REVIEW

Antiangiogenic Agents in Combination with Chemotherapy in Patients with Advanced Non-Small Cell Lung Cancer

Susanna V. Ulahannan and Julie R. Brahmer

Department of Oncology, Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University Hospital, Baltimore, Maryland, USA

Most patients with non-small cell lung cancer (NSCLC) present with advanced disease requiring systemic chemotherapy. Treatment with the antiangiogenic agent bevacizumab in combination with standard platinum-based doublet chemotherapy has been shown to improve outcomes in patients with advanced NSCLC. Several multitargeted antiangiogenic tyrosine kinase inhibitors (e.g., sorafenib, sunitinib, cediranib, vandetanib, BIBF 1120, pazopanib, and axitinib) are also being evaluated in combination with standard chemotherapy. Here we review current clinical data with combination therapy involving antiangiogenic agents and cytotoxic chemotherapy in patients with advanced NSCLC.

Keywords: Antiangiogenesis inhibitors; Non-small cell lung cancer; Bevacizumab

INTRODUCTION

Lung cancer remains the leading cause of cancer-related deaths in the United States, with approximately 219,440 new cases and 159,390 deaths expected in 2009 (1). Each year more deaths result from lung cancer than from breast, colorectal, and prostate cancers combined (2). Approximately 85% of all lung cancer cases are categorized as non-small cell lung cancer (NSCLC), and most patients present with advanced disease at the time of diagnosis (1, 3). The standard of care for patients with advanced disease is platinum-based doublet chemotherapy (4). Adding a third cytotoxic agent to the regimen increases toxicity and does not provide additional clinical benefits (4). The Eastern Cooperative Oncology Group (ECOG) conducted a large (N = 1,207) randomized study that compared four platinum-based doublet chemotherapy regimens in patients with NSCLC (5). None of the regimens was found to yield superior efficacy, though fewer episodes of toxicity were noted with the combination of carboplatin and paclitaxel (5). The median survival in this study was 8 months (5). Although there is a survival benefit with improved quality of life when chemotherapy is given to patients with advanced NSCLC, it appears that an efficacy plateau is reached when conventional chemotherapy is used alone.

Angiogenesis is the growth of new microvessels from pre-existing vasculature, a process that involves a fine balance of proangiogenic and antiangiogenic factors and coordination between multiple cell types such as macrophages, endothelial cells, and pericytes (6–9). Angiogenesis is necessary for cancer cells to proliferate beyond microscopic size and to metastasize (10). The vasculature associated with pathologic angiogenesis is abnormal in structure and function; it is characterized by tortuous, dilated, saccular vessels that are poorly organized and hyperpermeable (6–8). These vascular abnormalities lead to an abnormal tumor microenvironment with interstitial hypertension, hypoxia, and acidosis; this, in turn, increases the production of vascular endothelial growth factor (VEGF) and decreases the effectiveness of cytotoxic chemotherapy (11, 12).

The vascular endothelial growth factor plays a key role in regulation, both in normal and cancer cells, promoting endothelial cell migration and proliferation necessary for angiogenesis. VEGF is over expressed in a majority of malignant tumors, including NSCLC (12–15), and elevated blood levels of VEGF are associated with tumor aggressiveness and a poor prognosis (13). Three VEGF receptors (VEGFR) have been identified: VEGFR1, VEGFR2, and VEGFR3. The biological effects of VEGF are mediated by VEGFR1 and VEGFR2; VEGFR2 is believed to play the primary role in activating endothelial cells. VEGFR3 is associated primarily with lymphatic vessel growth (12, 14). Other growth factors, such as platelet-derived growth factor (PDGF) and fibroblast growth factor (FGF), also play key roles in promoting angiogenesis (16, 17).

Bevacizumab is a monoclonal antibody that targets circulating VEGF and inhibits VEGF binding to VEGFRs, thereby preventing its proangiogenic activity (18). In 2006, bevacizumab was approved by the US Food and Drug Administration for the first-line treatment of patients with advanced nonsquamous NSCLC in combination with carboplatin and paclitaxel (19). However, resistance often develops, and only approximately 50% of patients are actually eligible for bevacizumab treatment. Several mechanisms have been proposed that may account for the additive or synergistic activity of antiangiogenic agents and cytotoxic...
TARGETING ANGIOGENESIS WITH BEVACIZUMAB

First-line treatment

Bevacizumab is the first antiangiogenic agent to show a survival benefit when added to standard doublet chemotherapy in the first-line treatment of patients with advanced NSCLC (20). A randomized phase II trial of 99 patients with advanced NSCLC compared paclitaxel and carboplatin therapy with or without bevacizumab 7.5 or 15 mg/kg (Table 1) (21). The patients who received the higher dose of bevacizumab had a higher response rate (RR) (31.5% vs. 18.8%), longer time to progression (TTP; 7.4 months vs. 4.2 months; \( p = 0.023 \)), and a trend toward increased overall survival (OS) (17.7 months vs. 14.9 months; \( p = 0.63 \)) compared with patients given placebo. However, fatal hemoptysis was observed in four of 66 bevacizumab-treated patients and was apparently associated with squamous cell histology, tumor cavitation, centrally located tumors, and tumors close to major vessels (21).

Subsequently, ECOG conducted a large, randomized, multicenter, phase III study (E4599) that enrolled 878 patients with advanced or recurrent nonsquamous NSCLC (Table 1) (20). Carboplatin/paclitaxel was administered every 3 weeks for six cycles with or without bevacizumab 15 mg/kg (20). Treatment with bevacizumab was continued until evidence of disease progression. In order to reduce the risk of bleeding, patients with squamous cell histology, brain metastases, therapeutic anticoagulation, or a history of gross hemoptysis were excluded from the trial. The primary end point, OS, was statistically superior in patients who received bevacizumab (12.3 months vs. 10.3 months; hazard ratio \( [HR], 0.79; \ p = 0.003 \)) (20). These patients also showed a significant improvement in RR (35% vs. 15%; \( p < 0.001 \)) and progression-free survival (PFS) (6.2 months vs. 4.5 months; \( p < 0.001 \)) (20). Increased frequencies of bleeding, febrile neutropenia, hypertension, and proteinuria were reported in the bevacizumab arm (\( p < 0.05 \)). There was also a higher incidence of treatment-related deaths in patients given bevacizumab than in patients given chemotherapy alone (15 vs. 2; \( p = 0.001 \)) (20). The 15 deaths in the bevacizumab arm were attributed to pulmonary hemorrhage (\( N = 5 \)), complications of neutropenic fever (\( N = 5 \)), gastrointestinal (GI) bleeding (\( N = 2 \)), cerebrovascular events (\( N = 2 \)), and a probable pulmonary embolus (\( N = 1 \)) (20). Bevacizumab was subsequently approved based on the results of this trial.

The retrospective analyses from E4599 revealed that OS was not significantly improved with bevacizumab in women (20). However, OS with or without bevacizumab was higher in women than in men, though this difference did not reach statistical significance (20). There was no difference in OS in patients of >70 years of age, but they did have a higher degree of reported toxicity (38). The biomarkers VEGF, basic FGF, intercellular adhesion molecule (ICAM), and E-selectin were measured before and after treatment in E4599 (39). Low baseline ICAM levels were significantly associated with improved RR (32% vs. 14% in patients with high ICAM levels; \( p = 0.02 \)) and OS (\( p = 0.0005 \)) (39). This suggests that patients with low baseline ICAM levels could benefit from the addition of bevacizumab to standard chemotherapy regimens; however, this needs to be confirmed in prospective randomized trials.

A second phase III, randomized trial, AVAiL, evaluated bevacizumab 7.5 mg/kg and 15 mg/kg in combination with cisplatin and gemcitabine in patients with advanced nonsquamous NSCLC (Table 1) (33). This study showed significant improvement in the primary end point, PFS, with the addition of bevacizumab at either the high dose (6.5 months vs. 6.1 months; HR, 0.82; \( p = 0.03 \)) or the low dose (6.7 months vs. 6.1 months; HR, 0.75; \( p = 0.003 \)) compared with chemotherapy alone, at a median follow-up of ≥7 months (33). Response rates in the patients receiving high-dose bevacizumab, low-dose bevacizumab, and placebo were 30.4% (\( p = 0.0023 \)), 34.1% (\( p < 0.0001 \)), and 20.1%, respectively (33). After a median of ≥12.5 months of follow-up, median OS was not significantly different from chemotherapy alone with bevacizumab 7.5 mg/kg (13.1 months vs. 13.6 months; HR, 0.93; \( p = 0.42 \)) or 15 mg/kg (13.1 months vs. 13.4 months; HR, 1.03; \( p = 0.761 \)) (40). Although AVAiL trial was not powered to directly compare the two doses of bevacizumab, the results indicate similar efficacy and toxicity profiles (33). A retrospective analysis found that either dose of bevacizumab used as single-agent maintenance therapy might have clinical benefit (PFS, 4.6 months vs. 3.2 months with control), although bevacizumab was not associated with an OS benefit (41).

