The Potential of Antiangiogenic Therapy in Non–Small Cell Lung Cancer
Giuseppe Giaccone

Abstract
The long-term prognosis for patients with advanced non–small cell lung cancer (NSCLC) remains poor despite the availability of several cytotoxic chemotherapy regimens. The use of targeted therapies, particularly those against the key mediator of angiogenesis vascular endothelial growth factor (VEGF), has the potential to improve outcomes for NSCLC patients. Bevacizumab, a recombinant humanized monoclonal anti-VEGF antibody, is the most clinically advanced antiangiogenic agent in NSCLC. In a phase III study, bevacizumab showed significantly improved overall and progression-free survival when used in combination with standard first-line chemotherapy in patients with advanced NSCLC. Bevacizumab was generally well tolerated in patients with NSCLC; however, tumor-related bleeding adverse events have been noted in some patients, predominantly those with squamous cell histology or centrally located tumors. Several small-molecule VEGF receptor tyrosine kinase inhibitors have also shown promise in phase I and II trials in NSCLC. This review summarizes the most important findings of angiogenesis inhibitors in NSCLC and discusses the potential for the use of these novel agents in different settings of NSCLC.

Lung cancer is the most common malignancy and the leading cause of cancer death worldwide (1, 2). The prognosis for lung cancer is poor, with a 5-year survival rate of only 15% (2). Standard treatment for non–small cell lung cancer (NSCLC), which comprises 80% to 85% of all lung cancer cases, involves surgery, radiation therapy, and chemotherapy, with disease stage determining therapeutic options (3, 4). Surgery of curative intent is the mainstay treatment in patients with localized disease (stage I and II disease). Chemotherapy is the primary first-line treatment option for the 70% to 80% of patients who present with locally advanced (stage III) or metastatic (stage IV) disease. Chemotherapy is not curative in stage IV disease.

Standard first-line chemotherapy for patients with good performance status (0/1) is a platinum-based (i.e., cisplatin or carboplatin) doublet regimen incorporating a third-generation cytotoxic agent (e.g., gemcitabine, vinorelbine, paclitaxel, or docetaxel). This approach has improved survival compared with best supportive care; however, overall and 1-year survival (8–11 months and 27–47%, respectively) for patients with advanced disease remain low and further improvements from currently available chemotherapy agents seem unlikely (5, 6).

The optimal therapeutic approach for patients with stage IV disease, elderly (≥70 years) patients with earlier stage disease, and patients with poor performance is not fully defined, although many receive single-agent (third generation) chemotherapy or best supportive care (3, 7, 8).

Docetaxel and pemetrexed are currently approved for use as monotherapy in the treatment of locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen. Second-line docetaxel showed a 1-year survival benefit compared with supportive care. Approval of pemetrexed was based on demonstration of noninferiority versus docetaxel (9).

In recent years, the improved understanding of cancer biology has led to the investigation of several new targeted therapies directed against key biological processes in NSCLC development and progression. These agents, including monoclonal antibodies and small-molecule tyrosine kinase inhibitors (TKI), have the potential for increased selectivity and thereby reduced toxicity compared with standard chemotherapies. Two epidermal growth factor receptors (EGFR) TKIs, erlotinib and gefitinib, are currently approved for second- or third-line treatment of NSCLC in several countries. However, only erlotinib has shown improved survival versus best supportive care in this setting (10, 11). Interestingly, a subgroup analysis of a phase III survival study (ISEL) comparing gefitinib with placebo revealed a significant survival benefit in Asian patients receiving gefitinib, although the trial did not meet its primary end point of increasing overall survival benefit in the population as a whole (11). In the BR.21 study of erlotinib versus placebo, Asian patients also had a better survival than the other ethnicities, although the number of patients assessed in this study was only 91 (10). Gefitinib is no longer recommended in the National Comprehensive Cancer Network guidelines for NSCLC based on its failure to improve survival (4). Neither agent has shown any additional benefit when
combined with first-line chemotherapy for NSCLC (12–14). Targeted agents that inhibit tumor-associated angiogenesis have shown particular promise in preclinical and clinical studies and are the focus of this review.

**Antiangiogenesis in NSCLC: Targeting Vascular Endothelial Growth Factor**

Angiogenesis, the process of new blood vessel formation, is fundamental to the growth and dissemination of solid tumors. Tumors that are <2 mm³ receive nutrients and growth factors by diffusion; to grow any larger, tumors must establish a blood supply (15). Tumor cells also use newly formed blood vessels as a route for metastatic spread. The fact that tumors are dependent on angiogenesis for growth and metastasis has led to the development of antiangiogenic strategies for cancer treatment (see refs. 16–21 for recent reviews).

Angiogenesis is a complex process that is tightly controlled by factors that stimulate or inhibit the formation of new blood vessels. To grow, tumors trigger the development of their own blood supply by disrupting the delicate balance of proangiogenic and antiangiogenic factors (15, 22). Proangiogenic gene expression is increased by physiologic stimuli, such as hypoxia, which results from tumors compressing blood vessels and outstripping their blood supply as tumor tissue mass increases (16, 22). Oncogene activation or tumor suppressor mutation can also tip the balance in favor of proangiogenic factors, stimulating the development of new blood vessels in and around the tumor, thus enabling the tumor to expand, invade surrounding tissues, and metastasize (16, 22).

