Rationale for targeting VEGF, FGF, and PDGF for the treatment of NSCLC

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Abstract: Lung cancer remains a leading cause of death globally, with the most frequent type, nonsmall cell lung cancer (NSCLC), having a 5-year survival rate of less than 20%. While platinum-based doublet chemotherapy is currently first-line therapy for advanced disease, it is associated with only modest clinical benefits at the cost of significant toxicities. In an effort to overcome these limitations, recent research has focused on targeted therapies, with recently approved agents targeting the epidermal growth factor receptor and vascular endothelial growth factor (VEGF) signaling pathways. However, these agents (gefitinib, erlotinib, and bevacizumab) provide antitumor activity for only a small proportion of patients, and patients whose tumors respond inevitably develop resistance to treatment. As angiogenesis is a crucial step in tumor growth and metastasis, antiangiogenic treatments might be expected to have antitumor activity. Important targets for the development of novel antiangiogenic therapies include VEGF, fibroblast growth factor, platelet-derived growth factor, and their receptors. It is hypothesized that targeting multiple angiogenic pathways may not only improve antitumor activity but also reduce the risk of resistance. Several novel agents, such as BIBF 1120, sorafenib, sunitinib, and cediranib have shown promising preliminary activity and tolerability in Phase II studies, and results of ongoing Phase III randomized studies will be necessary to establish the potential place of these new therapies in the management of individual patients with NSCLC.

Keywords: angiogenesis, vascular endothelial growth factor, platelet-derived growth factor, fibroblast growth factor, tyrosine kinase inhibitor, nonsmall cell lung cancer

Introduction

Lung cancer is the leading cause of cancer-related death worldwide. 1 Nonsmall cell lung cancer (NSCLC) is the most frequent type of lung cancer, accounting for more than 80% of lung cancer cases. As NSCLC currently has a 5-year survival rate of less than 20%, 2 there is clearly a need for the development of more effective therapies.

Standard first-line treatment options depend on disease and patient characteristics, and may include surgery, platinum-based doublet chemotherapy, and targeted therapies. 3 However, surgical resection is only a curative option if diagnosis occurs at early stage I or stage II disease (Table 1). At times, surgery with or without radiation with a more limited curative potential is an option for selected stage III NSCLC patients. Chemotherapy with a platinum-based doublet regimen is currently first-line therapy for more advanced disease, but is associated with only modest clinical benefits at the cost of significant toxicities. 4,5 Furthermore, studies have shown no survival benefit and decreased quality of life with chemotherapy combinations beyond 4–6 cycles. 6–8 Thus, in an effort to overcome these limitations, recent research has focused on targeted
Table I: Staging of NSCLC

| Stage               | TNM* | Description                                                                 |
|---------------------|------|-----------------------------------------------------------------------------|
| Occult carcinoma    | Tx   | Tumor that cannot be assessed or detected radiologically or bronchoscopically but is proven histopathologically |
|                     | N0   | No regional node involvement                                               |
|                     | M0   | No distant metastases                                                      |
| 0                   | Tis  | Carcinoma in situ                                                          |
|                     | N0   | No regional node involvement                                               |
|                     | M0   | No distant metastases                                                      |
| IA                  | T1a  | Tumor ≤2 cm surrounded by lung or visceral pleura and involving lobar bronchus but not main bronchus |
|                     | T1b  | Tumor >2 cm but ≤3 cm surrounded by lung or visceral pleura and involving lobar bronchus but not main bronchus |
|                     | N0   | No regional node involvement                                               |
|                     | M0   | No distant metastases                                                      |
| IB                  | T2a  | Tumor >3 cm but ≤5 cm involving main bronchus ≥2 cm from carina or presence of atelectasis or obstructive pneumonitis that extends to the hilar region and involving invading visceral pleura |
|                     | N0   | No regional node involvement                                               |
|                     | M0   | No distant metastases                                                      |
| IIA                 | T1a  | Tumor ≤2 cm surrounded by lung or visceral pleura and involving lobar bronchus but not main bronchus |
|                     | T1b  | Tumor >2 cm but ≤3 cm surrounded by lung or visceral pleura and involving lobar bronchus but not main bronchus |
|                     | N1   | Involvement of ipsilateral peribronchial or hilar nodes and intrapulmonary nodes |
|                     | M0   | No distant metastases                                                      |
| Or                  | T2a  | Tumor >3 cm but ≤5 cm involving main bronchus ≥2 cm from carina or presence of atelectasis or obstructive pneumonitis that extends to the hilar region and involving invading visceral pleura |
|                     | N1   | Involvement of ipsilateral peribronchial or hilar nodes and intrapulmonary nodes |
|                     | M0   | No distant metastases                                                      |
| Or                  | T2b  | Tumor >5 cm but ≤7 cm involving main bronchus ≥2 cm from carina or presence of atelectasis or obstructive pneumonitis that extends to the hilar region and involving invading visceral pleura |
|                     | N0   | No regional node involvement                                               |
|                     | M0   | No distant metastases                                                      |
| IIB                 | T2b  | Tumor >5 cm but ≤7 cm involving main bronchus ≥2 cm from carina or presence of atelectasis or obstructive pneumonitis that extends to the hilar region and involving invading visceral pleura |
|                     | N1   | Involvement of ipsilateral peribronchial or hilar nodes and intrapulmonary nodes |
|                     | M0   | No distant metastases                                                      |
| Or                  | T3   | Tumor >7 cm involving main bronchus <2 cm from carina or presence of atelectasis or obstructive pneumonitis of the entire lung and involving direct invasion of chest wall, diaphragm, phrenic nerve, mediastinal pleura, or parietal pericardium and involving satellite tumor nodule(s) in same lobe as primary tumor |
|                     | N0   | No regional node involvement                                               |
|                     | M0   | No distant metastases                                                      |
| IIIA                | T1–T3| Involvement of ipsilateral mediastinal or subcarinal nodes                  |
|                     | N2   | No distant metastases                                                      |
|                     | M0   | No distant metastases                                                      |
| Or                  | T3   | Tumor >7 cm involving main bronchus <2 cm from carina or presence of atelectasis or obstructive pneumonitis of the entire lung and involving direct invasion of chest wall, diaphragm, phrenic nerve, mediastinal pleura, or parietal pericardium and involving satellite tumor nodule(s) in same lobe as primary tumor |
|                     | N1   | Involvement of ipsilateral peribronchial or hilar nodes and intrapulmonary nodes |