Activity was also observed in a phase II study with the combination of pemetrexed, carboplatin, and bevacizumab followed by maintenance therapy with pemetrexed and bevacizumab as first-line treatment in patients with advanced NSCLC (Table 1) (22). In the 49 patients assessed, RR was 55%, PFS was 7.8 months, and OS was 14.1 months. No grade 3/4 hypertension or pulmonary hemorrhage was observed, but four cases of grade 3/4 diverticulitis were reported (22). This was a small trial that included more women than men, which could explain the favorable survival rate. In light of the data from this trial, the large (\( N = 900 \)) phase III Pointbreak trial was initiated to compare (a) pemetrexed, carboplatin, and bevacizumab followed by maintenance therapy with pemetrexed and bevacizumab with (b) paclitaxel, carboplatin, and bevacizumab followed by maintenance bevacizumab (42). Several other phase II trials are evaluating the combination of bevacizumab with platinum-based doublet chemotherapy as first-line treatment in patients with advanced NSCLC (Table 1) (22, 23–28, 30–32, 43). In
addition, many other clinical studies are currently recruiting patients and will evaluate first-line bevacizumab in combination with chemotherapy and/or pemetrexed (Table 2).

**Second-line Treatment**

Bevacizumab has also been studied as second-line therapy (Table 1). One phase II trial evaluated the efficacy and toxicity of pemetrexed plus bevacizumab as second-line therapy in 48 patients with advanced NSCLC (36). A partial response (PR) was reported in five patients (10%) and stable disease (SD) was reported in 19 patients (40%), with a median PFS of 4.8 months and OS of 8.6 months (36). The grade 3/4 hematologic toxicities occurring in ≥10% of patients were neutropenia (19%), leukopenia (17%), and lymphopenia (13%) (36). The grade 3/4 nonhematologic toxicities occurring in ≥10% of patients were thrombosis (10%), dyspnea (10%), and fatigue (13%) (36). A separate phase II trial compared bevacizumab plus chemotherapy (docetaxel or pemetrexed), bevacizumab plus erlotinib, and chemotherapy alone in 120 patients with advanced nonsquamous NSCLC in the second-line treatment setting (29). Median PFS for bevacizumab–chemotherapy, bevacizumab–erlotinib, and chemotherapy alone was 4.8 months, 4.4 months, and 3.0 months, respectively, while median OS was 12.6 months, 13.7 months, and 8.6 months, respectively. There were no significant differences for these outcomes between the two bevacizumab arms, but superiority for disease progression or death was demonstrated for bevacizumab–chemotherapy versus chemotherapy alone (HR, 0.66, 95% CI, 0.38–1.16) and for bevacizumab–erlotinib versus chemotherapy alone (HR, 0.72, 95% CI, 0.42–1.23). Partial response or complete response (CR) was reported in five patients in each of the bevacizumab–chemotherapy and chemotherapy alone arms, and for seven patients in the bevacizumab–erlotinib arm (29). The grade 3/4 neutropenia occurred in eight patients receiving bevacizumab–chemotherapy, two patients receiving bevacizumab–erlotinib, and seven patients receiving chemotherapy alone.

These results and those of an earlier randomized phase III trial comparing pemetrexed and docetaxel suggest that the combination of bevacizumab and pemetrexed may provide clinical benefit in the treatment of NSCLC (44). Results from another phase II study suggest that the addition of oxaliplatin to bevacizumab/pemetrexed may further improve outcomes (Table 1) (37).

**Safety**

The toxicities associated with bevacizumab may be directly related to its mechanism of action. Hypertension, which occurs frequently, may be due to the decreased synthesis...
| Phase | Trial description | Identifier number |
|-------|-------------------|-------------------|
| **Early-stage NSCLC** | | |
| II | Neoadjuvant bevacizumab in combination with cisplatin-based chemotherapy versus neoadjuvant cisplatin and doceatxel, both followed by adjuvant bevacizumab, in patients with Stage IB–IIIA NSCLC undergoing surgical resection. | NCT00130780 |
| II | Neoadjuvant bevacizumab in combination with carboplatin and paclitaxel in patients with Stage IB–IIA NSCLC undergoing surgical resection. | NCT00960297 |
| II | Neoadjuvant bevacizumab in combination with cisplatin and gemcitabine, followed by cisplatin and etoposide after surgical resection, in patients with Stage IIA NSCLC. | NCT00924209 |
| II | Adjuvant bevacizumab in combination with carboplatin and docetaxel, followed by maintenance bevacizumab and erlotinib, in patients with surgically resected Stage IB–IIIA NSCLC. | NCT00621049 |
| II | Adjuvant bevacizumab in combination with chemotherapy versus chemotherapy alone in patients with surgically resected Stage IB–IIIA NSCLC. | NCT00324805 |
| **First-line in advanced NSCLC** | | |
| II | Bevacizumab in combination with carboplatin and gemcitabine. | NCT00150657 |
| II | Bevacizumab in combination with carboplatin and docetaxel, both followed by adjuvant bevacizumab, in patients with Stage IB–IIIA NSCLC undergoing surgical resection. | NCT00960297 |
| II | Bevacizumab in combination with carboplatin and paclitaxel, and erlotinib, in patients with asymptomatic untreated brain metastases. | NCT00924209 |
| II | Bevacizumab in combination with carboplatin and paclitaxel, or second-line bevacizumab in combination with erlotinib, in patients aged ≥70 years. | NCT00254319 |
| II | Bevacizumab in combination with carboplatin and gemcitabine and docetaxel, both followed by adjuvant bevacizumab, in patients with Stage IB–IIIA NSCLC undergoing surgical resection. | NCT00254319 |
| II | Bevacizumab in combination with carboplatin, paclitaxel, and erlotinib, in patients with surgically resected Stage IB–IIIA NSCLC. | NCT00961415 |
| II | Bevacizumab in combination with cisplatin and gemcitabine, followed by maintenance bevacizumab and pemetrexed. | NCT00762034 |
| II | Bevacizumab in combination with carboplatin and pemetrexed, followed by maintenance bevacizumab and pemetrexed. | NCT00762034 |
| II | Bevacizumab in combination with carboplatin and gemcitabine, followed by bevacizumab in combination with erlotinib at disease progression. | NCT00762034 |
| II | Bevacizumab in combination with carboplatin and paclitaxel, followed by second-line bevacizumab and pemetrexed or second-line pemetrexed alone. | NCT00762034 |
| II | Bevacizumab in combination with paclitaxel and pemetrexed. | NCT00762034 |
| **Second- or third-line in advanced NSCLC** | | |
| II | Second- or third-line bevacizumab in combination with carboplatin and paclitaxel. | NCT00753999 |
| II | Second-line bevacizumab in combination with vinorelbine. | NCT00753999 |
| II | Second-line bevacizumab in combination with carboplatin and paclitaxel. | NCT00753999 |
| II | Second-line bevacizumab in combination with carboplatin and paclitaxel. | NCT00753999 |
| II | Second-line bevacizumab in combination with pemetrexed. | NCT00753999 |
| II | Second-line bevacizumab in combination with pemetrexed versus pemetrexed alone. | NCT00753999 |
| II | Second-line bevacizumab in combination with erlotinib. | NCT00749567 |
| II | Second-line bevacizumab in combination with erlotinib. | NCT00436332 |
| II | Second-line bevacizumab in combination with ixabepilone. | NCT01057212 |

*ClinicalTrials.gov accessed on November 22, 2010.  
Abbreviations. ECOG: Eastern Cooperative Oncology Group; NSCLC: non-small cell lung cancer.
of nitrous oxide that occurs as a result of VEGF inhibition and leads to increased vascular tone (45). In addition, hypertension induced by bevacizumab may also contribute to proteinuria (46).

Bevacizumab has been associated with a large number of potentially serious adverse events (AEs) in patients with NSCLC. The most serious, and sometimes fatal, are GI perforation, wound healing complications, hemorrhage, arterial thromboembolic events, hypertension, nephrotic syndrome, neutropenia, and congestive heart failure (47). Common AEs in patients receiving bevacizumab include asthenia, abdominal pain, other pain, headache, hypertension, diarrhea, nausea, vomiting, anorexia, stomatitis, constipation, upper respiratory infection, epistaxis, dyspnea, exfoliative dermatitis, and proteinuria (47).