Of the different proangiogenic factors, vascular endothelial growth factor (VEGF or VEGF-A) is a key mediator of normal and tumor angiogenesis; it promotes the proliferation and survival of endothelial cells and increases vascular permeability (23). VEGF binds to two receptor tyrosine kinases, VEGF receptor (VEGFR) 1 (Flt-1) and VEGFR2 (KDR/Flk-1), as well as the neuropilin family of coreceptors. VEGFR2 is thought to be the main receptor responsible for the mitogenic, angiogenic, and permeability enhancing effects of VEGF. The binding of VEGF to VEGFR2 promotes receptor dimerization and ligand-dependent receptor tyrosine kinase phosphorylation, with subsequent activation of signaling pathways involved in endothelial cell proliferation, migration, and survival.

The central role of VEGF in tumor angiogenesis makes it an attractive target for anticancer therapy. VEGF inhibition has the potential to cause regression of immature tumor blood vessels and inhibit the development of new tumor vasculature without compromising healthy vasculature. Because the physiologic role of angiogenesis in healthy adults is limited to wound healing and the menstrual cycle (24), inhibiting VEGF should have minimal undesired effects on normal physiologic processes and thus have relatively few side effects. Two additional factors make VEGF an attractive therapeutic target. First, because VEGF circulates in the blood and acts directly on vascular endothelial cells, drugs that target VEGF do not need to penetrate tumor tissue to inhibit tumor angiogenesis. Second, VEGF acts on endothelial cells, which may be less likely to mutate to a treatment-resistant phenotype than genetically unstable tumor cells (25). Thus, endothelial cells may be a more attractive target than tumor cells for long-term therapy.

High intratumoral (evidenced by mRNA and immunohistochemical analyses) and/or circulating VEGF levels are associated with poor prognosis in patients with NSCLC (26–33). In addition to promoting tumor growth and survival via localized angiogenic mechanisms, evidence suggests that VEGF plays a role in the promotion of malignant pleural effusion and pleural dissemination in NSCLC (34, 35). Inhibition of VEGF or its receptor(s) inhibits vascularization and growth of human lung tumor xenografts (36–41). This effect has been observed in both newly implanted and well-established NSCLC tumors (37). In addition to inhibiting tumor angiogenesis, studies in lung cancer xenograft models suggest that antagonism of VEGF signaling promotes tumor cell apoptosis (42) and enhances the antitumor activity of chemotherapy (36). It has been suggested that these effects result from inhibition of VEGF-mediated tumor survival signals (43). Importantly, inhibitors of VEGF-mediated angiogenesis have shown clinically meaningful survival benefits, both as monotherapy or in combination with chemotherapy, in clinical trials with other types of solid tumors (44–48). Collectively, these findings suggest that targeting VEGF is a rational therapeutic approach in NSCLC. Several agents that inhibit angiogenesis by blocking the VEGF pathway are in clinical development for NSCLC (Table 1; Fig. 1). These agents take one of two approaches to inhibiting VEGF: targeting the VEGF molecule itself or targeting the cell surface receptors for VEGF.

**Bevacizumab.** The most clinically advanced of the targeted antiangiogenic agents is bevacizumab (Avastin, Roche, Basel, Switzerland; Genentech, Inc., South San Francisco, CA), a recombinant humanized monoclonal antibody against VEGF (49). Preclinical studies with bevacizumab or its parental murine antibody A4.6.1 have shown growth inhibition in a variety of tumor models (50), including NSCLC (36). Bevacizumab, combined with 5-fluorouracil–based chemotherapy, is currently approved in Europe and the United States for the first-line treatment of metastatic colorectal cancer and in the United States for the first-line treatment of advanced nonsquamous NSCLC. A pivotal phase III trial in patients with untreated metastatic colorectal cancer showed that the addition of bevacizumab (5 mg/kg every 2 weeks) to standard irinotecan/5-fluorouracil/leucovorin chemotherapy significantly improved median overall survival by 30% (20.3 versus 15.6 months; P < 0.001; ref. 45). Similarly, the addition of bevacizumab to 5-fluorouracil/leucovorin or FOLFOX4 significantly improved overall survival compared with chemotherapy alone (44, 48).

Bevacizumab has shown a survival benefit in other solid tumor types, including metastatic breast cancer and renal cell cancer. Bevacizumab monotherapy (10 mg/kg every 2 weeks) showed improved progression-free survival compared with placebo (4.8 versus 2.5 months; P < 0.001) in patients with metastatic renal cell cancer who were not optimal candidates for, or who had not responded to, interleukin-2 therapy (51). Additionally, an interim analysis from an ongoing phase III study in patients with metastatic breast cancer showed that bevacizumab plus paclitaxel significantly increased progression-free survival compared with paclitaxel alone [11.40 versus 6.11 months; hazard ratio (HR), 0.51; P < 0.0001; ref. 52].