(Continued)
Table 1 (Continued)

| Stage | TNM | Description |
|-------|-----|-------------|
| M0    | Or  | No distant metastases |
| T4    | N0–N1 | Tumor any size invading the mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, or carina; or tumor with satellite tumor nodule(s) in a different lobe, ipsilateral to that of the primary tumor; or involvement of ipsilateral peribronchial or hilar nodes and intrapulmonary nodes |
| M0    | No distant metastases |
| IIIB  | T1–T4 | Involvement of contralateral mediastinal or hilar nodes and ipsilateral or contralateral scalene or supraclavicular nodes |
| N2    | M0   | No distant metastases |
| M0    | T4   | Tumor any size invading the mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, or carina; or tumor with satellite tumor nodule(s) in a different lobe, ipsilateral to that of the primary tumor |
| IV    | Tx–T4 | Any T |
| Nx–N3 | M1a  | Satellite tumor nodule(s) in contralateral lobe to that of primary tumor or tumors with malignant pleural or pericardial effusion |
| M1b   | Distant metastases |

Notes: *Based on the Seventh Edition of TNM Staging of Lung Tumors; however, trials referred to in this review article have followed either the current or previous staging system depending on the time of their conduct; †The TNM system is based on tumor status, nodal status, and metastatic disease; ‡Nx indicates regional lymph nodes that cannot be assessed.

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Abbreviations: NSCLC, nonsmall cell lung cancer; TNM, tumor node metastasis.

therapies that may more selectively inhibit tumor cell growth while minimizing toxicity to healthy cells and tissue.

**Currently available targeted agents for NSCLC**

Currently approved targeted agents in NSCLC are limited to inhibition of the epidermal growth factor receptor (EGFR) and vascular endothelial growth factor (VEGF) signaling pathways. The EGFR family of receptor tyrosine kinases serve as mediators of cell signaling by extracellular growth factors, with binding of their ligands activating intracellular pathways that promote tumor growth and survival. An activating mutation in EGFR is observed in approximately 10% of unselected Western lung cancer patients and in a higher percentage of certain NSCLC subgroups, such as nonsmokers and those of Asian ethnicity. Reversible EGFR-targeting tyrosine kinase inhibitors such as gefitinib (Iressa; AstraZeneca; Wilmington, DE) and erlotinib (Tarceva; Genentech; South San Francisco, CA) inhibit EGFR signaling.

Initial Phase II results with gefitinib led to approval by the United States Food and Drug Administration (FDA) of this agent for NSCLC. These results showed overall objective response rates (ORR) of 19% (95% confidence interval [CI], 11.5–27.3) among 105 patients with stage III/IV NSCLC receiving a dose of 500 mg/day and 18.4% (95% CI, 12.1–27.9) of 103 patients receiving 250 mg/day in one study and 10.6% (95% CI, 6.0–16.8) with both doses in another study. However, addition of gefitinib to standard chemotherapy failed to prolong overall survival (OS) compared with chemotherapy alone in subsequent Phase III trials. Based on more recent Phase III data in which OS with gefitinib was noninferior or not significantly different to that obtained with docetaxel, a taxane, in patients with advanced or metastatic NSCLC who had been pretreated with platinum-based chemotherapy, the United States restricted treatment with gefitinib to patients who have previously benefited from it. However, in the European Union and Asia, gefitinib remains in use for NSCLC patients with EGFR-activating mutations.

Erlotinib was approved in the United States in 2004 for the treatment of patients with locally advanced or metastatic NSCLC whose disease has progressed following at least one chemotherapy regimen, based on prolongation of OS (6.7 months versus 4.7 months for placebo; hazard ratio (HR), 0.70; 95% CI, 0.58–0.85; P < 0.001) in a double-blind Phase III trial, BR21, involving 731 patients with stage IIIB/IV NSCLC.
Erlotinib was also recently approved for maintenance therapy in patients with locally advanced or metastatic NSCLC whose disease has not progressed after 4 cycles of platinum-based therapy,34 based on the SATURN trial. The SATURN Phase III trial (N = 884) showed erlotinib prolonged progression-free survival (PFS) versus placebo irrespective of EGFR mutation status (12.3 versus 11.1 weeks; HR, 0.71; 95% CI, 0.62–0.82; \( P < 0.0001 \)).25

Response rates in the gefitinib and erlotinib Phase III studies that were conducted in nonselected populations were typically around 10%, meaning that for many patients, their tumors fail to respond to these agents.26–28 Those who do respond to treatment eventually develop resistance to EGFR tyrosine kinase inhibitors, due either to a secondary mutation in the EGFR gene or amplification of mesenchymal-epithelial transition factor (MET), another receptor tyrosine kinase.12,29

The VEGF pathway controls angiogenesis, a necessary step in tumor growth, metastasis, and malignancy.30 Formation of new vasculature is required for larger tumors to obtain nutrients and oxygen; otherwise, nutrient supply is limited by diffusion, slowing tumor growth.31 Indeed, tumor vascularization is a prognostic indicator of disease progression in various cancers, including NSCLC.32–34 Thus, as tumor growth is dependent on developing and maintaining this blood supply, antiangiogenic treatments might be expected to have antitumor activity.