The ATLAS trial of maintenance bevacizumab and erlotinib (N = 598) (48), the PASSPORT trial of bevacizumab with first- or second-line chemotherapy (N = 106) (49), and the BeTa trial of bevacizumab with erlotinib in the second-line setting (N = 37) (50) all included patients with treated brain metastases, with some receiving therapeutic anticoagulation. Central nervous system (CNS) hemorrhages were reported in three patients participating in ATLAS, and five patients in ATLAS and three patients in PASSPORT-experienced pulmonary hemorrhages (48, 49). These data indicate that patients with treated brain metastases and patients receiving therapeutic anticoagulation may be treated with bevacizumab.

The most common AEs in AVAiL were hematologic and related to GI, with a similar incidence in the three treatment arms (low-dose bevacizumab, high-dose bevacizumab, and placebo) (51). Adverse events that occurred at a higher frequency with bevacizumab included hypertension (7% and 9% vs. 2%, proteinuria (2% and 3% vs. 0%), and bleeding (4% and 5% vs. 2%). Hemoptysis was reported in 0.5% and 1.2% of patients in the low- and high-dose bevacizumab arms and in 1.3% of patients in the placebo arm (51). Serious AEs were reported in 39%, 45%, and 36% of patients, respectively (51). Despite the fact that 9% of the study population was receiving therapeutic anticoagulation, no pulmonary hemorrhage was reported in the initial publication of the trial or the final safety analysis (33, 51).

Two large cohort studies (SAiL and ARIES) have focused on the safety of bevacizumab. SAiL, which enrolled 2,212 patients, evaluated the safety of first-line bevacizumab, 7.5 mg/kg and 15 mg/kg, in combination with chemotherapy. At baseline, 4% of the patients received anticoagulation therapy, with bleeding seen in 924 patients (34). However, significant bleeding and hemoptysis were rare and serious bleeding (grade ≥3) of any cause was reported in 81 patients. Arterial and venous thromboembolism occurred in 302 patients, and cerebral hemorrhage in seven patients (34). Congestive heart failure was observed in 17 patients. Hypertension occurred in 790 patients, but only 125 patients had grade ≥3 hypertension. Proteinuria was reported in 764 patients, and GI perforation was reported in 30 patients (34).

The ARIES trial (N = 1,518), which is evaluating bevacizumab in combination with first-line chemotherapy regimens, has enrolled patients with locally advanced or metastatic NSCLC. The most common first-line chemotherapeutic regimen used with bevacizumab was carboplatin/paclitaxel (64%) (35). Of the treated patients, 8% had brain metastases and 5% were receiving therapeutic anticoagulation. A total of 45 patients had a grade ≥3 bleeding event, one had CNS hemorrhage, and 22 had serious arterial thromboembolic events. Adverse effects in the overall population included hypertension (3.8%) and grade ≥3 bleeding events (GI hemorrhage, 1.1%; severe pulmonary hemorrhage, 0.7%; and CNS hemorrhage, 0.1%) (35).

Results from E4599 have suggested a longer OS in patients with hypertension (15.9 months vs. 11.5 months without hypertension) and improved PFS with the onset of hypertension during bevacizumab treatment (7.0 months vs. 5.5 months), although these results did not reach statistical significance (52). Similar findings regarding the relationship between bevacizumab-associated hypertension and improved survival have been reported in the CALGB 90206 trial involving patients with metastatic renal cell carcinoma (53). However, further investigation of this association is warranted. A recent presentation of a large study of approximately 5,900 patients across six placebo-controlled, phase III studies of bevacizumab showed hypertension arising during treatment did not predict improvement in PFS or OS (54).

A retrospective evaluation of risk factors associated with severe pulmonary hemorrhage in patients treated with carboplatin/paclitaxel plus bevacizumab suggests that baseline tumor cavitation was the only risk factor for early-onset pulmonary hemorrhage. Central tumor location was not predictive of risk (55).

SMALL-MOLECULE, ANTIANGIOGENIC TYROSINE KINASE INHIBITORS (TKIs)

The proangiogenic activity of VEGF is dependent on signaling through its cognate receptors (i.e., the VEGFRs); thus, blocking these receptors is another antiangiogenic strategy (56). The receptors can be inhibited using small-molecule TKIs, which compete with adenosine triphosphate (ATP) for the active site of the tyrosine kinase (TK) domain and block receptor activation (56). Many TKIs that inhibit VEGFR also inhibit other key pathways involved in angiogenesis, including FGF and PDGF and their respective receptors (56). It has been suggested that because of some redundancy in proangiogenic signaling, both the FGF and PDGF pathways may play a role in the development of resistance to VEGF blockade (57–60). Thus, by targeting multiple pathways, these agents may have the potential to overcome resistance to agents directed against only VEGF, such as bevacizumab (61, 62).

Sorafenib

Sorafenib is an oral multi-kinase inhibitor that targets tumor growth, survival, and angiogenesis, by inhibiting VEGFR2, VEGFR3, and PDGF receptor (PDGFR) TKs (63). It also targets the Raf kinases, key signaling molecules downstream of Ras that transmit proliferative and cell survival signals (63).
Table 3. Results from phase II and III trials of antiangiogenic TKIs in combination with chemotherapy in NSCLC.

| Reference          | Phase | Regimen                                                                 | N*   | RR (%)       | PFS (mo) | OS (mo) |
|--------------------|-------|--------------------------------------------------------------------------|------|--------------|----------|---------|
| Sorafenib          | Flaherty 2008 (66)   | CBDCA AUC 6 + PTX 225 mg/m² + sorafenib 100, 200, or 400 mg twice daily. | 39   | 26           | 10.1 (melanoma) | NR     |
| Scagliotti 2010 (67) | III   | CBDCA AUC 6 + PTX 225 mg/m² + placebo.                                   | 462  | 24           | 3.4 (other tumor types) | 10.6  |
|                    |       | CBDCA AUC 6 + PTX 225 mg/m² + sorafenib 400 mg twice daily.              | 464  | 27.4         | 4.6      | 10.7    |
| Cediranib          | Gadgeel 2009 (68)    | Pem 500 mg/m² + cediranib 30 mg/day.                                    | 31   | 16           | NR       | NR      |
| Vandetanib         | De Boer 2009 (69)    | Pem 500 mg/m² + vandetanib 100 mg/day.                                  | 10   | 10           | NR       | NR      |
|                    |       | Pem 500 mg/m² + vandetanib 300 mg/day.                                  | 11   | 0            | NR       | NR      |
| Heymach 2008 (70)  | II    | CBDCA AUC 6 + PTX 200 mg/m² + placebo.                                  | 52   | 25           | ~6 (23 weeks) | 12.6  |
|                    |       | CBDCA AUC 6 + PTX 200 mg/m² + vandetanib 300 mg/day.                    | 56   | 32           | ~6 (24 weeks) | 10.2  |
| Heymach 2007 (71)  | II    | TXT 75 mg/m² + placebo.                                                 | 41   | 12           | 2.8      | 13.4    |
|                    |       | TXT 75 mg/m² + vandetanib 100 mg/day.                                  | 42   | 26           | 4.3      | 13.1    |
| Herbst 2010 (72)   | III   | TXT 75 mg/m² + vandetanib 300 mg/day.                                  | 44   | 18           | 4.0      | 7.9     |
| De Boer 2009 (73)  | III   | TXT 75 mg/m² + vandetanib 100 mg/day.                                  | 697  | 10           | 3.2      | 9.9     |
|                    |       | TXT 75 mg/m² + vandetanib 300 mg/day.                                  | 694  | 17           | 4.0      | 10.3    |
|                    |       | Pem 500 mg/m² + vandetanib 300 mg/day.                                  | 278  | 7.9          | NR       | NR      |
|                    |       | Pem 500 mg/m² + vandetanib 100 mg/day.                                  | 256  | 19.1         | NR       | NR      |

*Patients evaluable for efficacy.

Abbreviations: AUC: area under the curve; CBDCA: carboplatin; NR: not reported; NSCLC: non-small cell lung cancer; OS: overall survival; Pem: pemetrexed; PFS: progression-free survival; PTX: paclitaxel; RR: response rate; TKI: tyrosine kinase inhibitor; TXT: docetaxel.

Single-agent sorafenib has shown activity in patients with advanced NSCLC in the first-line setting (64, 68). Sorafenib has been combined with conventional chemotherapy in multiple studies (Table 3) (66, 67). In one phase I/II trial, carboplatin/paclitaxel in combination with sorafenib was evaluated in patients with advanced NSCLC (66). Among 39 evaluable patients, nine achieved a PR, and one achieved a CR; however, all these patients had melanoma. Median PFS for patients without melanoma was 104 days. The drug-related AEs were similar to those reported with single-agent sorafenib and included rash, hand–foot syndrome, and GI side effects (66, 74). Based on these results, the randomized phase III ESCAPE trial was initiated. The ESCAPE trial enrolled 926 patients with advanced NSCLC who received carboplatin/paclitaxel with or without sorafenib as first-line therapy (67). There were no significant differences between the treatment arms in RR (24% vs. 27%), PFS (4.6 months vs. 5.4 months), or OS (10.7 months vs. 10.6 months), and as a result the trial was stopped early. There was a higher rate of drug-related infection in patients who received sorafenib than in those who received placebo (6.5% vs. 2.2%; p = .002). The grade 5 toxicity was observed more frequently in patients who received sorafenib versus those who received chemotherapy alone (14 patients vs. 4 patients; p < .001). In a subset analysis, shorter survival times were observed in patients with squamous cell histology who received sorafenib plus chemotherapy compared with those who received chemotherapy alone, though this observation was not statistically significant (67). Another ongoing large phase III trial, NExUS (NCT00449033), is evaluating gemcitabine/cisplatin with or without sorafenib as first-line therapy in patients with NSCLC (Table 3), and other studies are assessing second-line sorafenib monotherapy (Table 4).