Clinical trials have also established the efficacy and tolerability of bevacizumab in NSCLC. A randomized phase II trial in 99 patients with advanced or recurrent NSCLC evaluated the efficacy and safety of carboplatin (area under the curve of 6)
plus paclitaxel (200 mg/m²) with or without bevacizumab (7.5 or 15 mg/kg), administered every 3 weeks (53). Patients who received 15 mg/kg bevacizumab every 3 weeks had an improved median time to progression (7.4 versus 4.2 months; \(P = 0.023\)) and overall response rate (31.5% versus 18.8%) compared with chemotherapy alone. Additionally, 15 mg/kg bevacizumab every 3 weeks showed a small increase in survival, although this did not reach statistical significance (17.7 versus 14.9 months; \(P = 0.63\)). In this trial, 19 of 32 patients randomized to chemotherapy alone crossed over to bevacizumab monotherapy on disease progression; 5 of these patients achieved stable disease and median survival at 1 year was 47.4%. Bevacizumab was generally well tolerated, although adverse events of bleeding were noted, including major pulmonary hemorrhage (hemoptysis) that was associated with squamous cell histology, cavitated or necrotic tumors, and tumors located close to major blood vessels (the latter two features being common in patients with squamous cell NSCLC). The risk of bleeding seemed to be only slightly elevated in patients with nonsquamous histology (overall risk was \(\sim 4\%\)). In contrast to NSCLC, pulmonary bleeding has not been reported in trials of bevacizumab in breast, colorectal, prostate, or renal cell cancer.

A large phase III trial (Eastern Cooperative Oncology Group study 4599) evaluated bevacizumab plus chemotherapy in 878 treatment-naive patients with advanced nonsquamous NSCLC (54). Patients with brain metastases and patients with more than half a teaspoon of hemoptysis were excluded. Patients were randomized to receive carboplatin (area under the curve of 6) plus paclitaxel (200 mg/m²) with or without bevacizumab (15 mg/kg) every 3 weeks for six cycles; bevacizumab monotherapy (15 mg/kg every 3 weeks) was then continued until progressive disease or intolerable toxicity. Patients receiving bevacizumab had significantly improved median survival.

### Table 1. Angiogenesis inhibitors in clinical development for NSCLC

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism(s) of action</th>
<th>Molecular target(s)</th>
<th>Stage of clinical development</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bevacizumab</td>
<td>Anti-VEGF antibody</td>
<td>VEGF ligand</td>
<td>Phase III</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>TKI</td>
<td>Raf-1, VEGFR2, VEGFR3, PDGFR-(\alpha), Flt-3, c-Kit</td>
<td>Phase III</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>TKI</td>
<td>VEGFR1, VEGFR2, VEGFR3, Flt-3, PDGFR-(\alpha), PDGFR-(\beta), c-Kit</td>
<td>Phase II</td>
</tr>
<tr>
<td>Vatalanib</td>
<td>TKI</td>
<td>VEGFR1, VEGFR2, VEGFR3, PDGFR-(\beta), c-Kit, c-Fms</td>
<td>Phase II</td>
</tr>
<tr>
<td>AMG 706</td>
<td>Protein kinase inhibitor</td>
<td>VEGFR1, VEGFR2, VEGFR3, PDGFR-(\beta), PDGFR-(\alpha), c-Kit</td>
<td>Phase II</td>
</tr>
<tr>
<td>CP-547,632</td>
<td>TKI</td>
<td>VEGFR2</td>
<td>Phase II</td>
</tr>
<tr>
<td>AZD2171</td>
<td>TKI</td>
<td>VEGFR2</td>
<td>Phase II-III</td>
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<tr>
<td>AEE788</td>
<td>TKI</td>
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<td>Phase I/II</td>
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<tr>
<td>ZD6474</td>
<td>TKI</td>
<td>VEGFR2, VEGFR3, EGFR</td>
<td>Phase II</td>
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Fig. 1. Approaches to targeting VEGF or VEGFRs.
and response rates (27.2% versus 10.0%; progression-free survival (6.4 versus 4.5 months; overall survival (12.5 versus 10.2 months; the HR for survival was 0.96 (P = 0.80) for women. However, it is important to note that the primary end point of the study was met and that the study was not powered to show efficacy differences between subgroups. In addition, women did show significantly improved progression-free survival and response rates, arguing in favor of an overall benefit from the addition of bevacizumab. Other possible explanations for this finding include potential imbalances of prognostic factors and imbalances in the use of second- and third-line therapies.

The treatment combination was well tolerated, although there was a slightly increased incidence of grade 4/5 neutropenia, grade 3/4 hypertension, and treatment-related deaths in the bevacizumab arm. An increased incidence of hemorrhage was also observed in the bevacizumab arm, particularly pulmonary hemoptysis (1.9% versus 0.2%). However, restricting the population to patients with nonsquamous histology and minimal baseline hemoptysis substantially decreased the incidence of grade ≥3 hemoptysis from 6.1% (in the phase II study) to 1.9%.

