cancer is the leading cause of cancer death in the United States, with 219,440 new cases, and 159,390 deaths estimated to have occurred in 2009.[1] Approximately 85% of lung cancers are non-small cell lung cancers (NSCLCs), of which approximately one third have squamous histology. Squamous cell carcinomas tend to arise in the proximal large bronchi, potentially increasing the risk of pulmonary hemorrhage (PH) in patients with squamous tumors.

Bevacizumab (Avastin, Genentech Inc., South San Francisco, CA) is a recombinant, humanized monoclonal antibody directed against vascular endothelial growth factor, a key factor in tumor-associated angiogenesis. A randomized, phase II trial (AVF0757g) of carboplatin/paclitaxel (CP) ± bevacizumab for patients with advanced NSCLC initially showed that bevacizumab was effective for treatment. However, among 13 patients with squamous NSCLC, there were 4 (31%) cases of severe PH.[2–4] Consequently, patients with squamous NSCLC were excluded from the seminal phase II/III NSCLC trial conducted by the Eastern Cooperative Oncology Group (ECOG; Study E4599)[5] and have been generally excluded from the subsequent studies of bevacizumab for the treatment of NSCLC.[5,6] A case-control evaluation of clinical and radiographic factors associated with these events concluded that squamous cell histology and bevacizumab treatment were the principal risk factors for severe PH.[4]

Because in the AVF0757g trial the first dose of bevacizumab and chemotherapy was administered on day 1 of

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each treatment cycle, and because two of the four PH events in AVF0757g occurred early during the course of treatment (13 and 12 days after the first infusion),[2] it was hypothesized that delaying bevacizumab administration until after initial chemotherapy cycles might permit time for cytoreduction and epithelial healing, thereby protecting against occurrence of PH during early treatment. The AVF3744g pilot study (BRIDGE) described in this report was designed to explore whether such delay in initiation of bevacizumab treatment combined with selecting subjects without baseline risk factors for PH would result in a lower incidence of severe PH than was observed in the prior AVF0757g trial.

PATIENTS AND METHODS

Eligibility Criteria

Patients were eligible for this study if they had histologically or cytologically confirmed stage IIIB (with pleural effusion), stage IV, or recurrent predominantly squamous NSCLC; had measurable or evaluable disease; were 18 years or older; and had signed informed consent. An August 6, 2007 study amendment permitted enrollment of patients with previously treated brain metastases (formerly excluded). The 2007 study amendment also permitted the enrollment of patients with ECOG performance status (PS) 2 (formerly only ECOG PS 0–1 were permitted). However, only patients whose ECOG PS status was 0 or 1 by cycle 3 (i.e., after two cycles of chemotherapy) were permitted to receive any bevacizumab in this study.

Exclusion criteria included prior chemotherapy for metastatic disease; adjuvant or combined modality therapy within 6 months before study entry; extrathoracic metastases as the only sites of disease; untreated brain metastases; cavitation in intrathoracic lesions; gross hemoptysis within 3 months before study entry; major surgical procedure, open biopsy, or significant traumatic injury within 28 days before study; urinary protein creatinine ratio ≥1.0; and other general and laboratory-based exclusions. The following conditions were also reasons for exclusion: history of unstable angina; grade ≥2 congestive heart failure; abdominal fistula; gastrointestinal perforation; intraabdominal abscess; myocardial infarction; stroke; active symptomatic peripheral vascular disease within 6 months before study; history of significant vascular disease; evidence of bleeding diathesis or coagulopathy; and serious nonhealing wound, ulcer, or bone fracture. After a study amendment (June 12, 2006), the presence of tumor cavitation before initiation of bevacizumab therapy was added as an exclusion criterion based on a reanalysis of data from prior studies (bevacizumab; Genentech Inc.),[3] which indicated that cavitation might be associated with PH. After a second study amendment (August 6, 2007), patients with baseline evidence (radiologic or investigator determined) of tumor impingement or extension into the lumen of a major blood vessel (e.g., pulmonary artery or superior vena cava), or invading vascular structures, were also excluded.