Sunitinib

Sunitinib is a multitargeted small-molecule TKI that targets VEGFR1, VEGFR2, VEGFR3, PDGFR, fms-like TK-3 (Flt3), c-kit, and rearranged during transfection (RET) (75, 76). Sunitinib has shown single-agent activity in a multicenter phase II trial as second- or third-line therapy in patients with advanced NSCLC, when administered according to a schedule of 4 weeks with treatment followed by 2 weeks without treatment, at a starting dose of 50 mg/day (76). The trial resulted in a RR of 11%, PFS of 12 weeks, and OS of 23.4 weeks. These findings are comparable with those of currently approved agents in this treatment setting. The most common grade 3/4 nonhematologic AEs included fatigue/asthenia (29%), pain/myalgia (17%), dyspnea (11%), and nausea/vomiting (10%). The grade 3/4 hematologic AEs included lymphopenia (25%), thrombocytopenia (5%), and neutropenia (5%) (76). Notably, of the three patients in the study who suffered hemorrhage-related deaths, two had squamous NSCLC (both experienced pulmonary hemorrhage). In a separate, open-label phase II study, sunitinib was administered continuously (without a 2-week break) at a lower starting dose of 37.5 mg/day to 47 patients with advanced NSCLC as second- or third-line treatment (77). One patient achieved a PR, and 11 patients demonstrated SD. Median PFS and OS were 2.7 months and 8.6 months, respectively. The most frequently reported grade 3/4 AEs included fatigue (17.0%), hypertension (8.5%), and dyspnea (6.4%).

In a phase I study, sunitinib was combined with cisplatin and gemcitabine as first-line therapy in patients with advanced NSCLC (78). The combination resulted in a manageable toxicity profile and PRs were observed in five of 24 patients. A second phase I study evaluated the combination of sunitinib and docetaxel in 50 patients with advanced solid...
tumors, including 18 patients with NSCLC (79). PR was observed in three patients, SD was observed in 12 patients, and AEs were manageable. Ongoing clinical trials are further evaluating the benefits of adding sunitinib to standard therapies and as maintenance after first-line therapy (Table 4).

**Cediranib**

Cediranib is a highly potent and selective inhibitor of the VEGF pathway with activity against all three VEGF receptors, PDGFRs, and c-kit (80). In phase I studies, cediranib has demonstrated antitumor activity as a single agent with a manageable toxicity profile. The most frequently reported AEs include diarrhea, fatigue, dysphonia, and hypertension (81, 82).

Cediranib at doses of 20, 30, and 45 mg was evaluated in a phase I study in combination with four chemotherapy regimens (FOLFOX, irinotecan, docetaxel, and pemetrexed) in 46 heavily pretreated patients with advanced solid tumors (83). Of 35 patients who were evaluable for toxicity, grade 3/4 AEs observed across all four arms included fatigue, diarrhea, hand–foot syndrome, neutropenic fever, and hypertension (83). In another phase I study (N = 15), cediranib 30 mg and 45 mg was combined with standard doses of cisplatin/gemcitabine in patients with advanced NSCLC (84). The combination was associated with increased toxicity compared with chemotherapy alone (84). All 12 of the evaluable patients showed some degree of initial tumor shrinkage and four achieved PRs (84). In another phase II trial (N = 20), once-daily cediranib 30 mg and 45 mg in combination with carboplatin/paclitaxel administered every 3 weeks was evaluated as first-line treatment in patients with advanced NSCLC (85). Patients receiving anticoagulation were eligible, but patients with a history of hemoptysis or bleeding were excluded. Adverse events included fatigue, myalgia, hypertension, GI toxicities, and neutropenia (85). Progression-free survival was reported in nine patients, and all but one patient showed some evidence of tumor shrinkage; median TTP was 7.6 months (85). Antitumor activity was observed at both dose levels, but with no indication of a dose effect (85).
BR.24 is a randomized, double-blind, placebo-controlled phase II/III trial of cediranib 30 mg in combination with carboplatin/paclitaxel as first-line treatment in patients with NSCLC (86). This trial was not continued into phase III as there appeared to be excessive toxicity, although evidence of clinical activity was observed (86, 87). BR.29 will compare cediranib 20 mg in combination with carboplatin/paclitaxel with chemotherapy alone as first-line treatment in patients with NSCLC (Table 4).

An ongoing phase II trial is evaluating cediranib in combination with pemetrexed for second- or third-line treatment of advanced NSCLC (Table 3) (68). This study consists of two cohorts: patients who have not received prior bevacizumab (cohort A) and patients who have received prior bevacizumab (cohort B). In a preliminary analysis of the first 31 evaluable patients, the confirmed RR was 16% (10% in cohort A and 25% in cohort B) and the disease control rate was 71% (74% in cohort A and 67% in cohort B). The grade 3/4 nonhematologic AEs included fatigue (21%), diarrhea (9%), anorexia (6%), hypertension (3%), cardiac ischemia (3%), bronchopleural fistula (3%), and esophagitis (3%). The grade 3/4 neutropenia was reported in 21% of patients and febrile neutropenia occurred in 3% of patients (68).

Vandetanib
Vandetanib is a small-molecule inhibitor that blocks both the VEGFR and EGFR pathways, although it is more specific for the VEGFR pathway (88, 89). It is also a potent inhibitor of RET receptor TK activity (72). A number of studies have evaluated vandetanib in combination with chemotherapy (Table 3) (69–73). Response rates were increased in the combination arms compared to chemotherapy-only arms. In addition, most of these studies demonstrated a prolongation in PFS, but no improvement in OS. In a double-blind randomized, phase 3 trial (ZODIAC) the combination of vandetanib and docetaxel was evaluated as a second-line treatment in patients with advanced NSCLC (N = 1,391). The addition of vandetanib improved PFS (4.0 months in the Vandetanib group vs. 3.2 months in the placebo group) but no significant improvement in OS was reported (72). ZEIST, a randomized phase III trial (N = 1,240) in patients with advanced, previously treated NSCLC, demonstrated that single-agent vandetanib and erlotinib had equivalent efficacy by PFS (HR, 0.98; p = .721) and OS (HR, 1.01; p = .830), but that vandetanib was associated with a higher incidence of toxicity (90). Vandetanib is also being evaluated in the phase III trial (ZEPHYR) in patients with advanced NSCLC who have progressed after treatment with chemotherapy and an EGFR TKI, but preliminary results indicate that the trial did not reach its primary end point of OS (91). Regulatory submissions for vandetanib in patients with NSCLC have also been withdrawn (91).

BIBF 1120
BIBF 1120 is a TKI targeting VEGFR1, VEGFR2, VEGFR3, FGFR1, FGFR2, FGFR3, and PDGFR, with the potential to inhibit proangiogenic signaling pathways in vascular endothelial cells, pericytes, and smooth-muscle cells (92). BIBF 1120 was evaluated as a single agent in a phase II trial in 73 patients with advanced NSCLC who had received one to two prior chemotherapeutic regimens (93). Patients were randomly assigned to receive twice-daily BIBF 1120, 150 mg (N = 37) or 250 mg (N = 36). Median PFS was 1.6 months in the overall population (N = 73) and 2.9 months in patients with an ECOG performance status (PS) 0 to 1 (N = 57), while median OS was 22 weeks in the overall population and 38 weeks in patients with PS 0 to 1. One PR was achieved, and the SD rate was 48% for all patients and 59% in patients with a PS of 0 to 1. The grade 3/4 toxicities included reversible alanine aminotransferase (ALT) elevations (9.6%), diarrhea (9.6%), nausea (8.2%), fatigue (5.5%), and vomiting (4.1%) (93). BIBF 1120 was not associated with a high frequency of hypertension, which is commonly reported with other VEGF inhibitors (46, 93).