E4599 was the first study to show that addition of a targeted agent to standard first-line chemotherapy improves survival in patients with advanced NSCLC; it was also the first to suggest that triplet therapy is superior to doublet therapy. Based on these positive results, the bevacizumab/carboplatin/paclitaxel regimen used in the trial has been adopted as the new Eastern Cooperative Oncology Group standard of care for the first-line treatment of advanced NSCLC. The National Comprehensive Cancer Network has also recently incorporated bevacizumab (in combination with chemotherapy) into its treatment guidelines for NSCLC (4), and in October 2006, the Food and Drug Administration granted approval for the use of bevacizumab in combination with carboplatin/paclitaxel as first-line treatment for patients with advanced nonsquamous NSCLC.

A large phase III trial of cisplatin/gemcitabine with or without bevacizumab as first-line therapy in advanced nonsquamous NSCLC (BO17704) has completed recruitment in Europe. A total of 1,044 patients was randomized to three arms to receive cisplatin/gemcitabine with or without one of two doses of bevacizumab (either 7.5 or 15 mg/kg every 3 weeks). This trial will evaluate the efficacy of different bevacizumab doses and assess whether the benefit of bevacizumab extends to other chemotherapy doublet regimens.

Sorafenib. Sorafenib tosylate ( Nexavar, Bayer Pharmaceuticals, Inc., Westhaven, CT; Onyx Pharmaceuticals, Inc., Emeryville, CA) is a multitargeted TKI with activity against Raf-1, VEGFR1, VEGFR2, VEGFR3, platelet-derived growth factor receptor (PDGFR)-β, Flt-3, and c-Kit (55). In preclinical studies, sorafenib showed antitumor activity in a variety of human tumor xenograft models, including NSCLC, which was associated with down-regulation of the Raf/mitogen-activated protein kinase/extracellular signal-regulated kinase kinase/extracellular signal-regulated kinase tumor cell proliferation pathway and reduced vascularization (55). Clinical development of sorafenib is most advanced in relapsed/refractory renal cell cancer, and a recent phase III study in patients with previously treated advanced renal cell cancer showed increased progression-free survival compared with best supportive care (24 versus 12 weeks; ref. 47), leading to U.S. Food and Drug Administration and European Agency for the Evaluation of Medicinal Products approval in this indication. Preliminary results from a phase I study of sorafenib (200 or 400 mg twice daily) plus gefitinib (250 mg/d) in 32 patients with unresectable or recurrent advanced NSCLC showed that the combination was well tolerated with no dose-limiting toxicities; 1 patient achieved a partial response and 20 (63%) had stable disease (mean duration of response, 20.4 weeks; ref. 56). In a recent phase II trial, sorafenib monotherapy (400 mg/d) showed promising efficacy in 52 patients with advanced NSCLC, with 59% of patients achieving disease stabilization (57). A large randomized study is presently running comparing chemotherapy (carboplatin/paclitaxel) alone with chemotherapy plus sorafenib in patients with advanced NSCLC. This study includes all histologies, unlike the pivotal study done with bevacizumab. The planned targeted accrual is 900 patients and survival is the major end point in this study.

Sunitinib malate. Sunitinib malate (Sutent, SU11248, Pfizer, Inc., New York, NY) is a small-molecule TKI with activity against VEGFR1, VEGFR2, and VEGFR3 as well as Flt-3, PDGFR-α, PDGFR-β, and c-Kit (58, 59). Sunitinib malate prevented blood vessel formation in a tumor vascular window model but produced minimal effects on established blood vessels (60). In a NSCLC xenograft model, sunitinib malate markedly reduced tumor growth with histologic evidence of extensive tumor destruction, although no tumor regression was observed (61). Studies in a Lewis lung carcinoma model showed reduced tumor vascularization and reduced metastasis to the lung following excision of the s.c. tumor (60, 62). Combined treatment with sunitinib malate and radiation therapy or cisplatin in murine xenograft models showed enhanced antitumor activity compared with conventional therapy alone (58, 62).

Sunitinib malate was recently approved by the Food and Drug Administration for the treatment of previously treated patients with gastrointestinal stromal tumors and for metastatic renal cell cancer based on evidence from phase III and phase II trials, respectively (46, 63). Two ongoing phase II studies are evaluating sunitinib malate monotherapy in advanced NSCLC: the first in previously treated patients with metastatic disease and the second as consolidation therapy following first-line treatment with carboplatin/paclitaxel in locally advanced/metastatic disease. The agent is also under investigation in combination with erlotinib in previously treated advanced NSCLC.

Vatalanib. Vatalanib (PTK787/ZK 222584; Novartis Pharmaceuticals Corp., Basel, Switzerland) has activity against VEGFR1, VEGFR2, VEGFR3, PDGFR-β, c-Kit, and c-Fms (64). Preclinical studies showed that vatalanib inhibited endothelial cell proliferation, migration, and survival in vitro and down-regulated angiogenesis in vitro and in vivo (64). Vatalanib also inhibited the growth of a variety of human tumor xenografts; histologic analysis of a human epidermal tumor xenograft model showed that vatalanib inhibited the development of new microvessels in the interior of the tumor but did not affect larger, more established vessels (64). In mice with lung lesions and pleural effusion induced by injection of human NSCLC...
cells, vatalanib reduced the formation of pleural effusion, primarily by reducing vascular permeability, and reduced tumor vascularization, although it did not significantly reduce the number of lung lesions [65].