Bevacizumab (Avastin\(^{3}\), Genentech) is a monoclonal antibody directed against VEGF that is currently approved in combination with carboplatin, a platinum agent, and paclitaxel, a taxane, as first-line treatment of unresected, locally advanced, recurrent or metastatic nonsquamous NSCLC.35 Bevacizumab is only available for patients whose tumors have nonsquamous histology and is not recommended for patients with hemorrhage or recent hemoptysis.11,36,37 These exclusions are based on evidence from Phase II and III clinical trials. An early Phase II study randomized 99 patients with advanced (stage IIIB/IV or recurrent) NSCLC to receive bevacizumab 7.5 mg/kg or 15 mg/kg plus carboplatin and paclitaxel or chemotherapy alone.36 Bevacizumab 15 mg/kg significantly prolonged time to disease progression (TTP) (7.4 versus 4.2 months with chemotherapy alone; HR, 0.57; \( P = 0.023 \)) and provided a higher response rate (31.5% of 34 patients versus 18.8% of 32 patients) and a modestly increased median OS (17.7 versus 14.9 months; \( P = 0.63 \)). With the lower dose of bevacizumab, TTP was 4.3 months, ORR was 28.1% of 32 patients, and OS was 11.6 months. However, fatal hemoptysis was observed in 4 of 66 patients (6%) receiving bevacizumab. The study also correlated squamous histology with an increased risk of serious pulmonary hemorrhage, as four out of six cases of life-threatening bleeding occurred in patients with squamous carcinomas.36

The Phase III Eastern Cooperative Oncology Group (ECOG) 4599 trial\(^{38} \) evaluated bevacizumab 15 mg/kg in combination with carboplatin and paclitaxel in 878 chemotherapy-naïve patients. Patients with squamous histology, brain metastases, inadequate organ function, clinically significant hemoptysis, or ECOG performance status \( \geq 1 \) were excluded. The ORR was higher with bevacizumab (133 out of 381 patients, 35%) compared with carboplatin and paclitaxel alone (59 out of 392 patients, 15%; \( P < 0.001 \)). The addition of bevacizumab also prolonged median OS (12.3 versus 10.3 months; HR, 0.80; \( P = 0.003 \)) and PFS (6.2 versus 4.5 months; HR, 0.66; \( P < 0.001 \)) compared with chemotherapy alone. Grade \( \geq 3 \) (lowest possible grade of an adverse event is 1 [mild adverse event] and highest possible grade is 5 [death]) bleeding events were reported in 19 out of 427 patients receiving bevacizumab plus chemotherapy (4.4%), while eight patients (1.9%) experienced hemoptysis.38 Fifteen treatment-related deaths were observed in the bevacizumab arm compared with two deaths in the carboplatin plus paclitaxel alone arm (\( P < 0.001 \)), five of which were caused by hemorrhage. Evaluable patients receiving bevacizumab plus carboplatin and paclitaxel (\( n = 427 \)) experienced higher rates of grade 4 neutropenia (25.5% versus 16.8% in 440 patients receiving carboplatin and paclitaxel alone; \( P = 0.002 \)) and thrombocytopenia (1.6% versus 0.2%; \( P = 0.04 \)) as well as grade 3 febrile neutropenia (4% versus 1.8%; \( P = 0.02 \)), grade 3–4 hyponatremia (3.5% versus 1.1%; \( P = 0.02 \)), grade 3–4 hypertension (6.8% versus 0.5%; \( P < 0.001 \)), grade 3 headache (0.5% versus 3%; \( P = 0.003 \)), grade 3 rash (2.3% versus 0.5%; \( P = 0.02 \)), and grade \( \geq 3 \) bleeding events (0.7% versus 4.4%; \( P < 0.001 \)).38

In the similarly designed Phase III AVAiL trial, first-line treatment with bevacizumab 7.5 or 15 mg/kg in combination with cisplatin and gemcitabine versus cisplatin and gemcitabine alone was evaluated in 1043 patients with recurrent or advanced NSCLC.39 Bevacizumab prolonged PFS at both 7.5 mg/kg (6.7 versus 6.1 months for placebo; HR, 0.75; \( P = 0.003 \)) and 15 mg/kg (6.5 months; HR, 0.82; \( P = 0.03 \) versus placebo),39 but OS was not significantly different, possibly due to the high use of post-study second-line treatments.40 The incidence of pulmonary hemorrhage was only 1.5% with bevacizumab 7.5 mg/day (5 out of 330 patients) and 0.9% with bevacizumab 15 mg/kg (3 out of 329 patients).39 The rates of grade \( \geq 3 \) hypertension, vomiting, neutropenia, and bleeding were numerically higher in patients who received bevacizumab than in patients who did not.
Another Phase III trial, the ATLAS study, compared bevacizumab 15 mg/kg plus erlotinib with bevacizumab alone as a maintenance therapy after 4 cycles of combined treatment with bevacizumab and platinum-based doublet chemotherapy in 768 patients with advanced NSCLC.41 Patients with treated brain metastases and peripheral or extrathoracic squamous tumors were allowed to participate in this study. Preliminary efficacy results showed that the combination of erlotinib plus bevacizumab increased PFS (4.8 versus 3.7 months for bevacizumab alone; HR, 0.72; 95% CI, 0.59–0.88; \( P = 0.0012 \)) but did not significantly prolong OS (15.9 versus 13.9 months; HR, 0.90; \( P = 0.2686 \)). Safety data (n = 598) have been reported for the initial chemotherapy phase of the trial.42 The most common grade ≥3 adverse event was hypertension, reported for 13 out of 303 patients receiving bevacizumab with carboplatin and paclitaxel (4.3%), 9 out of 183 patients receiving bevacizumab with carboplatin and gemcitabine (4.9%), and 3 out of 112 receiving carboplatin plus docetaxel (2.7%). Grade ≥2 pulmonary or central nervous system hemorrhage each occurred in less than 2% of patients, as did grade ≥3 gastrointestinal perforations. Overall hemorrhage rates (all grades) were reported for seven patients (2.3%) with bevacizumab plus carboplatin and paclitaxel, nine patients (4.9%) with bevacizumab plus carboplatin and gemcitabine, and nine patients (8%) with carboplatin plus docetaxel.

The Phase II BRIDGE study examined whether paclitaxel and carboplatin in combination with delayed bevacizumab administration would improve tolerability in patients with previously untreated squamous NSCLC; out of 31 patients treated with bevacizumab, one patient (3.2%) experienced a grade 3 pulmonary hemorrhage.43 Ongoing follow-up Phase II and III trials are currently evaluating bevacizumab therapy in combination with other targeted agents as well as standard chemotherapy in both first-line and second-line settings for multiple malignancies, including NSCLC.40,44–47 While bevacizumab is the only angiogenic therapy currently approved for NSCLC, there are several other compounds currently in clinical development, including monoclonal antibodies to VEGF and inhibitors of the intracellular tyrosine kinase domain of the VEGF receptor, as described later in this review. Because of the issues of resistance and eligibility associated with currently approved targeted agents in NSCLC, there is a critical need for improved therapies. The subsequent sections of this review highlight important antiangiogenic targets as well as emerging clinical data regarding novel antiangiogenic compounds for NSCLC treatment.