Results from phase I studies confirmed the feasibility of combining BIBF 1120 with chemotherapy (94, 95). In a phase I trial (N = 25), BIBF 1120 in combination with carboplatin/paclitaxel was evaluated in chemonaive patients with advanced NSCLC (94). The maximum tolerated dose (MTD) of BIBF 1120 was 200 mg twice daily, and no clinically relevant changes to carboplatin/paclitaxel pharmacokinetic parameters were observed (94). In another phase I dose-escalation study, BIBF 1120 plus pemetrexed (500 mg/m²) was administered to 26 patients with NSCLC who had received prior first-line, platinum-based chemotherapy (95). The MTD of BIBF 1120, in combination with standard-dose pemetrexed, was 200 mg twice daily, with no clinically relevant effects of BIBF 1120 pharmacokinetics observed in combination with pemetrexed (95). During the first treatment cycle, dose-limiting toxicities (DLTs) (all grade 3) occurred in seven patients for all doses and included transaminase elevations, fatigue, confusion, anorexia, and GI disorders (95). Among the 26 evaluable patients, one patient achieved a CR and 13 (50%) patients had SD. Based on these data, two randomized phase III studies are under way to evaluate BIBF 1120 in combination with docetaxel or pemetrexed for patients with advanced NSCLC after failure of first-line therapy (Table 4).

Pazopanib
Pazopanib is a multitargeted TKI that blocks VEGFR1, VEGFR2, VEGFR3, PDGFR, and c-kit (96). Preclinical studies indicate that pazopanib is effective in inhibiting angiogenesis (97). Pazopanib has been used as neoadjuvant monotherapy in patients with early-stage NSCLC (98). Of a total of 35 patients, three achieved a PR. The grade 3 toxicities were observed in five patients and included ALT elevations, hypertension, dyspnea, pneumonia, urinary tract infection, rash, increase in blood potassium, and lymphopenia. One patient experienced grade 4 bilateral pulmonary emboli 11 days after surgery (98). In a separate exploratory analysis of cytokines and angiogenic factors (C/AFs) in the serum of patients with early-stage NSCLC who received preoperative treatment with pazopanib, significant changes in eight C/AFs were reported (99). In particular, plasma levels of VEGFR2 (p < .0001) and placental growth factor (PIGF; p < .0001) were significantly
decreased after pazopanib treatment. There was also a correlation between serum levels of VEGFR2 and tumor shrinkage ($p < .05$), suggesting its potential for use as a predictive marker of response (99). The efficacy and tolerability of pazopanib in advanced NSCLC, either alone or in combination with chemotherapy, is being evaluated in numerous clinical trials (Table 4).

**Axitinib**

Axitinib is a potent small-molecule TKI of VEGFR1, VEGFR2, VEGFR3, PDGFR, and c-kit (100). In a phase I trial in 36 patients with advanced solid tumors, single-agent axitinib demonstrated antitumor activity in multiple tumor types, including NSCLC (101). The most common toxicities of any grade were hypertension (61%), fatigue (28%), nausea (19%), and diarrhea (17%) (101). Based on these data, a phase II study was conducted in 32 patients with advanced NSCLC (102). Nine patients had not received prior chemotherapy for metastatic disease and 23 patients received ≥1 prior regimen (102). Response rate was 9% and median PFS was 4.9 months in the overall study population and 9.2 months in treatment-naive patients. Median OS was 14.8 months in the overall population and 14.8 months in patients who received axitinib as first-line therapy. One-year survival rates were 57% and 78%, respectively. Of the grade 1 or 2 AEs that occurred in at least 15% of patients, those that also occurred at grade 3 severity included fatigue, hypertension, diarrhea, and vomiting (102).

Axitinib was combined with standard paclitaxel/carboplatin and gemcitabine/cisplatin chemotherapy in a phase I trial of 47 patients with NSCLC and other solid tumors (103). Response rate in the paclitaxel/carboplatin cohort was 29%, and in the gemcitabine/cisplatin cohort RR was 26% (103). The dose-limiting toxicities included fatigue, proteinuria, and rashes (103). A subcohort analysis of patients with squamous cell histology showed that axitinib plus paclitaxel/carboplatin was well tolerated, with no evidence of grade ≥3 hemoptysis (103). Trials with single-agent axitinib and combination therapy with axitinib in advanced NSCLC are ongoing (Tables 3 and 4).

**CONCLUSIONS**

The availability of treatment options for patients with advanced NSCLC has expanded. As seen in the E4599 trial of bevacizumab, therapy aimed at blocking angiogenesis can be effective when combined with standard doublet chemotherapy in patients with NSCLC. While a large number of patients were initially excluded from bevacizumab treatment because of safety concerns, some of these patients are now eligible, including patients with brain metastases and those receiving anticoagulation therapy. Patients with squamous histology remain ineligible. Subgroup analyses have shown limited efficacy and increased toxicity in the elderly, in whom bevacizumab should be used with caution.

Several multitargeted, antiangiogenic TKIs in clinical development for NSCLC have shown feasibility for combination with standard chemotherapy. The clinical advantages of this class of drugs are their oral administration and activity against multiple targets. However, improved OS in combination with chemotherapy has yet to be demonstrated in phase III trials. To date, toxicity profiles with these agents seem acceptable. Large phase III trials will determine the role of these agents in the treatment of patients with advanced NSCLC.

How do we personalize treatment strategies with antiangiogenic agents to achieve maximal efficacy with minimal toxicity? The identification of effective biomarkers will be critical. Several biomarkers have already been evaluated (although not validated) and may be predictive of treatment benefit. The development of hypertension may also be a surrogate marker of efficacy in patients treated with bevacizumab. Molecular markers and genetic mapping will be important for individualizing treatment regimens, predicting which patients might benefit from specific regimens, and evaluating the efficacy of specific antiangiogenic therapies.

**Prior publication statement:** This manuscript has neither been published nor submitted for publication elsewhere.

**ACKNOWLEDGMENTS**

This work was supported by Boehringer Ingelheim Pharmaceuticals, Inc (BPI). Editorial assistance was provided by Johnathan Maher, PhD, of BlueSpark Healthcare Communications, and Alyssa Tippets, PhD, of MedErgy, which were contracted by BPI for these services. The authors meet criteria for authorship as recommended by the International Committee of Medical Journal Editors (ICMJE), were fully responsible for all content and editorial decisions, and were involved in all manuscript development stages. The authors received no compensation related to the development of this manuscript.

**DECLARATION OF INTEREST**

Dr. Ulahannan reports no conflicts of interest. Dr. Brahmer has served on advisory boards for GlaxoSmithKline, Eli Lilly and Company, AstraZeneca, Genentech, Inc., Roche, and ImClone Systems and has received research funding from Merck & Co., Inc., Bristol-Myers Squibb Company, Regeneron Pharmaceuticals, Inc., and Synta Pharmaceuticals Corp.