Study Design

This was an open-label, single-arm, multicenter pilot study to evaluate the safety and efficacy of first-line CP plus bevacizumab (see study schematic, Figure 1). The study was

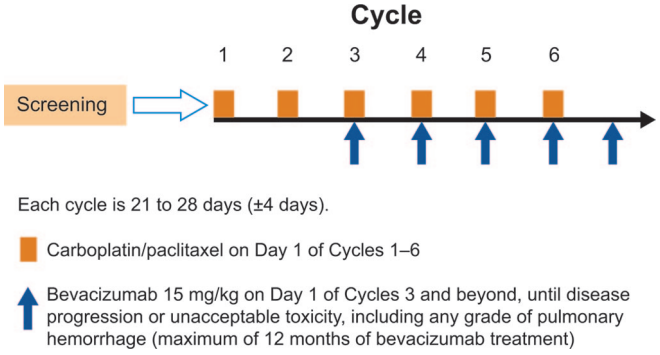

FIGURE 1. Schematic of the study design for BRIDGE.

divided into three treatment intervals: CP alone (cycles 1 and 2), CP plus bevacizumab (cycles 3–6), and bevacizumab alone (cycles 7 and beyond).

The primary objective of BRIDGE was to estimate the rate of grade ≥3 PH associated with delayed administration of bevacizumab for the treatment of patients with locally advanced, recurrent, or metastatic squamous NSCLC. Secondary objectives were to describe the incidence of select adverse events (AEs) in patients who received bevacizumab treatment through the safety follow-up period and to estimate progression-free survival (PFS) among patients who completed two cycles of chemotherapy and received bevacizumab. Baseline and post-baseline factors, including radiographic factors, were assessed for correlations with the risk of severe PH.

Enrollment of 40 subjects was planned, at approximately 25 centers in the United States, to achieve 30 bevacizumab-treated subjects. Study safety was monitored through review of AEs by the sponsor and a Scientific Advisory Board. Enrollment and bevacizumab treatment were to be stopped if three or more Grade ≥3 PH events were observed among 30 bevacizumab-treated patients (estimated incidence of approximately 10%) on-study or up to 60 days after discontinuing bevacizumab. Stopping rules, if implemented, would halt enrollment and bevacizumab treatment (for subjects on study) and would initiate a thorough reexamination of safety.

Although concurrent full-dose anticoagulation with aspirin (>325 mg) or full-dose warfarin (or its equivalent) was not permitted, low-dose (1–2 mg) warfarin was permitted for prophylaxis of intravascular catheters. Subcutaneous (prophylactic) heparin was permitted.

Data Collection

Tumor assessments were conducted on computed tomography (CT) or magnetic resonance imaging scans of the chest, abdomen, and other known or suspected sites of disease and were evaluated according to institutional standards. In addition to individual institutional review, imaging (CT or magnetic resonance imaging chest scans) assessment was conducted by an independent review facility (RadPharm Inc., Princeton, NJ). ECOG PS assessment was conducted at each treatment cycle.

Protocol-specified select AEs to be collected included the following: any grade PH, non-PH, or gastrointestinal

perforation, grade ≥2 arterial thromboembolic events, grade ≥2 left ventricular systolic dysfunction, grade ≥3 proteinuria, grade ≥3 hypertension, any serious AE, and any AE leading to study treatment discontinuation. The study was amended (June 12, 2006) to provide additional specific information on reversible posterior leukoencephalopathy syndrome and hypertensive encephalopathy.

Treatment Discontinuation and Modification Criteria

Bevacizumab treatment was to be discontinued in the event of any grade PH, venous thrombosis, arterial thromboembolic event, and wound dehiscence; grade ≥2 gastrointestinal perforation; grade ≥3 non-PH; grade 4 hypertension, proteinuria, left ventricular systolic dysfunction, or other events considered related to bevacizumab for up to 6 weeks. Patients were discontinued from the study before receiving first dose of bevacizumab (cycle 3) for any of the discontinuation criteria described earlier, disease progression, ECOG PS ≥2, significant toxicity precluding continuation of CP therapy, grade ≥2 PH before the start of bevacizumab treatment, or grade ≥2 symptomatic central nervous system hemorrhage.

Bevacizumab dose reduction was not permitted because there is no dose-response relationship for known bevacizumab toxicities. However, bevacizumab treatment interruption was permitted for subjects who experienced certain AEs: any grade non-PH; grade ≥2 bowel obstruction; grade ≥3 hypertension, proteinuria, left ventricular systolic dysfunction, or other events considered related to bevacizumab.

Data Analysis and Statistics

Descriptive statistics, including *n* (%) or median and range, are presented for demographic and patient characteristics and discontinuation and treatment characteristics. Incidence of select AEs is presented for the safety-evaluable population that included patients who received at least one dose of bevacizumab. For incidence of grade ≥3 PH, 90% confidence intervals (CI) were estimated using the Blyth-Still-Casella exact method.