Vatalanib has been studied in patients with a variety of cancers, including colorectal, pancreatic, renal cell, ovarian, and hematologic malignancies. A phase I study in patients with advanced solid tumors established that the maximum tolerated oral dose was 750 mg/d, whereas the biologically active dose was ≥1,000 mg/d [66]. Two large phase III trials in patients with untreated (CONFIRM-1) and previously treated (CONFIRM-2) metastatic colorectal cancer are ongoing. An interim analysis of CONFIRM-1, by independent central review, showed no increase in progression-free survival with vatalanib plus FOLFOX4 compared with FOLFOX4 alone (median, 7.7 versus 7.6 months; HR, 0.88; \( P = 0.118 \); ref. 67). However, an interim analysis of CONFIRM-2 found that vatalanib plus FOLFOX4 improved progression-free survival compared with FOLFOX4 alone (5.6 versus 4.1 months; \( P = 0.026 \)) but did not improve overall survival (12.1 versus 11.8 months; \( P = 0.51 \); ref. 68). Clinical evaluation is ongoing in NSCLC with a phase II trial (GOAL) of vatalanib monotherapy in relapsed or refractory NSCLC currently recruiting patients.

**AMG 706.** AMG 706 (Amgen, Inc., Thousand Oaks, CA) is an oral multikinase inhibitor of VEGFR1, VEGFR2, VEGFR3, PDGFR, c-Kit, and c-Ret. In preclinical studies, AMG 706 caused regression of tumor xenografts and inhibited vascular blood flow and/or permeability [69]. A phase I/II trial of AMG 706 in combination with paclitaxel/carboplatin and the anti-EGFR monoclonal antibody panitumumab in patients with advanced NSCLC is ongoing, and a phase II trial of AMG 706 or bevacizumab in combination with chemotherapy in patients with advanced NSCLC is planned.

**CP-547,632.** CP-547,632 (Pfizer/OSI Pharmaceuticals, Inc., Melville, NY) is a selective VEGFR2 TKI [70]. Preliminary results from a phase I trial of CP-547,632 (200 mg/d) in combination with carboplatin/paclitaxel as first-line therapy for advanced NSCLC indicated that this treatment was well tolerated [71]. Efficacy data from 30 evaluable patients revealed a 20% partial response rate, a stable disease rate of 50%, and a progressive disease rate of 30%. Based on these results, a phase I/II trial in chemo-naive NSCLC patients is ongoing.

**AZD2171.** AZD2171 (AstraZeneca, Macclesfield, United Kingdom) is a potent inhibitor of VEGFR2 tyrosine kinase activity [72]. The growth of established tumor xenografts of different tumor types, including NSCLC, is inhibited by AZD2171. A phase I study determined good tolerability of this compound, although the classic class toxicities (i.e., hypertension) were noted. A phase I study of AZD2171 has been done in combination with standard carboplatin-paclitaxel in patients with untreated advanced NSCLC, which has identified the optimal dose for combination (45 mg/d; ref. 73). The National Cancer Institute of Canada cooperative group is running a randomized phase II study of AZD2171 in combination with carboplatin-paclitaxel, and the study will continue to full-blown phase III if no unexpected toxicities are encountered in the phase II part. All patients, including those with squamous carcinoma histology and brain metastases, are included in this study, as with all other studies with VEGFR TKIs in lung cancer.

**VEGF Trap.** VEGF Trap (Regeneron, Tarrytown, NY; Sanofi-Aventis, Paris, France) is a composite, soluble recombinant decoy receptor comprising portions of VEGFR1 and VEGFR2 fused to a Fc segment of IgG1. In animal xenograft models, VEGF Trap has been shown to block growth of new vessels and disrupt preexisting vasculature [74]. A phase II trial to determine the overall objective response rate of patients with platinum- and erlotinib-resistant locally advanced or metastatic non–small cell lung adenocarcinoma receiving VEGF Trap (4 mg/kg every 2 weeks) is ongoing.

**Enzastaurin.** Enzastaurin (Eli Lilly, Indianapolis, IN) is an orally active inhibitor of protein kinase C, glycogen synthase kinase-3, and Akt. An ongoing phase II trial will compare time to disease progression in patients receiving docetaxel/carboplatin or pemetrexed/carboplatin with or without enzastaurin.

**Thalidomide.** Thalidomide is an oral inhibitor of the effects of tumor necrosis factor-α. Phase II studies of thalidomide in patients with advanced NSCLC have shown promising activity for this agent in terms of tumor remissions and stable disease [75, 76]. Several ongoing trials are examining the potential role of thalidomide for the treatment of advanced NSCLC. A phase II trial will determine the response rates of 37 patients with stage III or IV NSCLC treated with second-line docetaxel and thalidomide, whereas a second trial will determine the response rates of 21 patients with stage II or IIIA NSCLC receiving neoadjuvant carboplatin, gemcitabine, and thalidomide. A phase III trial aims to recruit 588 patients with stage III NSCLC to compare their survival and time to progression when treated with carboplatin/paclitaxel and radiotherapy with or without thalidomide (Eastern Cooperative Oncology Group 3598).