## Rationale for targeting angiogenic pathways in NSCLC

### VEGF signaling

Important proangiogenic targets for the development of antiangiogenic therapies include VEGF, fibroblast growth factor (FGF), and platelet-derived growth factor (PDGF), along with their corresponding receptors (VEGFR, FGFR, and PDGFR, respectively). The VEGF-related family of proangiogenic signaling factors comprises VEGF-A (commonly referred to as VEGF), VEGF-B, VEGF-C, VEGF-D, VEGF-E, and placental growth factor (PlGF).48 In addition to tumor angiogenesis, VEGF signaling mediates several other pathological conditions including inflammatory disorders, female reproductive processes, and intraocular neovascularization syndromes.49 The VEGF ligands mediate their angiogenic effects via three receptor tyrosine kinases: VEGFR-1 (also known as fms-like tyrosine kinase 1 [flt-1]), VEGFR-2 (also known as kinase-insert domain receptor [KDR]), and VEGFR-3 (flt-4). The primary receptor for VEGF is VEGFR-2.49 Binding of VEGF to its receptors causes receptor dimerization, autophosphorylation, and downstream signaling through a variety of pathways, including phosphoinositide (PI)-3 kinase (PI3K), v-src sarcoma viral oncogene homolog (Src), and phospholipase-C-γ (PLCγ), which can activate proliferation and migratory pathways driving angiogenesis (Figure 1).49 Neurupillin-1 and neurupillin-2, members of the neuropilin family of receptors, are expressed on endothelial cells and may be activated by VEGF, dimerize with VEGFR-1 and -2, and activate downstream signaling;49 inhibitors of neurupillin-VEGF interaction are undergoing preclinical evaluation for the treatment of cancer.51,52 In animal tumor models, VEGF is produced both by tumor cells and also by stromal tissue, although stromal expression of VEGF was not observed in a study of NSCLC samples from patients.53 Upregulation of VEGF and VEGFR have been observed in NSCLC tumor samples, with expression correlated with tumor angiogenesis, shorter postoperative recurrence time, and shorter survival time.54 A meta-analysis of NSCLC studies has also suggested that VEGF expression is an unfavorable prognostic factor for survival (HR, 1.48; 95% CI, 1.27–1.72).55

### FGF signaling

The FGF family comprises 22 ligands that have a diverse array of biological functions. For example, FGF signaling plays a role in fetal development; mutations in FGFR1 are associated with bone disorders, and mutations in FGFR2 are known to cause various craniosynostosis syndromes.
Figure 1 Connections between VEGF/VEGFR signaling and angiogenic processes. Depiction of the role of VEGFR signaling in tumor angiogenesis.

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Abbreviations: Akt, protein kinase B; BAD, Bcl-2–associated death promoter; cPLA, cytoplasmic phospholipase A; DAG, diacyl-glycerol; eNOS, endothelial nitric oxide synthase; ERK, extracellular signal-regulated kinase; FAK, focal adhesion kinase; HSP, heat shock protein; IP3, inositol triphosphate; mAbs, monoclonal antibodies; MAPKAPK, mitogen-activated protein kinase-activated protein kinase; MEK, mitogen-activated protein kinase kinase; NOS, nitrous oxide synthase; PI3K, phosphatidylinositol 3-kinase; PI4P, phosphatidylinositol 4,5-bisphosphate; PI(3,4,5)P3, phosphatidylinositol 3,4,5-trisphosphate; PKC, protein kinase C; PLC, phospholipase C; Raf, v-raf 1 murine leukemia viral oncogene homolog 1; Ras, retrovirus-associated DNA sequences; TKIs, tyrosine kinase inhibitors; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.
PDGF signaling

PDGF ligands are released from platelets upon vascular damage. There are five dimeric PDGF ligands, PDGF-AA, -BB, -CC, -DD, and -AB, and two receptor tyrosine kinases, PDGFR-α and PDGFR-β, which mediate downstream effects through some of the same pathways activated by VEGFR (Figure 1). These receptors are expressed on endothelial cells, pericytes, and vascular smooth muscle cells, which aid in development of tumor microvessels. Release of PDGF-BB by endothelial cells recruits pericytes and vascular muscle cells, which, in turn, control vascular integrity, development, and stabilization. In a preclinical chorioallantoic membrane (CAM) model involving chick eggs, PDGF-AA, -AB, and -BB induced development of new blood vessels, while in another model, PDGF-BB but not -AA stimulated the migration of rat brain capillary endothelial cells. Enhanced PDGF signaling has been associated with tumorigenesis and angiogenesis, as well as other pathological events such as atherosclerosis and re-stenosis of vessels after balloon angiography and coronary artery bypass grafting. In addition, PDGF inhibition may be a rational strategy for treatment of fibrotic liver disease, pulmonary fibrosis, and the development of proliferative vitreoretinopathy.

The rationale for targeting the above signaling pathways arose from preclinical models, in which inhibition of VEGF/VEGFR, FGF/FGFR, or PDGF/PDGFR signaling resulted in reduced angiogenesis and impaired tumor proliferation. For example, treatment with a VEGF monoclonal antibody inhibited the growth of tumor cell lines that had been injected into nude mice, but did not affect the growth rate of the same cell lines in vitro, supporting the explanation that treatment was acting against angiogenesis rather than directly against tumor cells. Furthermore, activation of PDGF and FGF pathways has been implicated in the development of resistance to VEGF inhibition. In a mouse model of pancreatic cancer, relapse after treatment with an anti-VEGF monoclonal antibody was associated with tumor revascularization secondary to hypoxia-mediated induction of other proangiogenic factors, including increased FGF-2 expression. Upon combination treatment with both VEGF and FGF inhibitors, tumor revascularization and growth were reduced. Likewise, expression of PDGFR has also been associated with resistance to VEGF-targeted therapy in the mouse pancreatic cancer model, with combined targeting of VEGF and PDGF signaling producing regression of established tumor blood vessels and inhibiting tumor growth. In fact, the VEGF, PDGF, and FGF signaling pathways appear to be highly integrated, suggesting that compensation and/or synergism between pathways occurs in angiogenesis. Thus, targeting multiple receptor tyrosine kinases may be required for effective antiangiogenic therapies.