The efficacy population consisted of all subjects who received at least one dose of bevacizumab. PFS was defined as the time from enrollment to documented disease progression based on RECIST criteria (investigator assessment) or death. Kaplan–Meier methodology was used to characterize the distribution of PFS and to estimate the probability of PFS of ≥6 months.

RESULTS

Study Population

From April 2006 to April 2008, 47 patients were enrolled in the study and received CP chemotherapy. Of these 47 patients, 31 met the protocol-specified eligibility criteria and received bevacizumab after two cycles of chemotherapy. These 31 patients had not experienced disease progression or exclusionary toxicities (including PH). The other 16 patients did not proceed to receive bevacizumab for the following reasons: progression ($n = 5$), AEs ($n = 6$), patient decision ($n = 2$), or other reasons ($n = 3$) (data not shown).

Approximately two thirds of the patients (31) who went on to receive bevacizumab were male (Table 1). No patients with ECOG PS 2 or treated brain metastases received bevacizumab in this study. Eighty-one percent of the 31 patients had stage IV disease; 13% had recurrent disease. Seven patients (23%) had received prior radiotherapy (four to the lung and one to the mediastinum); 26% had a prior thoracic surgery.

TABLE 1. Demographics and Baseline Characteristics[a]

Characteristics	Bevacizumab Treated ($n = 31$)
Age (yr)	
Mean (SD)	65.0 (7.9)
Median	65.0
Range	48–80
Age category, yr (%)	
<65	14 (45.2)
≥65	17 (54.8)
Sex, *n* (%)	
Male	21 (67.7)
Female	10 (32.3)
Race, *n* (%)	
White	30 (96.8)
African American	1 (3.2)
Baseline Eastern Cooperative Oncology Group performance status, *n* (%)	
0	12 (38.7)
1	19 (61.3)
No. of metastatic sites	
Mean (SD)	2.4 (1.1)
Median	2.0
Range	1–5
Patients with brain metastases, *n* (%)	
No	31 (100.0)
Subjects with prior radiotherapy, *n* (%)	
Yes	7 (22.6)
No	24 (77.4)
Site of prior radiotherapy, *n* (%)	
n	7[b]
Lung	4 (57.1)
Bone	2 (28.6)
Other	1 (14.3)
Mediastinum	1 (14.3)
Subjects with prior thoracic surgery, *n* (%)	
Yes	8 (25.8)
No	23 (74.2)
Subjects with prior adjuvant or neoadjuvant systemic therapy, *n* (%)	
Yes	3 (9.7)
No	28 (90.3)
Clinical stage, *n* (%)	
IIIb	2 (6.5)
IV	25 (80.6)
Recurrent	4 (12.9)

[a] Characteristics of patients who received >1 dose of bevacizumab are shown.
[b] One patient received prior radiotherapy to both "lung" and "other" sites.

TABLE 2. Incidence of Grade ≥3 Adverse Events[a]

	Patients with Grade 3 Events (n = 31)	Patients with Grade 4 Events (n = 31)
Any grade ≥3 adverse events, total, n (%)	14 (45.2)	6 (19.4)
Listing of adverse events, n (%)		
Hypertension	5 (16.1)	0
Dyspnea	2 (6.5)	1 (3.2)
Pulmonary hemorrhage	0	1 (3.2)
Arthralgia	2 (6.5)	0
Deep vein thrombosis	2 (6.5)	0
Basal ganglia infarction	0	1 (3.2)
Cerebral ischemia	0	1 (3.2)
Pain	0	1 (3.2)
Proteinuria	0	1 (3.2)
Asthenia	1 (3.2)	0
Chest pain	1 (3.2)	0
Confusional state	1 (3.2)	0
Congestive heart failure	1 (3.2)	0
Hemoptysis[b]	1 (3.2)	0
Hip fracture	1 (3.2)	0
Infection	1 (3.2)	0
Peripheral neuropathy	1 (3.2)	0
Pneumonia	1 (3.2)	0
Small bowel obstruction	1 (3.2)	0

[a] The highest grade of event is reported for each patient.
[b] This event occurred in the same patient who had grade 4 pulmonary hemorrhage.

Safety

The estimated incidence of grade ≥3 PH was 3.2% (90% CI 0.3–13.5%) among the 31 patients who received ≥1 dose of bevacizumab (Table 2). A grade 4 event occurred in a patient who did not have cavitation at baseline or at cycle 3 screening but developed cavitation before cycle 4. The patient discontinued from the study after a grade 3 PH and then experienced the grade 4 PH event 10 days later. The patient subsequently died of progressive disease. In addition, there was one grade 1 PH (hemoptysis) that occurred in a patient who had cavitation pre-cycle 3. Therefore, a total of two patients (6.5%) experienced a PH event of any grade. However, given the 2006 protocol amendment excluding patients with cavitation, this patient should not have continued in the study. No other grade ≥3 bleeding events occurred in this study. The relationship between timing of prior radiotherapy and risk of early bleeding, a secondary objective, could not be addressed in this study. There were no PH events among the 16 patients who did not receive bevacizumab.