### Combined Inhibition of the VEGF and EGFR Pathways

Combined targeting of the VEGF and EGFR signaling pathways represents an attractive approach to treating NSCLC. Preclinical studies have shown that combined treatment with EGFR and VEGF signaling inhibitors has at least additive antitumor activity [77–79], indicating that the mechanisms of action of such agents are different but complementary [80, 81]. In addition, EGFR inhibitors could act to sensitize cells to antiangiogenic therapy by lowering the tumor survival threshold because one of the signaling pathways leading to cell growth and survival is shut down [82]. Moreover, it has been postulated that “overactivation” of non-EGF pathways driving VEGF expression (independent of EGFR) results in resistance to EGFR inhibitors due to the inability of these agents to downregulate VEGF to “critical” nonangiogenic levels, thus reducing the antiangiogenic potential of these antagonists [82]. This could potentially be overcome by combining EGFR inhibition with an anti-VEGF agent.

Two approaches to combining VEGF and EGFR inhibition are possible. First, these factors can be inhibited using two specific agents (e.g., bevacizumab and erlotinib), a single agent that inhibits both VEGF and EGFR can be used. Both approaches are being examined clinically and have potential benefits. Inhibition using two drugs allows for treatment individualization and potentially dose titration to ensure optimal target inhibition. Use of a dual inhibitor means that only one drug needs to be administered. However, whether both targets are optimally inhibited is difficult to assess.

**AEE788.** AEE788 (Novartis Pharmaceuticals) is an oral EGFR and VEGFR TKI. Preclinical studies have shown that
AEE788 inhibits EGFR, HER2, HER4, KDR, and Flt-1 with IC50 values of 2, 6, 160, 77, and 59 nmol/L, respectively, and is antiproliferative in cells overexpressing EGFR and HER2 (83, 84). A phase I/II dose escalation trial of AEE788 in patients with recurrent or relapsed glioblastoma multiforme is currently ongoing; preliminary results indicate that it is generally well tolerated (85).

**ZD6474.** ZD6474 (Zactima, AstraZeneca) is a small-molecule inhibitor of VEGFR2, VEGFR3, and EGFR (86, 87). ZD6474 was shown to potently inhibit VEGF-induced proliferation of endothelial cells in vitro (87). It also inhibited the growth of a variety of human tumor xenografts, including A549 lung adenocarcinoma and Calu-6 NSCLC, even in large tumors with established vasculature (87). Studies in PC-9 human lung adenocarcinoma xenografts suggest that the antitumor activity of ZD6474 may largely reflect inhibition of the EGFR as evidenced by its cross-resistance with gefitinib (ZD6474 had greater activity in gefitinib-sensitive tumors than those resistant to gefitinib, with no reduction in tumor cell proliferation or vascular density in the latter tumor type; ref. 88). However, the antitumor activity of ZD6474 in Calu-6 xenografts, which are responsive to inhibitors of VEGFR but not EGFR, supports proposed mechanisms of additional antiangiogenic activity.

A phase I dose escalation trial in 77 patients with solid tumors established that a dose of 300 mg/d was well tolerated; the most common dose-limiting toxicities were diarrhea, hypertension, and rash (89). A phase II study is evaluating docetaxel with or without ZD6474 (100 or 300 mg/d) in patients with previously treated locally advanced or metastatic NSCLC. The preliminary results from the run-in phases of two phase II randomized trials indicate that ZD6474 plus docetaxel in patients with locally advanced or metastatic NSCLC, or ZD6474 plus carboplatin/paclitaxel in treatment-naive patients with locally advanced or metastatic NSCLC, are both generally well tolerated (90, 91). ZD6474 (300 mg/d) has also been investigated in comparison with gefitinib (250 mg/d) as second- or third-line treatment in patients with advanced NSCLC in a phase II study. Preliminary data from 168 patients showed that estimated median time to progression was significantly longer in patients receiving ZD6474 compared with gefitinib (11.9 versus 8.1 weeks; HR, 0.632; P = 0.011; ref. 92). A phase III study investigating ZD6474 plus docetaxel versus docetaxel alone (study 32) has started accruing patients with advanced NSCLC who failed first-line chemotherapy. The planned accrual is 1,200 patients, and progression-free survival is the major end point of this study.