In the clinical development of antiangiogenic therapies, two approaches have been used: the first has been to inhibit ligand binding and receptor activation using targeted antibodies, while the second has been to inhibit receptor activation using tyrosine kinase inhibitors targeting VEGFR, FGF, and/or PDGFR. Results of Phase II and Phase III clinical trials of agents discussed in this review in NSCLC are summarized in Table 3.
80,81 In preclinical models, α through VEGFR-1, -2, and -3, PDGFR-β is an orally available multitargeted TKI that inhibits signaling of resistance to antitumor agents. In addition, using a multitargeted approach, multiple tumorigenic pathways (such as angiogenesis and cell survival) may be inhibited and so influence tumorigenesis, a number of potential advantages may exist with agents that inhibit multiple targets simultaneously. For example, this approach may prevent the development of resistance to antitumor agents. In addition, using a multitargeted approach, multiple tumorigenic pathways (such as angiogenesis and cell survival) may be inhibited and so maximize antitumor activity.

BIBF 1120 (Boehringer Ingelheim, Ingelheim, Germany) is an orally available multitargeted TKI that inhibits signaling through VEGFR-1, -2, and -3, PDGFR-α/β, and FGFR-1, -2, and -3 as well as Src and flt-3.80,81 In preclinical models, including human tumor xenografts in nude mice and rat tumor models, BIBF 1120 reduced tumor vessel density and integrity, resulting in inhibition of tumor growth.80 In Phase I studies, the most common drug-related adverse events observed with BIBF 1120 were reversible serum liver enzyme elevations and mild fatigue.82–84 When BIBF 1120 was combined with pemetrexed, a folate antimetabolite,18 stable disease was achieved in 13 out of 26 patients (50%) with recurrent advanced NSCLC who had previously received one prior platinum-based chemotherapy regimen.84 In this study, grade 3 fatigue was reported by six patients (23%), and grade 3 increases in alanine transaminase (ALT) were observed in three patients (11%). In Phase I studies of BIBF 1120 monotherapy in patients with advanced solid tumors, the first study (N = 61) observed grade 3 liver enzyme elevations in three patients receiving once-daily dosing with BIBF 1120 and no patients receiving twice daily dosing,85 while the second study (N = 21) showed grade 3 elevations of ALT and γ-glutamyl transpeptidase (γ-GT) in six patients each and grade 3 elevation of aspartate aminotransferase (AST) in three patients.83 A Phase II trial tested BIBF 1120 monotherapy in 73 patients with relapsed NSCLC for which one or two lines of chemotherapy had previously failed and who had an ECOG performance status of 0–2.85 Patients were assigned one of two doses: 150 mg (n = 37) or 250 mg (n = 36) twice daily. For all patients, median OS was 21.9 weeks, and median PFS was 6.9 weeks; one patient exhibited a partial response, and 48% of patients exhibited stable disease. Patients with an ECOG performance status of 0–1 (n = 56) exhibited a median PFS of 11.6 weeks and a median OS of 37.7 weeks. Grade 3 and 4 toxicities included ALT elevations (9.6%), diarrhea (8.2%), nausea (6.8%), γ-GT elevations (4.1%), abdominal pain (2.7%), vomiting (2.7%), anorexia (1.4%), AST

### Table 2 Approved and emerging antiangiogenic therapies for NSCLC

| Agent | Type | Target(s) | Current phase of clinical development |
|-------|------|-----------|--------------------------------------|
| Bevacizumab81 | Monoclonal antibody | VEGF | Approved for NSCLC |
| Ramucirumab78 | Monoclonal antibody | VEGFR-2 | |
| Aflibercept11 | Fusion protein | VEGF | |
| BIBF 112080 | TKI | VEGFR-1, -2, -3, PDGFR-α/β, FGFR-1, -2, -3, Src, flt-3 | Phase III |
| Sorafenib87 | TKI | VEGFR-2, -3, PDGFR-β, Raf, flt-3, c-kit | Phase III |
| Sunitinib92 | TKI | VEGFR-1, -2, -3, PDGFR-α/β, c-kit, flt-3, RET | Phase III |
| Cediranib94 | TKI | VEGFR-1, -2, -3, PDGFR-β, FGFR-1, c-kit | Phase III |
| Motesanib102 | TKI | VEGFR-1, -2, -3, PDGFR-β, c-kit, RET | Phase III |
| Pazopanib107 | TKI | VEGFR-1, -2, -3, PDGFR-α/β, FGFR-1, -3, c-kit | Phase III |
| Axitinib109 | TKI | VEGFR-1, -2, -3, PDGFR-β | Phase II |
| ABT-869110 | TKI | VEGFR-1, -2, -3, PDGFR-β | Phase II |

Abbreviations: c-kit, stem cell factor receptor; FGFR, fibroblast growth factor receptor; flt-3, fms-like tyrosine kinase 3; NSCLC, nonsmall cell lung cancer; PDGFR, platelet-derived growth factor receptor; Raf, v-raf 1 murine leukemia viral oncogene homolog 1; Ret, rearranged during transfection receptor; Src, v-src sarcoma viral oncogene homolog; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.
elevations (1.4%), and fatigue (1.4%). Phase III trials are currently testing BIBF 1120 in combination with docetaxel in the LUME-Lung 1 study (NCT00805194) and pemetrexed in the LUME-Lung 2 study (NCT00806819). Of note, the LUME-Lung 2 study only includes patients with NSCLC of nonsquamous histology to conform with the FDA-approved indication of pemetrexed.88