No grade 5 AEs were reported in this study. The most frequently reported grade ≥3 events were hypertension (16.1%), dyspnea (9.7%), deep vein thrombosis (a venous thromboembolic event; 6.5%), and arthralgia (6.5%; Table 2). The protocol-specified selected AEs (AEs) of any grade reported in >5% of safety-evaluable patients included hypertension (19.4%; six patients: 5 patients, grade 3; 1 patient, grade 2); deep vein thrombosis (6.5%; two patients, grade 3); and PH (6.5%; two patients: one patient, grade 4; one patient, grade 1). There were no reports of reversible posterior leukoencephalopathy syndrome or hypertensive encephalopathy.

Tumor Characteristics

Independent review facility analysis of radiographic scans collected at baseline showed an average of 2.7 intrathoracic lesions per patient (data not shown). Five patients (11%) had baseline cavitations; two of these patients were discontinued from the study and did not receive any bevacizumab; the other three patients received ≥1 dose of bevacizumab on-study. Eight additional patients had evidence of de novo cavitation at the pre-cycle 3 screening; three of these patients did not receive any bevacizumab in the study, and the remaining five patients received ≥1 cycle of bevacizumab. After the pre-cycle 3 scan, new cavitations were observed in nine of the patients who had received bevacizumab.

Extent of Exposure and Patient Disposition

The median total dose of bevacizumab received was 5730 mg, for a median of six cycles (data not shown). Ten patients completed six cycles of bevacizumab plus chemotherapy and went on to receive single-agent bevacizumab. Of the 31 patients who received bevacizumab, three had delays in ≥1 treatment cycle (21 days).

Of the 31 bevacizumab-treated patients, 52% discontinued bevacizumab because of progressive disease (Table 3). Ten patients (32.2%) discontinued because of an AE: grade 4 cerebral ischemia, dyspnea, and proteinuria; grade 3 deep vein thrombosis (in two patients), hypertension, peripheral neuropathy, and congestive heart failure; grade 2 cerebral infarction; and grade 1 pulmonary embolism. Nineteen patients were still alive as of the data cutoff (July 6, 2009). Twelve patients (38.7%) had bevacizumab treatment interruptions (median of 14 days).

TABLE 3. Exposure to Study Treatment and Patient Disposition

	Bevacizumab-Treated Patients (n = 31)
No. of cycles of bevacizumab	
Mean (SD)	6.3 (4.6)
Median	6.0
Range	1–18
No. of cycles of chemotherapy	
Mean (SD)	5.2 (1.0)
Median	6.0
Range	3–6
Patient disposition, n (%)	
Completed 12 mo of bevacizumab treatment	2 (6.5)
Discontinued treatment, total	29 (93.5)
Due to disease progression	16 (51.6)
Due to adverse event	9 (29.0)
Due to patient's decision	1 (3.2)
Due to other reason	3 (9.7)
Still alive as of study cutoff	19 (61.3)

Median PFS among the bevacizumab-treated patients (n = 31) was 6.2 months (95% CI 5.32–7.62 months). Approximately 57% of bevacizumab-treated subjects had PFS of 6 months or more.

DISCUSSION

The BRIDGE study was designed to explore whether the risk of PH would be reduced in patients with squamous NSCLC by delaying the start of bevacizumab treatment (by two cycles) and by excluding patients with baseline risk factors for PH, including baseline cavitation, tumor impingement or extension into major blood vessels, history of hemoptysis or significant vascular disease, or evidence of bleeding diathesis or coagulopathy. Many of these risk factors were first identified in the phase II trial of bevacizumab for NSCLC (AVF0757g).[2,4] Delayed administration of bevacizumab was based on the hypothesis that this may permit cytoreduction and epithelial healing. This study had the largest sample size of bevacizumab-treated patients with squamous NSCLC to date.