**REFERENCES**

1. American Cancer Society. Cancer Facts & Figures, 2009. American Cancer Society, Inc.: Atlanta, GA, 2009.
2. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics, 2009. CA Cancer J Clin 2009;59(4):225–249.
3. Juergens R, Brahmer J. Targeting the epidermal growth factor receptor in non-small-cell lung cancer: who, which, when, and how? Curr Oncol Rep 2007;9(4):255–264.
4. Stinchcombe TE, Socinski MA. Current treatments for advanced stage non-small-cell lung cancer. Proc Am Thorac Soc 2009;6(2):233–241.
5. Schiller JH, Harrington D, Belani CP, Langer C, Sandler A, Krook J, Zhu J, Johnson DH. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. N Engl J Med 2002;346(2):92–98.
6. Blau HM, Banfi A. The well-tempered vessel. Nat Med 2001;7(5):532–534.
7. Folkman J. Angiogenesis: an organizing principle for drug discovery? Nat Rev Drug Discov 2007;6(4):273–286.
8. Jain RK. Normalizing tumor vasculature with anti-angiogenic therapy: a new paradigm for combination therapy. Nat Med 2001;7(9):987–989.
9. Ferrara N, Kerbel RS. Angiogenesis as a therapeutic target. Nature 2005;438(7070):967–974.
10. Folkman J. What is the evidence that tumors are angiogenesis dependent? J Natl Cancer Inst 1990;82(1):4–6.
11. Carmeliet P, Jain RK. Angiogenesis in cancer and other diseases. Nature 2000;407(6801):249–257.
12. Carmeliet P. VEGF as a key mediator of angiogenesis in cancer. Oncology 2005;69(Suppl 3):4–10.
13. Bremnes RM, Camps C, Sirera R. Angiogenesis in non-small cell lung cancer: the prognostic impact of neoangiogenesis and the cytokines VEGF and bFGF in tumours and blood. Lung Cancer 2006;51(2):143–158.
14. Ferrara N, Cobos M, Paredes A, Mendez M, Munoz-Langa J, Rueda A, Alverez de Mon M, Sanchez-Hernandez A, Gallego R, Torregro J. Phase II study of bevacizumab in combination with cisplatin and docetaxel as first-line treatment of patients (p) with metastatic nonsquamous non-small cell lung cancer (NSCLC). J Clin Oncol 2009;27(15S). Abstract e19099.
15. Leon L, Vazquez S, Gracia JM, Lazaro M, Firvida JL, Casal J, Amenedo M, Santome L, Gallego R, Anido U. Bevacizumab (B), cisplatin, and vinorelbine in chemotherapy-naive patients (p) with nonsquamous non-small cell lung cancer (NSCLC): a Galician Lung Cancer Group phase II study. J Clin Oncol 2008;26(3):511–515.
16. Lilenbaum R, Raza L, Tseng J, Seigel L, Davila E. Efficacy and safety of oxaliplatin and gemcitabine with bevacizumab in advanced non-small cell lung cancer. J Thorac Oncol 2008;3(5):511–515.
17. Heist RS, O’Neill VJ, Feihrenbacher L, Belani CP, Bonomi PD, Hart L, Melnyk O, Ramies D, Lin M, Sandler A. Phase II study of efficacy and safety of bevacizumab in combination with chemotherapy or erlotinib compared with chemotherapy alone for treatment of recurrent or refractory non-small cell lung cancer. J Clin Oncol 2007;25(30):4743–4750.
18. Ramalingam SS, Dahlberg SE, Langer CJ, Gray R, Belani CP, Munn N, Stroiakovski D, Thatcher N, Tsai CM, Wu YL, Zhou C. Safety and efficacy of first-line bevacizumab-based therapy for advanced non-squamous non-small cell lung cancer (SAiL, MO19390): a phase II study. Clin Oncol 2010;28(4):614–619.
19. Heist RS, Fidias P, Gribesminster B, Sequist LV, Temel JS, Lynch T. A phase II study of bevacizumab plus carboplatin and gemcitabine in advanced non-squamous non-small cell lung cancer. J Clin Oncol 2008;26(15S). Abstract 19018.
39. Dowlati A, Gray R, Sandler AB, Schiller JH, Johnson DH. Cell adhesion molecules, vascular endothelial growth factor, and basic fibroblast growth factor in patients with non-small cell lung cancer treated with chemotherapy with or without bevacizumab— an Eastern Cooperative Oncology Group Study. Clin Cancer Res 2008;14(5):1407–1412.

40. Reck M, von PJ, Zatloukal P, Ramlau R, Gorbounova V, Hirsh V, Leigh N, Mezger J, Archer V, Moore N, Manegold C. Overall survival with cisplatin-gemcitabine and bevacizumab or placebo as first-line therapy for nonsquamous non-small-cell lung cancer: results from a randomised phase III trial (AVAiL). Ann Oncol 2010;21(9):1804–1809.

41. Mezger J, von Pawel J, Reck M. Bevacizumab (Bv) single-agent maintenance following Bv-based chemotherapy in patients with advanced non-small cell lung cancer (NSCLC): results from an exploratory analysis of the AVAiL study. J Clin Oncol 2009;27(15S, May 20 Supplement). Abstract e19001.

42. Patel JD, Bonomi P, Sosinski MA, Govindan R, Hong S, Obasaju C, Pennella Ej, Girvan AC, Guba SC. Treatment rationale and study design for the pointbreak study: a randomized, open-label, phase III study of pemetrexed/carboplatin/bevacizumab followed by maintenance pemetrexed/bevacizumab versus paclitaxel/carboplatin/bevacizumab followed by maintenance bevacizumab in patients with stage IIIB or IV nonsquamous non-small-cell lung cancer. Clin Lung Cancer 2009;10(4):252–256.

43. William WN Jr, Kies MS, Fossella FV, Liu DD, Gladish G, Tse WH, Lee J, Hong WK, Lippman SM, Kim ES. Phase 2 study of carboplatin, docetaxel, and bevacizumab as front-line treatment for advanced non-small cell lung cancer. Cancer 2010;116(10):2401–2408.

44. Hanna N, Shepherd FA, Fossella FV, Pereira JR, de MF, von PJ, Gatzemeier U, Tsao TC, Pless M, Muller T, Lim HL, Desch C, Szondy K, Gervais R, Shahzaryar, Manegold C, Paul S, Paolotti E, Einhorn L, Bunn PA Jr. Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small cell lung cancer previously treated with chemotherapy: J Clin Oncol 2004;22(9):1589–1597.

45. Bhargava P. VEGF kinase inhibitors: how do they cause hypertension? Am J Physiol Regul Integr Comp Physiol 2009;297(1):R1–R5.

46. van Heeckeren WJ, Ortiz J, Cooney MM, Remick SC. Hypertension, proteinuria, and antagonism of vascular endothelial growth factor signaling: clinical toxicity, therapeutic target, or novel biomarker? J Clin Oncol 2007;25(21):2993–2995.

47. Cohen MH, Gootenberg J, Keegan P, Pazdur R. FDA drug approval summary: bevacizumab (Avastin) plus carboplatin and paclitaxel as first-line treatment of advanced/metastatic recurrent nonsquamous non-small-cell lung cancer. Oncologist 2007;12(6):713–718.

48. Polikoff J, Hainsworth JD, Fehrenbacher L, Rorer-Joo S, Mu Y, Strickland DK, Miller VA. Safety of bevacizumab (Bv) therapy in combination with chemotherapy in subjects with non-small cell lung cancer (NSCLC) treated on ATLAS. J Clin Oncol 2008;26(15S). Abstract 8079.

49. Sosinski MA, Lenger CJ, Huang JE, Kolb MM, Compton P, Wang L, Akerley W. Safety of bevacizumab in patients with non-small cell lung cancer and brain metastases. J Clin Oncol 2009;27;5255–5261.

50. Otterson GA, O'Connor PG, Lin M, Herbst RS, for the BETA Lung Investigators. Safety of bevacizumab (B) and erlotinib (E) therapy in patients (pts) with treated brain metastases (mets) in the phase III, placebo (P)-controlled, randomized BETA trial for pts with advanced non-small cell lung cancer (NSCLC) after failure of standard first-line chemotherapy. J Clin Oncol 2009;27(15S). Abstract e19005.

51. Hirsh V, Ramlau R, von Pawel J, Zatloukal P, Vera G, Leigh N, Mezger J, Archer V, Reck M. Final safety results of BO17704 (AVAiL): a phase III randomized study of first-line bevacizumab (Bv) and cisplatin/gemcitabine (CG) in patients (pts) with advanced or recurrent nonsquamous non-small-cell lung cancer (NSCLC). J Clin Oncol 2009;27(15S). Abstract 8039.

52. Dahlberg SE, Sandler AB, Brahmer JR, Schiller JH, Johnson DH. Clinical course of advanced non-small cell lung cancer patients experiencing hypertension during treatment with bevacizumab in combination with carboplatin and paclitaxel on ECOG 4599. J Clin Oncol 2010;28(6):949–954.

53. Rini BI, Halabi S, Rosenberg JE, Stadler WM, Vaena DA, Archer L, Atkins JN, Picus J, Czaykowski P, Dutcher J, Small EJ. Phase II trial of bevacizumab plus interferon alfa versus interferon alfa monotherapy in patients with metastatic renal cell carcinoma: final results of CALGB 90206. J Clin Oncol 2010;28(13):2137–2143. Epub 2010 Apr 5. PMID: 20368558.

54. Hurwitz H, Douglas PS, Middleton JP, Sledge GW, Johnson DH, Reardon DA, Chen D, Rosen O. Analysis of early hypertension (HTN) and clinical outcome with bevacizumab (BV). J Clin Oncol 2010;28(7S). Abstract 3039.

55. Sandler AB, Schiller JH, Gray R, Dimery I, Brahmer J, Samant M, Wang LJ, Johnson DH. Retrospective evaluation of the clinical and radiographic risk factors associated with severe pulmonary hemorrhage in first-line advanced, unresectable non-small cell lung cancer treated with Carboplatin and Paclitaxel plus bevacizumab. J Clin Oncol 2009;27(9):1405–1412.

56. Ivy SP, Wick JY, Kaufman BM. An overview of small-molecule inhibitors of VEGFR signaling. Nat Rev Clin Oncol 2009;6(10):569–579.

57. Batchelor TT, Sorensen AG, di TE, Zhang WT, Duda DG, Cohen KS, Kozak KR, Cahill DP, Chen PJ, Zhu M, Ancukiewicz M, Mru gala MM, Plotkin S, Drappatz J, Louis DN, Ivy P, Scadden DT, Benner T, Loeffler JS, Wen PY, Jain RK. AZD2171, a pan-VEGFR tyrosine kinase inhibitor, normalizes tumor vasculature and alleviates edema in glioblastoma patients. Cancer Cell 2007;11(1):83–95.