Other small molecule multitargeted tyrosine kinase inhibitors are currently in clinical development. Sorafenib (Bay 43-9006; Nexavar®, Bayer, Leverkusen, Germany) targets tumor cell growth and angiogenesis by inhibiting signaling through VEGFR-2 and -3, PDGFR-β, v-raf 1 murine leukemia viral oncogene homolog 1 (Raf), flt-3, and stem cell factor receptor (c-kit).87 In a Phase II study of single-agent sorafenib in 51 patients with relapsed or refractory advanced nonsquamous NSCLC, there were no responses, but 30 patients (59%) exhibited stable disease.88 Median PFS was 2.7 months, while median OS was 6.7 months. The most common grade 3 and 4 adverse events included hypertension in two patients (4%) and hand-foot skin disease in five patients (10%). In a larger Phase II study involving 342 patients with pretreated NSCLC and no evidence of brain metastases, patients were treated with sorafenib for two cycles; patients who responded continued on sorafenib for the second stage of the study, patients with stable disease were randomized to sorafenib or placebo, and those with progression discontinued. Preliminary results from the 97 patients randomized in stage 2 of the study show that sorafenib treatment prolonged PFS to 3.6 months compared with 1.9 months with placebo (P = 0.01) and resulted in stable disease for 16 patients (29%) compared with two patients with placebo (5%; P = 0.002).89 The most common grade 3 or 4 adverse events were rash or hand-foot syndrome (15%) and fatigue (11%). Two patients receiving sorafenib in the first stage of the study and one patient in the second stage experienced grade ≥3 hemoptysis.

The Phase III ESCAPE trial evaluated sorafenib in combination with carboplatin plus paclitaxel in 926 patients with advanced untreated nonsquamous or squamous NSCLC,90 but the study was halted when an interim analysis showed median OS was 10.7 months with sorafenib plus chemotherapy and 10.6 months with chemotherapy alone (HR, 1.15; 95% CI, 0.94–1.41; P = 0.915). Likewise, there was no significant difference between treatments in PFS (4.6 versus 5.4 months, respectively; HR, 0.99, 95% CI, 0.84–1.16; P = 0.433) or ORR (27.4% versus 24.0%; P = 0.1015). Among patients with squamous histology, those receiving sorafenib (n = 109) had a lower OS (8.9 versus 13.7 months; HR, 1.85; 95% CI, 1.22–2.81) and PFS (4.3 versus 5.8 months; HR, 1.31; 95% CI, 0.94–1.83) compared with patients receiving chemotherapy alone (n = 114), whereas patients with other nonsquamous histologies had similar OS and PFS in the two treatment groups. The most common sorafenib-related grade ≥3 adverse events in all patients included rash (8%), hand-foot skin reaction (8%), and diarrhea (4%). The histological subtype of NSCLC did not appear to affect the overall tolerability of treatment; patients receiving sorafenib plus chemotherapy with nonsquamous versus squamous histologies had similar rates of drug-related adverse events occurring at all grades (77% versus 87%), grade 3 (26% versus 33%), and grade 4 (9% versus 9%), respectively. However, four out of six fatal hemorrhagic or bleeding events observed in this study (four with sorafenib and two with chemotherapy alone) occurred in patients with squamous histology (two in each arm).90 The results of the ESCAPE study led to the exclusion of patients with squamous histology from the subsequent NExUS trial, which aimed to compare first-line treatment with sorafenib in combination with gemcitabine and cisplatin versus gemcitabine and cisplatin alone in a planned 900 patients with advanced NSCLC (NCT00449033). However, the NExUS trial was also halted because it did not meet the primary endpoint for improving OS.91

Sunitinib (SU11248; Sutent®, Pfizer; New London, CT) targets signaling through VEGFR-1, -2, and -3, PDGFR-α/β, rearranged during transfection (RET), as well as c-kit and flt-3.92 Sunitinib single-agent therapy was investigated in a Phase II trial of 63 patients with advanced NSCLC that had progressed after platinum-based chemotherapy.93 Patients were excluded from this study if they had experienced a grade 3 hemorrhage or hemoptysis within 4 weeks before the start of the treatment; additionally, patients who had received prior antiangiogenic therapy were excluded. Seven patients achieved a partial response with sunitinib, resulting in an ORR of 11.1% (95% CI, 4.6–21.6), while 18 patients (28.6%) exhibited stable disease for ≥8 weeks. Median PFS was 12 weeks (95% CI, 10.0–16.1), median OS was 23.4 weeks (95% CI, 17.0–28.3), and the 1-year survival rate was 20.2% (95% CI, 10.0%–30.4%). The most common grade ≥3 adverse events were fatigue or asthenia in 18 patients (29%), lymphopenia in 15 patients (25%), pain or myalgia in 11 patients (14%), and dyspnea in seven patients (11%). Another second-line Phase II study of 47 patients with advanced NSCLC that had been treated with at least two chemotherapy regimens reported a partial response in one patient, giving an ORR of 2.1% (95% CI, 0.1–11.3), with 11 patients (23.4%) exhibiting stable disease for ≥8 weeks.94
Table 3 Results from Phase II and III trials of VEGF, FGF, and PDGF inhibitors in NSCLC