The estimated incidence of grade ≥3 PH (3.2%, 90% CI 0.3–13.5%, one patient) in this study was less than expected based on prior experience (31% of patients with squamous NSCLC in AVF0757g),[2–4] and was acceptable as defined by the study protocol (up to 2 grade ≥3 events among ≥30 bevacizumab-treated patients). The patient with grade ≥3 PH did not have baseline or pre-cycle 3 evidence of cavitation but developed cavitation by cycle 4. PH events of any grade occurred in two patients (6.5%; grades 1 and 4). There were no reports of grade ≥3 bleeding events except for PH. The median PFS in this study (6.2 months, 95% CI 5.32–7.62) is favorable compared with historical data on first-line chemotherapy for patients with metastatic nonsquamous NSCLC, but interpretation is confounded by issues of patient selection: radiographically stable or responding disease after two cycles of CP (favorable), versus predominantly male population and preponderance of cigarette smoking in a population of patients with squamous histology (unfavorable), and the small number of patients in this study. Although the results from this study are encouraging compared with prior experience, this small single-arm study was not designed to directly address whether delaying the administration of bevacizumab by two cycles and selecting subjects without baseline risk factors reduced the risk of PH or improved the efficacy of CP. This would require a randomized design. Overall, the results of this study suggested an acceptable risk to benefit ratio in the setting of delayed bevacizumab administration.

A retrospective assessment of CT scans for features associated with PH concluded that cavitation and baseline hemoptysis were potential risk factors for PH in the setting of nonsquamous and mixed histology NSCLC.[4] Squamous histology is more likely to be associated with cavitation in NSCLC. In the BRIDGE study, there was no evidence of baseline cavitation in the patient with grade ≥3 PH. There was an initial increase in the rate of cavitation development in patients precycle 3 (chemotherapy alone). The number and size of cavitated lesions did not seem to increase after cycle 3; however, the small number of patients in this study does not permit conclusions to be made. Eligibility criteria in other studies of bevacizumab for NSCLC treatment have excluded patients with NSCLC of predominantly squamous histology; however, patients with mixed histologies that are composed primarily of nonsquamous elements have received bevacizumab in these other studies.

A recent European study (BO19734, AVASQ) assessed the safety of treatment with cisplatin-gemcitabine or CP with the addition of bevacizumab from cycle 2 onward in patients with advanced squamous NSCLC who were at risk for development of PH (defined as patients presenting with central tumors of any size or peripheral tumors with longest diameter ≥2 cm that had not been irradiated previously). All patients received a short course of radiation therapy 3 weeks before starting chemotherapy. Patients who had experienced grade ≥2 hemoptysis up to 3 months before study entry were not eligible. Among the first 20 patients to receive bevacizumab, two (10%, 90% CI 2.7–25.9) experienced grade ≥3 PH events: a grade 3 and a grade 5 event (in a patient who was found after central review to have tumor involvement in major blood vessels). The study was terminated early.

It is unclear whether factors at the molecular level should be considered in the treatment of squamous versus nonsquamous NSCLC. Although histology has not been traditionally considered among the prognostic factors associated with survival in the setting of NSCLC,[9,10] a phase III trial recently showed that pemetrexed plus cisplatin had lower efficacy against squamous NSCLC than gemcitabine plus cisplatin, whereas pemetrexed and cisplatin had greater efficacy against adenocarcinoma NSCLC.[11–13] Squamous cell carcinoma had no correlative associations with *KRAS* or *EGFR* mutations in NSCLC.[14,15] These findings underscore the need to discover biomarkers associated with predictive or prognostic value for squamous NSCLC.

There is an ongoing need to assess therapies that may improve survival in metastatic squamous NSCLC. Other drugs that are undergoing assessment in clinical trials for squamous NSCLC include monoclonal antibodies against the insulin-like growth factor type I receptor (figitumumab,[16] AMG-479,[17] and MK0646[18]) and axitinib, a small molecule inhibitor of vascular endothelial growth factor receptors 1, 2, and 3.[19] However, two recent trials involving patients with squamous cell carcinoma of the lung were either terminated early (CP-751,871, an insulin-like growth factor type 1 inhibitor) or resumed with only nonsquamous patients (motesanib, a multitargeted tyrosine kinase inhibitor). Bevacizumab was shown to be well tolerated in two studies in other cancers of squamous histology (squamous cancer of the head and neck[20–22] and squamous esophageal cancer[23]) with encouraging response rates.

In conclusion, the BRIDGE study, in which the start of bevacizumab treatment was delayed and in which patients with baseline risk factors for PH were excluded, showed a lower rate of grade ≥3 PH (1/31 [3.2%] patients, 90% CI 0.3–13.5%) than was observed in an earlier phase II study including patients with squamous NSCLC. Although the observed rate of PH was low, this was a small

study (31 patients received bevacizumab), and treatment of squamous NSCLC with bevacizumab should be considered experimental.

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