58. Casanovas O, Hicklin DJ, Bergers G, Hanahan D. Drug resistance by evasion of anti-angiogenic targeting of VEGF signaling in late-stage pancreatic islet tumors. Cancer Cell 2005;8(4):299–309.

59. Bergers G, Song S, Meyer-Morse N, Bergland E, Hanahan D. Benefits of targeting both pericytes and endothelial cells in the tumor vasculature with kinase inhibitors. J Clin Invest 2003;111(9):1287–1295.

60. Erber R, Thurnher A, Katsen AD, Groth G, Kerger H, Hamms HP, Menger MD, Ullrich A, Vajkoczy P. Combined inhibition of VEGF and PDGF signaling enforces tumor vessel regression by interfering with pericyte-mediated endothelial cell survival mechanisms. FASEB J 2004;18(2):338–340.

61. Bergers G, Hanahan D. Modes of resistance to anti-angiogenic therapy. Nat Rev Cancer 2008;8(8):592–603.

62. Jubb AM, Oates AJ, Holden S, Koeppen H. Predicting benefit from anti-angiogenic agents in malignancy. Nat Rev Cancer 2006;6(8):626–635.

63. Wilhelm SM, Carter C, Tang L, Wilkie D, McNabola A, Rong H, Chen C, Zhang X, Vincent P, McHugh M, Cao Y, Shujat J, Gawlak S, Eveleigh D, Rowley B, Liu L, Adnane L, Lynch M, Auc lair D, Taylor I, Gedrich R, Voznesensky A, Riedl B, Post LE, Bollag G, Trail PA. BAY 43–9006 exhibits broad-spectrum oral activity and targets the RAF/MEK/ERK pathway and receptor tyrosine kinase inhibitors in vitro. Cancer Res 2005;65(10):4539–4544.

64. Adjei AA, Molina JR, Hillman SL, Luyun RF, Reuter NF, Rowland KM, Jr, Jett JR, Mandrekar SJ, Schild SE. A front-line window of opportunity phase II study of sorafenib in patients with advanced non-small cell lung cancer: a North Central Cancer Treatment Group study. J Clin Oncol 2007;25(18S). Abstract 7547.

65. Horn L, Sandler AB. Emerging data with anti-angiogenic therapies in early and advanced non-small-cell lung cancer. Clin Lung Cancer 2009;10(Suppl 1), s7–s16.

66. Flaherty KT, Schiller J, Schuchter LM, Liu G, Tuveson DA, Redlinger M, Lathia C, Xia C, Petrenciu O, Hingorani SR.
Jacobetz MA, Van Belle PA, Elder D, Brose MS, Weber BL, Albertini MR, O’Dwyer PJ. A phase I trial of the oral, multikine inhibitor sorafenib in combination with carboplatin and paclitaxel. Clin Cancer Res 2008;14(15):4836–4842.

67. Scaglotti G, Novello S, von PJ, Beck M, Peruzzo JR, Thomas M, brao Miziara JF, Balint R, de MF, Keller A, Aorn O, Cossik M, Albert I, Barrios CH, Grossi F, Krazowski M, Capit J, Cihon F, DiMatteo S, Hanna N. Phase II study of carboplatin and paclitaxel alone or with sorafenib in advanced non-small cell lung cancer. J Clin Oncol 2009;28(11):1835–1842.

68. Gadgeel SM, Wozniak A, Edelman MJ, Valdivieso M, Heilbrun L, Venkatramanamoorthy R, Shields A, LoRusso P, Hackstock D, Ruckdeschel J. Cediranib, a VEGF receptor 1, 2, and 3 inhibitor, and pemetrexed in patients (pts) with recurrent non-small cell lung cancer (NSCLC). J Clin Oncol 2009;27(15S). Abstract e19007.

69. De Boer R, Humblet Y, Wolf J, Nagova L, Ruffert K, Milenkova T, Smith R, Godwood A, Vansteenkiste J. An open-label study of vandetanib plus pemetrexed in patients with previously treated non-small cell lung cancer. Ann Oncol 2009;20(3):486–491.

70. Heymach JV, Paz-Ares L, De BF, Sebastian M, Stewart DJ, Eberhardt WE, Ranade AA, Cohen G, Trigo JM, Sandler AB, Bonomi PD, Herbst RS, Krebs AD, Vasselli J, Johnson BE. Randomized phase II study of vandetanib alone or with pemetrexed and carboplatin as first-line treatment for advanced non-small-cell lung cancer. J Clin Oncol 2009;26(33):5407–5415.

71. Heymach JV, Johnson BE, Prager D, Csada E, Roubec J, Pesek M, Spasova I, Belani CP, Bodrogi I, Gadgeel S, Kennedy SJ, Hou J, Herbst RS. Randomized, placebo-controlled phase II study of vandetanib plus docetaxel in previously treated non-small cell lung cancer. J Clin Oncol 2007;25(27):4207–4227.

72. Herbst RS, Sun Y, Eberhardt WE, Germonpre P, Saito N, Zhou C, Wang J, Li L, Kabbabinvar F, Ichinose Y, Qin S, Zhang L, Biess M, Heymach JV, Langmuir P, Kennedy SJ, Tada H, Johnson BE. Vandetanib plus docetaxel versus docetaxel as second-line treatment for patients with advanced non-small cell lung cancer (ZD-JIAC): a double-blind, randomised, phase 3 trial. Lancet Oncol 2010;11(17):619–626.

73. De Boer R, Arrieta O, Gottfried M, Blackhall FH, Raats J, Yang CH, Langmuir P, Milenkova T, Read J, Vansteenkiste J, Western Hospital, Melbourne, Australia, Instituto Nacional de Cancerologia (INCan), Mexico City, Mexico, Meir Medical Center, Kfar Saba, Israel, Christie Hospital NHS Trust, Manchester, UK, Panorama Medical Center, Capetown, South Africa, National Taiwan University Hospital, Taipei, Taiwan, AstraZeneca, Wilmington, DE, AstraZeneca, Macclesfield, UK, University Hospital Leuven, Leuven, Belgium. Vandetanib plus pemetrexed versus pemetrexed as second-line therapy in patients with advanced non-small-cell lung cancer (NSCLC): a randomized, double-blind phase III trial (ZEAL). J Clin Oncol 2009;27(suppl):409s. Abstract 8010.

74. Blumenschein GR Jr, Gatzemeier U, Fossella F, Stewart DJ, Cud, pit L, Cihon F, O’Leary J, Reck M. Phase II, multicenter, uncontrolled trial of single-agent sorafenib in patients with relapsed or refractory, advanced non-small-cell lung cancer. J Clin Oncol 2009;27(26):4274–4280.

75. Socinski MA. The current status and evolving role of sunitinib in non-small cell lung cancer. J Thorac Oncol 2008;3(6, Suppl 2):S119–S123.

76. Socinski MA, Novello S, Brahmer JR, Rosell R, Sanchez JM, Belan CP, Govindan R, Atkins JN, Gillenwater HH, Pallares C, Tye L, Selaru F, Chao RC, Scaglotti GV. Multicenter, phase II trial of sunitinib in previously treated, advanced non-small cell lung cancer. J Clin Oncol 2008;26(4):650–656.

77. Novello S, Scaglotti GV, Rosell R, Socinski MA, Brahmer J, Atkins J, Pallares C, Burgess R, Tye L, Selaru P, Wang E, Chao R, Govindan R. Phase II study of continuous daily sunitinib dosing in patients with previously treated advanced non-small cell lung cancer. Br J Cancer 2009;101(9):1543–1548.

78. Reck M, Frickhofen N, Cedres S, Gatzemeier U, Heigener D, Fuhr HG, Thall A, Lanzalone S, Stephenson P, Ruiz-Garcia A, Chao R, Filip E. Sunitinib in combination with gemcitabine plus cisplatin for advanced non-small cell lung cancer: a phase I dose-escalation study. Lung Cancer 2010;70(2):180–187. Epub 2010 Feb 25.

79. Robert F, Sandler A, Schiller JH, Liu G, Harper K, Verkl H, Huang X, Ijagan J, Tye L, Chao R, Traylor AM. Sunitinib in combination with docetaxel in patients with advanced solid tumors: a phase I dose-escalation study. Cancer Chemother Pharmacol 2010;66(4):669–680.

80. Nikoliananos P, Heymach JV. The tyrosine kinase inhibitor cediranib for non-small cell lung cancer and other thoracic malignancies. J Thorac Oncol 2008;3(6 Suppl 2):S131–S134.

81. Dreyes J, Siegert P, Medinger M, Mross K, Streeker R, Zirrgeibel U, Harder J, Blum H, Robertson J, Jurgensmeier JM, Puchalski TA, Young H, Saunders O, Unger C. Phase I clinical study of AZD2171, an oral vascular endothelial growth factor signaling inhibitor, in patients with advanced solid tumors. J Clin Oncol 2007;25(21):3045–3054.