| Trial                  | Patient population                                      | Treatment | RR  | TTP   | PFS       | OS        | Grade 3/4 AEs (≥5%)                                      |
|------------------------|---------------------------------------------------------|-----------|-----|-------|-----------|-----------|--------------------------------------------------------|
| **VEGFR-targeting agents** |                                                         |           |     |       |           |           |                                                        |
| Phase II, N = 9936     | Untreated, advanced (stage IIIB/IV) or recurrent NSCLC; ECOG PS 0–2 | Bevacizumab 15 mg/kg + C/P | 31.5% | 7.4 mo; | NR        | 17.7 mo    | Leukopenia, 38%; thrombotic events, 15%; fever, headache, hypertension, infection, nausea, peripheral neuritis (each 6%) |
|                        |                                                        | Bevacizumab 7.5 mg/kg + C/P | 28.1% | 4.3 mo; | 11.6 mo   |            | Leukopenia, 31%; diarrhea, 9%; hemoptysis, 9%; fever, hemorrhage, thrombotic events (each 6%) |
|                        |                                                        | C/P       | 18.8%| 4.2 mo; |           | 14.9 mo    | Leukopenia, 22%; thrombotic events, 9%                 |
| E4599, Phase III, N = 87888 | Untreated, advanced (stage IIIB/IV) nonsquamous NSCLC; ECOG PS 0–1 | Bevacizumab 15 mg/kg + C/P | 35%  | NR     | <0.001    | 6.2 mo; P < 0.001 12.3 mo; P < 0.001 | Neutropenia, 25% (P = 0.002); febrile neutropenia, 5.2% (P = 0.02); hypertension, 7% (P < 0.001) |
| AVAIL, Phase III, N = 104339 | Untreated, advanced (stage IIIB/IV) or recurrent nonsquamous NSCLC; ECOG PS 0–1 | C/P       | 15%  | 4.5 mo; | 10.3 mo   |            |                                                        |
|                        |                                                        | Bevacizumab 15 mg/kg + C/G | 30%  | NR     | 6.5 mo; P = 0.03 >13 mo in all arms |            |                                                        |
|                        |                                                        | Bevacizumab 7.5 mg/kg + C/G | 34.1%| NR     | <0.0001  | 6.7 mo; P = 0.003 | Neutropenia, 40%; thrombocytopenia, 27%; anemia, 10%; vomiting, 7%; hypertension, 6%; thrombotic events, 7%; asthenia, 5% |
|                        |                                                        | C/G       | 20.1%| 6.1 mo  |           |            |                                                        |
| **Small molecule tyrosine kinase inhibitors** |                                                         |           |     |       |           |           |                                                        |
| Phase II, N = 7385 | Advanced (stage IIIB/IV) relapsed NSCLC; ECOG PS 0–2 (ECOG PS 0–1; n = 56) | BIBF 1120 150 or 250 mg twice daily | 1.4% | NR     | 6.9 wks (PS 0–2); | 21.9 wks (PS 0–2); | ALT elevation, 9.6%; diarrhea, 8.2%; nausea, 6.8% |
| Phase II, N = 5180 | Relapsed or refractory advanced (stage IV) nonsquamous NSCLC; ECOG PS 0–2 | Sorafenib 400 mg twice daily | 0%   | NR     | 2.7 mo    | 6.7 mo     | Hand-foot skin reaction, 10% |
| Phase II, N = 34289 | NR; ECOG PS 0–1 | Sorafenib 400 mg twice daily Placebo | 0%   | NR     | 3.6 mo; P = 0.01 | NR | Hand-foot syndrome, 15%; fatigue, 11% |
| ESCAPE, Phase III, N = 92680 | First-line treatment, advanced (stage IIIB/IV) NSCLC; ECOG PS 0–1 | Sorafenib 400 mg twice daily + C/P | 27.4%| NR     | 4.6 mo    | 10.7 mo    | Neutropenia, 9%; rash, 8% (P < 0.001); hand-foot skin reaction, 8% (P < 0.001); fatigue, 5% |
| Phase II, N = 6393 | Pretreated, advanced (stage IIIB/IV) NSCLC; ECOG PS 0–1 | Sorafenib 400 mg twice daily + C/P | 24.0%| NR     | 5.4 mo    | 10.6 mo    | Neutropenia, 6%; rash, 1%; hand-foot skin reaction, 0%; fatigue, 2% |
|                        |                                                        | C/P       |      |        |           |           |                                                        |
|                        |                                                        | Sunitinib 50 mg/day | 11.1%| NR     | 12 wks    | 23.4 wks   | Fatigue/asthenia, 29%; lymphopenia, 25%; pain/myalgia, 17%; dyspnea, 11%; nausea/vomiting, 10%; dehydration, 8%; anorexia, headache, hypertension, neutropenia, thrombocytopenia (each 5%) |
| Trial | Stage | Treatment | RR | Grade 3 Events | Median PFS | Median OS |
|-------|-------|-----------|----|----------------|------------|-----------|
| Sunitinib | Pretreated, advanced (stage IIIB/IV) NSCLC; ECOG PS 0–1 | 2.1% | NR | 11.9 wks | 37.1 wks |
| Cediranib | Untreated, advanced (stage IIIB/IV) NSCLC; ECOG PS 0–1 | 38% | NR | 5.6 mo | 10.5 mo |
| Pazopanib | Preoperative, early stage (stage I/II) NSCLC; ECOG PS 0–1 | NR | NR | NR | NR |
| Axitinib | Pretreated, advanced (stage IIIB/IV) NSCLC; ECOG PS 0–1 | 9% | NR | 4.9 mo | 14.8 mo |
| Cediranib | Untreated, advanced (stage IIIB/IV) NSCLC; ECOG PS 0–1 | 38% | NR | 5.6 mo | 10.5 mo |
| Sunitinib | Pretreated, advanced (stage IIIB/IV) NSCLC; ECOG PS 0–1 | 2.1% | NR | 11.9 wks | 37.1 wks |
| Cediranib | Untreated, advanced (stage IIIB/IV) NSCLC; ECOG PS 0–1 | 38% | NR | 5.6 mo | 10.5 mo |
| Pazopanib | Preoperative, early stage (stage I/II) NSCLC; ECOG PS 0–1 | NR | NR | NR | NR |
| Axitinib | Pretreated, advanced (stage IIIB/IV) NSCLC; ECOG PS 0–1 | 9% | NR | 4.9 mo | 14.8 mo |

**Notes:**
- RR: response rate
- Grade 3 events are those that are serious or life-threatening.
- Median PFS and OS were 11.9 weeks (95% CI, 8.6–14.1) and 37.1 weeks (95% CI, 31.1–69.7), respectively.