**Bevacizumab plus erlotinib.** Bevacizumab (up to 15 mg/kg every 3 weeks) was evaluated in combination with erlotinib (up to 150 mg/d) in a phase I/II study in 40 patients with previously treated advanced nonsquamous NSCLC (93). Eight (20%) patients achieved a partial response, and 26 (65%) had stable disease. The median progression-free survival and overall survival were 7.0 and 12.6 months, respectively. Treatment was well tolerated with generally mild-to-moderate adverse events, and no dose-limiting toxicity was observed. A phase II trial has evaluated bevacizumab (15 mg/kg every 3 weeks) combined with chemotherapy (75 mg/m² docetaxel or 500 mg/m² pemetrexed) or combined with erlotinib (150 mg/d) in patients with recurrent or refractory NSCLC (94). Median progression-free survival was 3 months for chemotherapy alone, 4.8 months for bevacizumab plus chemotherapy (HR versus chemotherapy alone, 0.66), and 4.4 months for bevacizumab plus erlotinib (HR versus chemotherapy alone, 0.72). Median overall survival was 8.6 months for chemotherapy alone, 12.6 months for bevacizumab plus chemotherapy (HR versus chemotherapy alone, 0.74), and 13.7 months for bevacizumab plus erlotinib (HR versus chemotherapy alone, 0.76). The combination of bevacizumab and erlotinib was generally well tolerated; no new or unexpected safety signals were noted, and the rate of pulmonary hemorrhage was consistent with previous trials of bevacizumab in NSCLC. The toxicity profile of the bevacizumab/erlotinib combination compares favorably with either chemotherapy-containing group.

Two ongoing phase II trials will evaluate bevacizumab plus erlotinib in the first-line setting. The multicenter ML19389 phase II trial (n = 109) will investigate the efficacy of bevacizumab (15 mg/kg every 3 weeks) plus erlotinib (150 mg/d) given until disease progression or toxicity followed by chemotherapy [gemcitabine (1,250 mg/m²) plus cisplatin (80 mg/m²) or carboplatin (area under the curve of 5)] every 3 weeks for six cycles or until progression. The MO18632 phase II trial (n = 46) will evaluate the efficacy of bevacizumab (15 mg/kg every 3 weeks) plus erlotinib (150 mg/d) as measured by the rate of nonprogression at 6 weeks.

In addition, a large phase III trial (ATLAS) will recruit 1,150 patients with advanced or metastatic nonsquamous NSCLC to evaluate first-line bevacizumab with or without erlotinib, whereas a second phase III trial (BeTa Lung) is accruing 650 patients to investigate erlotinib with or without bevacizumab in the second-line treatment of nonsquamous advanced NSCLC. These two studies may provide an insight as to the relative contribution of VEGF and EGFR inhibition to the clinical outcome in the second-line setting and the potential role for bevacizumab maintenance therapy.

**AZD2171 plus gefitinib.** This combination has been studied in a large phase I study, including several tumor types (95). Activity has been observed in patients, including those with lung cancer. However, there are presently no plans to develop this combination further in Western countries, given the fact that gefitinib is not readily available for this indication any more in those countries.

**Future Directions**

The wealth of new molecular therapies currently approved or in clinical development indicates that antiangiogenic therapy has enormous potential for improving patient outcomes in NSCLC, but several issues remain. First and foremost is the question of the best clinical setting for antiangiogenic agents. In the first-line setting, the monoclonal antibody bevacizumab is the first agent of any kind to show a survival advantage in NSCLC when combined with a standard doublet chemotherapy regimen. Consequently, bevacizumab plus carboplatin/paclitaxel have now become the new Eastern Cooperative Oncology Group reference standard for future trials in advanced nonsquamous NSCLC. To determine whether the benefits of bevacizumab will extend to other platinum-based doublets in the first-line setting, ongoing trials in the United States and Europe are investigating combinations of bevacizumab with several other chemotherapy regimens. Antiangiogenic agents may also have potential in the (neo)adjuvant setting. There is...
Angiogenesis Inhibitors in NSCLC

Evidence to suggest that tumor dependence on angiogenesis may decrease as the cancer progresses (96), providing a rationale for early intervention with antiangiogenic agents. Moreover, applying antiangiogenic therapy earlier in the disease process may help reduce the risk of metastases and bleeding. This concept is currently being investigated in the ongoing BEACON trial, a phase II study of bevacizumab plus chemotherapy (docetaxel/cisplatin) in the neoadjuvant setting for patients with resectable stage IIB to IIIA NSCLC.

Given that lung cancer is a heterogeneous disease expressing many different targets, combinations of different biological agents to target multiple pathways simultaneously may lead to novel treatment paradigms for NSCLC. Both VEGF and EGFR inhibition have been shown to extend survival in NSCLC, leading to the expectation that dual inhibition will confer greater clinical benefit than inhibition of a single pathway. Encouraging results from phase I trials of AEE788 and ZD6474, two small-molecule inhibitors of EGFR and VEGFRs, indicate that this approach has potential. An early clinical trial of bevacizumab plus erlotinib has also shown promise, and several phase II and III clinical trials of this combination in the first- and second-line setting are under way to establish whether dual inhibition will become a future treatment paradigm for NSCLC. Whether the use of a single dual inhibitor or separate anti-VEGF and anti-EGFR agents will provide different efficacy and safety remains to be determined.