82. Yamamoto M, Tamura T, Yamamoto N, Yakada K, Nokihara H, Fujiwara Y, Takahashi T, Murakami H, Boku N, Yamazaki P, Puchalski TA, Shin E. Phase I dose escalation and pharmacokinetic study of cediranib (RECENTIN), a highly potent and selective VEGF signaling inhibitor, in Japanese patients with advanced solid tumors. Cancer Chemother Pharmacol 2009;64(6):1165–1172.

83. LoRusso PM, Heath E, Valdivieso M, Pilat M, Wozniak A, Gadgeel S, Shields A, Puchalski T, Evesusuedo R. Phase I evaluation of AZD2171, a highly potent and selective inhibitor of VEGF signaling, in combination with selected chemotherapy regimens in patients with advanced solid tumors. J Clin Oncol 2006;24(18S). Abstract 3034.

84. Goss G, Shepherd FA, Laurie S, Gauthier I, Leighl N, Chen E, Field R, Powers J, Seymour L. A phase I and pharmacokinetic study of daily oral cediranib, an inhibitor of vascular endothelial growth factor tyrosine kinases, in combination with cisplatin and gemcitabine in patients with advanced non-small cell lung cancer: a study of the National Cancer Institute of Canada Clinical Trials Group. Eur J Cancer 2009;45(5):782–788.

85. Laurie SA, Gauthier I, Arnold A, Shepherd FA, Ellis PM, Chen E, Goss G, Powers J, Walsh W, Tu D, Robertson J, Puchalski TA, Seymour L. Phase I and pharmacokinetic study of daily oral AZD2171, an inhibitor of vascular endothelial growth factor tyrosine kinases, in combination with carboplatin and paclitaxel in patients with advanced non-small cell lung cancer: the National Cancer Institute of Canada clinical trials group. J Clin Oncol 2008;26(11):1871–1878.

86. Goss GD, Arnold A, Shepherd FA, Dediu M, Cialeanu TE, Fenton D, Zukin M, Waldie D, Laberge F, Vincent MD, Ellis PM, Laurie SA, Ding K, Frymire E, Gauthier I, Leighl NB, Ho C, Noble J, Lee CW, Seymour L. Randomized, double-blind trial of carboplatin and paclitaxel with either daily oral cediranib or placebo in advanced non-small cell lung cancer: NCIC Clinical Trials Group BR24 study. J Clin Oncol 2010;28(1):49–55.

87. AstraZeneca. AstraZeneca provides update on cediranib (RECENTINdeclspec, AZD2171) clinical development programme. HORIZON colorectal cancer programme continues into Phase III; BR24 non-small cell lung cancer trial will not progress. Retrieved on April 8, 2010, from http://www.astrazeneca-us.com/search/?itemId=2289031

88. Ciardiello F, Caputo R, Daniano V, Caputo R, Troiani T, Vitagliano D, Carlomagno F, Venerziani BM, Fici F, Panicini G, Bianco AR, Tortora G. Antitumor effects of ZD6474, a small molecule vascular endothelial growth factor receptor tyrosine kinase inhibitor, with additional activity against epidermal growth factor receptor tyrosine kinase. Clin Cancer Res 2003;9(4):1546–1556.

89. Wedge SR, Ogilvie DJ, Dukes M, Kendrew J, Chester R, Jackson JA, Boffey SJ, Valentine PJ, Curwen JO, Musgrove HL,
Graham GA, Hughes GD, Thomas AP, Stokes ES, Curry B, Richmond GH, Wadsworth PF, Bigley AL, Hennequin LF. ZD6474 inhibits vascular endothelial growth factor signaling, angiogenesis, and tumor growth following oral administration. Cancer Res 2002;62(16):4645–4655.

90. Natale RB, Thongprasert S, Greco FA, Thomas M, Tsai CM, Sunpawaravong P, Ferry D, Langmuir P, Rowbottom JA, Goss GD. Vandetanib versus erlotinib in patients with advanced non-small cell lung cancer (NSCLC) after failure of at least one prior cytotoxic chemotherapy: a randomized, double-blind phase III trial (ZEST). J Clin Oncol 2009;27(15S):409s. Abstract 8009.

91. AstraZeneca. AstraZeneca Annual Report 2009. Therapy Area Review: Oncology. Retrieved on April 14, 2010, from http://www.astrazeneca-annualreports.com/2009/directors_report/therapy_area_review/oncology/index.html

92. Hilberg F, Roth GJ, Krssak M, Kautschitsch S, Sommergruber W, Tontsch-Grunt U, Garin-Chesa P, Bader G, Zoephel A, Quant J, Heckel A, Retig WJ. BIBF 1120: triple angiokinase inhibitor with sustained receptor blockade and good antitumor efficacy. Cancer Res 2008;68(12):4774–4782.

93. von Pawel J, Kaiser R, Eschbach C, Love J, Staab A, Freiwald M, Bruno R, Stopfer P. Efficacy, safety and pharmacokinetic (PK) results of a phase II study with the triple angiokinase inhibitor BIBF 1120 in patients suffering from advanced non-small cell lung cancer (NSCLC). J Thorac Oncol 2008;3(4 suppl 1):S61. Abstract 163O.

94. Camidge DR, Conkling P, Stephenson J, Glassman PM, Zhao Y, Kaiser R, Stopfer P. Pharmacokinetic (PK) analysis of a phase I study of continuous oral treatment with the angiokinase inhibitor, BIBF 1120, in combination with carboplatin and paclitaxel in patients with advanced non-small cell lung cancer (NSCLC). J Clin Oncol 2008;26(15S). Abstract 3567.

95. Ellis PM, Kaiser R, Zhao Y, Stopfer P, Gyorffy S, Hanna N. Phase I open-label study of continuous treatment with BIBF 1120, a triple angiokinase inhibitor, and pemetrexed in pretreated non-small cell lung cancer patients. Clin Cancer Res 2010;16(10): 2881–2889.

96. Kumar R, Knick VB, Rudolph SK, Johnson JH, Crosby RM, Crouthamel MC, Hopper TM, Miller CG, Harrington LE, Onori JA, Mullin RJ, Gilmer TM, Truesdale AT, Epperly AH, Boloor A, Stafford JA, Luttrel DK, Cheung M. Pharmacokinetic-pharmacodynamic correlation from mouse to human with pazopanib, a multikinase angiogenesis inhibitor with potent anti-tumor and antiangiogenic activity. Mol Cancer Ther 2007;6(7):2012–2021.

97. Sloan B, Scheinfeld NS. Pazopanib, a VEGF receptor tyrosine kinase inhibitor for cancer therapy. Curr Opin Investig Drugs 2008;9(12):1324–1335.

98. Altorki N, Lane ME, Bauer T, Lee PC, Guarino MJ, Pass H, Felip E, Peylan-Ramu N, Gurpide A, Grannis FW, Mitchell JD, Tachdjian S, Swann RS, Huff A, Roychowdhury DF, Reeves A, Ottesen LH, Yankelevitz DF. Phase II proof-of-concept study of pazopanib monotherapy in treatment-naive patients with stage I/II resectable non-small cell lung cancer. J Clin Oncol 2010;28(19): 3131–3137.

99. Nikolinakos PG, Altorki N, Yankelevitz D, Tran HT, Yan S, Rajagopalan D, Bordogna W, Ottesen LH, Heymach JV. Plasma cytokine and angiogenic factor profiling identifies markers associated with tumor shrinkage in early-stage non-small cell lung cancer patients treated with pazopanib. Cancer Res 2010;70(6):2171–2179.

100. Choueiri TK. Axitinib, a novel anti-angiogenic drug with promising activity in various solid tumors. Curr Opin Investig Drugs 2008;9(6):658–671.

101. Rugo HS, Herbst RS, Liu G, Park JW, Kies MS, Steinfeld HM, Pithavala YK, Reich SD, Freed JD, Wilding G. Phase I trial of the oral antiangiogenesis agent AG-013736 in patients with advanced solid tumors: pharmacokinetic and clinical results. J Clin Oncol 2005;23(24):5474–5483.

102. Schiller JH, Larson T, Ou SH, Limentani S, Sandler A, Vokes E, Kim S, Liau K, Bycott P, Olzsanski AJ, von PJ. Efficacy and safety of axitinib in patients with advanced non-small cell lung cancer: results from a phase II study. J Clin Oncol 2009;27(23): 3836–3841.

103. Martin LP, Kozloff MF, Krzakowski M, Samuel TA, Rado TA, Tarazi J, Rosbrook B, Tortorici M, Olzsanski AJ, Cohen RB, Axitinib (AG-013736; AG) combined with chemotherapy in patients (pts) with advanced non-small cell lung cancer (NSCLC) and other solid tumors. J Clin Oncol 2009;27(15S). Abstract 3559.