**Abbreviations:**
- AE: adverse event
- ALT: alanine transaminase
- C/G: cisplatin/gemcitabine
- C/P: carboplatin/paclitaxel
- ECOG: Eastern Cooperative Oncology Group
- FGF: fibroblast growth factor
- mo: months
- NR: not reported
- NSCLC: nonsmall cell lung cancer
- ORR: overall response rate
- OS: overall survival
- PFS: progression-free survival
- PDGF: platelet-derived growth factor
- PS: performance status
- RR: response rate
- TSH: thyroid-stimulating hormone
- TTP: time to disease progression
- veGF: vascular endothelial growth factor
- veGFR: vascular endothelial growth factor receptor
- wks: weeks
NSCLC patients with disease progression after prior treatment.101 An initial report on 24 patients receiving a 0.10 mg/kg daily dose and 24 patients receiving a 0.25 mg/kg daily dose showed 33% of all patients exhibited PFS of 16 weeks or longer. Median PFS was 109 and 108 days in the high- and low-dose groups, respectively. The most common grade ≥3 adverse events were hypertension (23% in the high-dose group), hand-foot syndrome (8% in the high-dose group), and fatigue (7% and 8% in the high- and low-dose groups, respectively).101

Motesanib (AMG 706; Amgen, Thousand Oaks, CA) inhibits signaling through VEGFR-1, -2, and -3, PDGFR-β, c-kit, and RET, and inhibits VEGF-induced angiogenesis in tumor cell xenograft models.102 Motesanib is currently undergoing evaluation in patients with NSCLC in combination with chemotherapy.103,104 In an initial Phase Ib study involving 26 patients with solid tumors, grade ≥3 deep vein thrombosis and neutropenia were reported in one patient each, one patient had a partial response, and seven patients achieved stable disease at 52 days (although none showed stable disease for longer than 24 weeks).104 In a subsequent Phase II study, 181 patients with advanced nonsquamous NSCLC received treatment with motesanib 125 mg once daily or 75 mg twice daily or bevacizumab 15 mg/kg in combination with carboplatin and paclitaxel.103 Preliminary results showed partial responses in 23% and 22% of patients in the 125 mg and 75 mg motesanib groups, respectively, and 29% in the bevacizumab group, while median PFS was 7.4 months (95% CI, 5.3–8.5), 5.2 months (95% CI, 4.2–6.8), and 6.8 months (95% CI, 4.4–8.8) in the three treatment groups, respectively. The most common grade ≥3 adverse events in the three groups were diarrhea (19%, 13%, and 3%), dehydration (17%, 8%, and 3%), fatigue (17%, 5%, and 8%), anorexia (12% 2%, and 3%), and nausea (10%, 3%, and 2%). The ongoing Phase III MONET1 study (NCT00460317) was initially suspended because of a higher incidence of mortality and hemoptysis in patients with squamous NSCLC treated with motesanib plus carboplatin and paclitaxel compared with those who had nonsquamous NSCLC. The trial has since resumed with an expected enrollment of 1400 patients, but recruitment is now limited to patients who have tumors with nonsquamous histology.105

Pazopanib (GW786034; GlaxoSmithKline, London, UK) inhibits VEGFR-1, -2, and -3, FGFR-1, PDGFR-α/β signaling, and c-kit.106,107 Pazopanib as preoperative monotherapy was investigated in a Phase II trial involving 35 patients with NSCLC scheduled for resection.108 Patients with a history of hemoptysis or evidence of bleeding were excluded from the study. Of 35 patients, three had a partial response and 30 patients (86%) showed tumor-volume reduction (two of whom had a volume reduction of 50% or more). The most common grade ≥3 adverse event was an increase in serum ALT levels, reported for two patients.

Axitinib (AG-013736; Pfizer, New London, CT) targets VEGFR-1, -2, -3, and PDGFR-β.108 Axitinib was evaluated in an open-label, single-arm Phase II study of 32 patients with NSCLC after at least one prior regimen of chemotherapy.110 Patients were excluded from this study if they had a history of grade ≥2 hemoptysis or brain metastases. Three patients demonstrated a partial response, giving an ORR of 9%, while 10 patients (31%) experienced stable disease for 16 weeks or longer. Median PFS was 4.9 months (95% CI, 3.6–7.0 months), and median OS was 14.8 months (95% CI, 10.7–not estimable). Common grade ≥3 adverse events included fatigue in seven patients (22%), hypertension in three patients (9%), and hyponatremia in three patients (9%). Phase II clinical trials are currently evaluating first-line axitinib in combination with cisplatin and pemetrexed for patients with nonsquamous advanced NSCLC (NCT00768755) or in combination with cisplatin and gemcitabine in the treatment of advanced squamous NSCLC (NCT00735904).

Aflibercept (VEGF Trap; Regeneron, Tarrytown, NY), a fusion protein made up of portions of VEGFRs and human immunoglobulin G, has also shown activity in a Phase I clinical trial of patients with advanced solid tumors.111 In a Phase II trial of patients with platinum-resistant, erlotinib-resistant adenocarcinoma of the lung, aflibercept was associated with an RR of 2%, median PFS of 2.7 months, and median OS of 6.2 months among 89 evaluable patients; the most common grade ≥3 adverse events included hypertension (23%), dyspnea (21%), and proteinuria (10%).112 A Phase III trial is ongoing to evaluate aflibercept as second-line therapy in combination with docetaxel in patients with metastatic NSCLC (NCT00532155).

**Conclusion**

Challenges associated with currently approved targeted therapies in NSCLC include the development of resistance and patient eligibility, and so there is a need for more effective therapies that improve clinical benefit with minimal toxicity. Ongoing studies are evaluating new antiangiogenic treatments, with potentially promising antitumor activity suggested in Phase II studies of agents that target multiple angiogenic pathways (e.g., VEGFR, PDGFR, and FGF pathways). However, while Phase III combination trials with monoclonal antibodies such as bevacizumab have been...
promising, recently completed combination trials with TKIs have been disappointing. Nonetheless, results from ongoing studies are eagerly awaited to help determine how these new antiangiogenic agents may be best used either alone or in combination with traditional chemotherapy regimens to improve outcomes in individual patients.

Acknowledgments
This work was supported by Boehringer Ingelheim Pharmaceuticals, Inc (BIPI). Writing and editorial assistance was provided by Robert Lee, PhD, of MedErgy, which was contracted by BIPI for these services. The authors received no compensation related to the development of the manuscript. 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 at all stages of manuscript development.

Dr Chachoua has served on the Speakers Bureau for Eli Lilly, Genentech, and Response Genetics, Inc. Dr Ballas has received past honoraria from Eli Lilly.

Disclosure
The authors report no conflicts of interest in this work.

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