Recent preclinical studies suggest that certain chemotherapeutic agents have antiangiogenic activity if they are administered frequently at low doses (a tenth to a third of the maximum tolerated dose), with no prolonged drug-free breaks (97, 98). This approach, referred to as “metronomic” chemotherapy, may reduce certain toxicities and have better efficacy than conventional maximum tolerated dose regimens (99). The efficacy of metronomic chemotherapy may be further enhanced by the addition of specific antiangiogenic agents (99). Because metronomic chemotherapy targets the endothelial cells of the tumor, this approach has potential applications for tumors that have developed resistance to chemotherapy. The value of metronomic chemotherapy as antiangiogenic therapy for patients with NSCLC remains to be validated by randomized phase III trials, but encouraging preliminary data have been reported; in one trial, patients with NSCLC responded to a more frequent but low-dose administration of the topoisomerase enzyme inhibitor etoposide after having progressed on a conventional schedule of the same drug (100). However, several challenges must be overcome to enable the integration of metronomic chemotherapy into clinical practice. If metronomic chemotherapy in combination with angiogenesis inhibitors is to become a new paradigm for controlling cancer by long-term therapy, future studies will need to ascertain which chemotherapeutic agents are the most effective for metronomic dosing regimens, identify more effective ways to combine the newest antiangiogenic agents with metronomic chemotherapy, select optimal antiangiogenic doses that are nontoxic yet effective, and design appropriate schedules.

Establishing the safety profile of new antiangiogenic agents over prolonged periods will also become important. Due to the cytostatic action of angiogenesis inhibitors, chronic therapy may be required to prevent tumor progression. Indeed, bevacizumab has continued to be administered after the end of chemotherapy in the studies done to date. Studies investigating the role of prolonged bevacizumab administration will have to be done in light of the potential hazard of prolonged treatment with angiogenesis inhibitors. A large planned phase III trial (MO19390) will evaluate the safety profile of 15 mg/kg bevacizumab every 3 weeks combined with platinum-based chemotherapy as first-line treatment for 2,000 patients with advanced nonsquamous NSCLC. Safety studies are also required to address the issue of bleeding events in bevacizumab-treated patients. In a planned phase II trial (AVASQ) to investigate the feasibility of bevacizumab and chemotherapy in patients with squamous cell NSCLC, who are considered to be at risk of pulmonary bleeding, patients will receive radiotherapy to the central lesion as a preventive measure to reduce the risk of bleeding before receiving bevacizumab. A second phase II trial (BRIDGE) will determine whether delayed bevacizumab administration will improve safety in patients with squamous cell NSCLC; ~40 patients will receive two cycles of carboplatin/paclitaxel followed by four cycles of chemotherapy plus bevacizumab (15 mg/kg every 3 weeks) and then bevacizumab until disease progression. The primary end point of these two studies is the incidence of grade ≥3 pulmonary hemorrhage.

Interestingly, the studies that are presently ongoing with several TKIs of VEGFRs do not seem to induce the same degree of bleeding as reported with bevacizumab, although formal comparisons have yet to be done. Most phase III studies of novel VEGFR TKIs include all histologies. It will be interesting to see whether the inhibition of receptor signaling has similar efficacy as inhibiting the growth factor VEGF.

Finally, how should patients be selected for treatment with antiangiogenic therapies? Bevacizumab is currently contraindicated in patients with predominantly squamous cell NSCLC due to the occurrence of severe pulmonary hemorrhage in four patients with squamous cell histology in a phase II trial of bevacizumab plus carboplatin/paclitaxel. In addition, exclusion of patients with central nervous system metastases from bevacizumab trials became a regulatory requirement following a single central nervous system bleeding event in a patient with hepatocellular carcinoma in an early phase I/II trial. Consequently, the risk of central nervous system bleeding in patients with central nervous system metastases receiving bevacizumab cannot be estimated. Data from ongoing trials will be analyzed to evaluate the risk of bleeding events in patients who develop central nervous system metastases while receiving bevacizumab therapy to provide further insight into this issue. Interestingly, the large trials ongoing with small-molecule VEGFR inhibitors do not exclude patients with squamous cell histology or brain metastases. Several trials are ongoing to determine whether patients with predominantly squamous cell NSCLC can be safely treated with bevacizumab. These analyses may expand the eligible patient population for bevacizumab. Currently, few data are available to indicate that any molecular biomarker is predictive of the effect of antiangiogenic therapy. A prospective analysis of biomarkers in the E4599 trial of bevacizumab in NSCLC indicated that baseline intercellular adhesion molecule levels are prognostic for survival and response to chemotherapy (101). However, further prospective data from randomized trials will be necessary to determine the clinical relevance of these findings.
describe the sensitivity and specificity of a standardized test kit, and identify appropriate cutoffs for clinical use. It should be noted that, in metastatic colorectal cancer, the benefits of bevacizumab treatment were found to be independent of standard tumor markers and VEGF levels (102). This suggests that factors other than VEGF expression level may be important in determining the response to therapy, such as the degree of dependence of tumors on VEGF signaling. At present, there is no consensus as to which form of VEGF (tumor versus circulating) is the most clinically relevant to evaluate, and there is no standard detection method. These factors underscore the current difficulties in using potential markers for patient selection. Because all tumors depend on angiogenesis to some degree, it can be argued that all patients with solid tumors should be considered potential candidates for antiangiogenic therapy. Further studies are required to fully confirm this and to define the optimal role of antiangiogenic agents in the NSCLC treatment paradigm.

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The Potential of Antiangiogenic Therapy in Non–Small Cell Lung Cancer

Giuseppe Giaccone


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